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Protocol

Development and Application of a Metaverse-Based Social Skills Training Program for Children With Autism Spectrum Disorder to Improve Social Interaction: Protocol for a Randomized Controlled Trial

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Abstract

Background: Autism spectrum disorder (ASD) is characterized by abnormalities in social communication and limited and repetitive behavioral patterns. Children with ASD who lack social communication skills will eventually not interact with others and will lack peer relationships when compared to ordinary people. Thus, it is necessary to develop a program to improve social communication abilities using digital technology in people with ASD.

Objective: We intend to develop and apply a metaverse-based child social skills training program aimed at improving the social interaction abilities of children with ASD aged 7-12 years. We plan to compare and analyze the biometric information collected through wearable devices when applying the metaverse-based social skills training program to evaluate emotional changes in children with ASD in stressful situations.

Methods: This parallel randomized controlled study will be conducted on children aged 7-12 years diagnosed with ASD. A metaverse-based social skills training program using digital technology will be administered to children who voluntarily wish to participate in the research with consent from their legal guardians. The treatment group will participate in the metaverse-based social skills training program developed by this research team once a week for 60 minutes per session for 4 weeks. The control group will not intervene during the experiment. The treatment group will use wearable devices during the experiment to collect real-time biometric information.

Results: The study is expected to recruit and enroll participants in March 2022. After registering the participants, the study will be conducted from March 2022 to May 2022. This research will be jointly conducted by Yonsei University and Dobrain Co Ltd. Children participating in the program will use the internet-based platform.

Conclusions: The metaverse-based Program for the Education and Enrichment of Relational Skills (PEERS) will be effective in improving the social skills of children with ASD, similar to the offline PEERS program. The metaverse-based PEERS program

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offers excellent accessibility and is inexpensive because it can be administered at home; thus, it is expected to be effective in many children with ASD. If a method can be applied to detect children's emotional changes early using biometric information collected through wearable devices, then emotional changes such as anxiety and anger can be alleviated in advance, thus reducing issues in children with ASD.

Trial Registration: Clinical Research Information Service KCT0006859; https://tinyurl.com/4r3k7cmj

International Registered Report Identifier (IRRID): PRR1-10.2196/35960

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KEYWORDS

metaverse; social skills; Autism; ASD; digital therapy; Roblox; RCT; social skill; social interaction; human interaction; child; youth; development; wearable; biometric; communication; digital technology; eHealth; mhealth; stress; emotional change; online platform

Introduction

Autism spectrum disorder (ASD) is a complex developmental condition that involves persistent challenges in social interaction, speech, and nonverbal communication, with restricted or repetitive behaviors [1]. In You's study, deficits in social-emotional exchange, such as social communication disorder in interactions covering the present or past developmental period, are discussed along with deficits in nonverbal communication in social interaction and relationship formation appropriate to the developmental level. Impaired social functioning, which often requires lifetime treatment, is a characteristic of ASD [2]. Typically, school-aged children and adolescents acquire and develop the basic rules of social etiquette through observation of peer behavior or specific parental instruction [3]; however, some school-aged children with developmental disabilities, or some children and adolescents with ASD, have difficulties in acquiring the social etiquette necessary for peer relationships and they require additional intervention. As they lack social interaction skills, they are more likely to be isolated from their peers, making it evident that the etiquette necessary for relationships is lacking [4]. Furthermore, without treatment, many adults with ASD will have fewer interactions and friendships than an average person [5]. Imparting people with ASD the skills to make and retain friends to people with ASD is expected to have a lasting and significant impact on their lives. The prevalence of ASD has increased worldwide. Hong and Lee investigated the economic burden of ASD in South Korea using a nationally representative data source. The direct medical, nonmedical, and indirect costs resulting from ASD were estimated. The total prevalence was 5.04 (per 100,000 people) in 2008 and 10.97 in 2015. The economic cost of ASD was estimated at US $2,700,596 in 2008 and US $9,645,503 in 2015. The results of this study suggest that the increase in economic costs is greater than the increase in the prevalence [6]. Consultation with child psychiatrists for ASD diagnosis, psychological evaluation, and treatment, including ASD testing, are primarily available in cities, necessitating long waiting times and incurring high costs. Furthermore, even after diagnosis, treatments including speech therapy, psychotherapy, play therapy, and occupational therapy are centrally operated in cities, and treatment costs are high [7]. Therefore, appropriate treatment for many children with ASD is delayed. Furthermore, it is difficult for children from low-income families to receive timely diagnosis and treatment because of the high cost of treatment in facilities concentrated in cities.

Various treatment strategies for ASD include educational and behavioral interventions that target its core features. Well-designed interventions, such as risperidone and aripiprazole, have been reported to have strong and beneficial effects [8,9]. The Program for the Education and Enrichment of Relational Skills (PEERS) is a manualized evidence-based social skills program developed from ASD intervention programs [10]. The PEERS program used in this study has been designed to improve social and friendship skills in adolescents with high-function ASD. The results of a previous randomized controlled study examining the efficacy of PEERS in improving social abilities and friendship skills in high-functioning adolescents with ASD showed that the group involved in the program significantly improved its knowledge of social skills compared to the control group that was not part of the program. The frequency of meeting with friends increased and the overall social skills improved [11,12]. The Korean version of the PEERS social skills program appears to be effective for adolescents with ASD in Korea after modest adjustments for cultural differences. In a randomized controlled trial (RCT), participants who received the PEERS treatment showed significant improvement in social skill knowledge, interpersonal skills, state anxiety or depressive symptoms, as well as a decrease in ASD symptoms [2]. For adolescents with ASD who had previously received the PEERS program face to face, the program was suspended or postponed because of the COVID-19 outbreak, owing to the restrictions declared by many government statutes [13]. Children with ASD require continuous long-term training to improve their cognitive development and behavior. Due to the lack of social reciprocity and communication, special education teachers, regular training activities, and training locations are relatively fixed. However, the sudden COVID-19 outbreak disrupted the familiar and routine training activities of preschoolers with ASD, and limitations in the children's physical environment may exacerbate behavioral problems [14]. Therefore, there is an increasing need to shift traditional therapeutic environments from face-to-face learning to internet-based play. According to the World Health Organization, telemedicine refers to the use of communication and virtual technologies to provide health care [15]. The advantages of telemedicine include the ability to receive

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treatment in a comfortable environment, ensuring continuity of care, low cost, high accessibility, and easy dissemination. Recent studies have shown that telemedicine interventions can improve the behavior of children with ASD [14,16-18]. Education was delivered using virtual reality (VR) technology to increase sociality for children and adults with ASD, and as a result, previous studies have reported improved sociality [19-21]. We designed the study to use a metaverse-based interactive game platform rather than VR equipment. Roblox, MineCraft, Whyville, and Zepeto are internet-based virtual world game platforms on which users can socialize, be creative, and play using their imagination [22,23]. Internet-based virtual world game platforms provide various types of cooperative activities in which children and adolescents can participate. Collaborative activities include solving problems and challenges, forming teams to execute missions through collaboration and organization, creating and decorating avatars, and practicing digital literacy skills, such as coding and writing. Internet-based multiplayer games can strengthen healthy communication and social connections as well as alleviate social isolation [24]. Playing games on internet-based gaming platforms can help foster a sense of belonging and develop friendships that are essential for the social and emotional development of children and adolescents. Developing a social skills training program using an internet-based virtual world game will be effective in improving social skills and will be an important treatment method during the COVID-19 pandemic situation, especially in the case of children and adolescents with ASD.

To improve the social skills of children with ASD, it is necessary to predict their anxiety early by collecting biometric information using wearable devices. Anxiety is a common problem in children, adolescents, and adults with ASD. Anxiety caused by emotion regulation impairments in children with ASD can lead to many behavioral problems, such as aggression and irritability [25]. Furthermore, problematic behavior, including self-harm in children with ASD, can be a significant barrier to accessing community services, including education, and can affect social improvement by limiting peer group formation or social participation in schools. Using wearable devices, early detection of abnormal signals in the biometric information of children with ASD, and conversion of problem behavior to prediction, mitigation, or alternative behaviors in advance will help improve children's sociality.

The following are the objectives of this study: (1) developing a metaverse-based youth social skills training program using digital technology to improve the social interaction skills of children with ASD; (2) validating the effectiveness of the program developed as a metaverse for "Being a Good Sportsman," which is part of the PEERS program, as well as validate the improvement of social interaction skills required by children with ASD; and (3) analyzing biometric information collected through wearable devices to confirm emotional changes in children with ASD during stressful situations.

Methods

Study Design

Summary

This study is a parallel randomized controlled study (trial registration: KCT0006859) involving children aged 7-12 years diagnosed with ASD who volunteered to participate in the study with the consent of a legal guardian. The study will include an intervention group and a control group at a 1:1 ratio. Participants will be publicly recruited through the internet to enroll in a clinical trial through the Korean-Wechsler Intelligence Scale for Children-IV (K-WISC-IV) test administered by a professional clinical psychologist. Following neuropsychological evaluation, the children eligible for this study will be assigned randomly to the intervention or the control group for 4 weeks. Randomization will be performed using the PROC PLAN method in the SAS software program (version 9.4, SAS Institute). In this study, we plan to develop and apply a social skills training program for children with high-function ASD that can be implemented within the metaverse platform based on the PEERS program using digital technology. The PEERS is a social skills training program developed for children with ASD who face difficulties in making or retaining friends. The PEERS program has 14 sessions. The 1st session gives the introduction and trading information; the 2nd session is about conversational skills; the 3rd session is on electronic communication; the 4th session is about choosing appropriate friends; the 5th session is regarding the appropriate use of humor; the 6th session is about peer entry strategies; the 7th session is regarding peer exit strategies; the 8th session is about get togethers, the 9th is on good sportsmanship; the 10th is about handling teasing; the 11th is on handling bullying and bad reputations; the 12th is regarding arguments and disagreements; the 13th is about handling rumors and gossip; and the 14th one includes a graduation party and ceremony [12]. Under the guidance of a clinical psychologist (with a PhD in education) and a clinical specialist in psychiatry, "Becoming a Good Sportsman," which is part of the PEERS program, was selected and conducted as a proof-of-concept study. Socializing with peers is important for children and adolescents with ASD to build close friendships and engage in positive peer interactions. To reduce the burden of discussing a wide range of topics, it is better to proceed with activities that go well together. "Becoming a Good Sportsman" was selected because experts considered it suitable for a test study because it is composed of activity-based socializing to become a good sportsman, which corresponds to the ninth session selected in our study [26]. To maintain the consistency of the program, a professional clinical psychologist trained during the study period will conduct it. To verify the effectiveness of the program, the results of neuropsychological evaluation, including social development indicators and biometric information (heart rate, heart rate variability, saturation, respiratory rate, and stress index), will be collected through wearable devices. Children enrolled in the study will be randomized into 2 groups with the same baseline characteristics. To verify the effectiveness of the program, for each group, first the differences between the neuropsychological evaluation results, including the social development index

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determined before the experiment and the test results after the experiment, will be compared and analyzed using a statistical method. Second, the differences in the neurophysiological scores between the groups will be compared and analyzed. Based on the results of these 2 processes, the effectiveness of the metaverse-based social skills training program using digital technology will be verified.

Neuropsychological Test

To confirm that the children who wished to participate in the study meet the research criteria, the K-WISC-IV test, an intelligence test that comprehensively evaluates the overall intellectual ability of children, will be performed before the start of the study [27]. To compare and evaluate the effectiveness of the metaverse-based social skills training program developed in this study, a series of neuropsychological tests will be performed before and after the study to evaluate sociability. Neuropsychological tests to be used in the study include the Social Responsiveness Scale (SRS), evaluated by parents, as a tool to verify the effectiveness of children's social interactions. Furthermore, the Korean version of the Child Behavior Checklist (K-CBCL) and the Korean version of the Vineland Adaptive Behavior Scale-2 (K-VABS-2) test are used as evaluation tools to verify the children's overall problematic behavior, adaptability, and sociability-related effects as determined through a parental survey. The Children’s Depression Inventory (CDI) and revised Children’s Manifest Anxiety Scale (RCMAS) are used as assessment tools to compare mental health levels, such as stress relief, depression, and anxiety before and after intervention.

Biometric Information

During the 4 weeks of this study, all children participating in the study will use a wearable device shaped like a smartwatch (Fitbit) to minimize discomfort. In addition to collecting the children's biometric information using the smartwatch, a webcam will be used to record the children's behavior and facial expressions in real time during the program. The biometric information of the children with ASD will be compared and analyzed using the internet-based (metaverse) program with the biometric information of children with ASD and real-time biometric information recorded daily. Based on the study results, the effectiveness of the metaverse-based social skills training program using digital technology will be verified, and the children's anxiety and stress levels will be measured. The improvement of social interaction abilities has an important effect on children's adaptation to school life; therefore, its effect on improving mental health while alleviating stress and anxiety will also be verified.

Intervention Group Receiving the Metaverse-Based Social Skills Training Program

The intervention group will receive the metaverse-based social skills training program developed by the researchers for 60 minutes per session once a week for 4 weeks. The program consists of direct instruction (rules for being a good sportsman) and practical training (playing sport games). Table 1 summarizes the metaverse-based social skills training program content. When the program is applied to metaverse, a wearable device will collect the child's biometric information in real time. In addition to internet-based and offline recording modes, the children's actions will be recorded using a webcam during the program.

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Table 1. Contents of the metaverse-based social skills training program.

Week	Session	Goal	Content
1	Introduction and preneuropsychological test (offline)	Orient the participants to the program	1. Explaining the process involved in the program and the basic rules and the use of the wearable device 2. Preneuropsychological evaluation
2	Being a Good Sportsman 1(internet): awareness of the need for rules and results	Learn and develop the right behavior for replacing inappropriate behavior; avoid uncontrolled negative behavior to achieve positive behavior	1. Subject and modulator introducing themselves to each other 2. Self-introduction by team 3. Forming rules 4. Playing sports games in metaverse 5. Giving session feedback and homework
3	Being a Good Sportsman 2 (internet): understanding the situation and participating in team activities	Learn social understanding by noticing situations and conflicts that occur during team activities	1. Greeting therapists and participants 2. Checking the homework from the last session 3. Reminding rules 4. Playing sports games in metaverse 5. Giving session feedback and homework
4	Being a Good Sportsman 3 (internet): responding appropriately to negative behavior experiences and negative emotions	Learn to accept the result of rule violations, failures, etc experienced in team activities and understand appropriate emotional response	1. Greeting therapists and participants 2. Checking the homework from the last session 3. Educating and practicing negative emotion acceptance and coping skills 4. Playing sports games in metaverse 5. Giving session feedback and homework
5	Being a Good Sportsman 4 (internet): knowing and accepting individual differences	To be able to recognize the characteristics of other team members and accept similarities and differences with friends while working as a team	1. Greeting therapists and participants 2. Checking the homework from the last session 3. Educating and practicing “knowing and accepting” skills. 4. Playing sports games in metaverse 5. Giving session feedback
6	Neuropsychological test (offline)	Conducting postneuropsychological evaluation	Postneuropsychologital evaluation: 1. K-SCQ[a] 2. SRS 2[b] 3. K-CBCL[c] 4. K-VABS-2[d] 5. SCL-R[e] 6. CDI[f] 7. RCMAS[g]

[a]K-SCQ: Korean Version of the Social Communication Questionnaire.

[b]SRS-2: Social Responsiveness Scale-2

[c]K-CBCL: Korean version of the Child Behavior Checklist.

[d]K-VABS-2: Korean version of the Vineland Adaptive Behavior Scale-2.

[e]SCL-R: Symptom Checklist-Revision.

[f]CDI: Children’s Depression Inventory.

[g]RCMAS: revised Children’s Manifest Anxiety Scale

Control Group

The control group will not intervene. Only neuropsychological tests will be conducted between the first and last week.

Measures

K-WISC-IV Test

The K-WISC-IV is used to establish a baseline for the participating children. This test evaluates the overall cognitive function of children using 15 subtests, such as common sense, missing places, and vocabulary. The K-WISC-IV is an individual test tool used to evaluate the cognitive abilities of

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children aged 6-16 years [27]. The evaluation items include the verbal comprehension index (VCI), visual spatial index (VSI), fluid reasoning index (FRI), working memory index (WMI), and processing speed index (PSI) that are combined to evaluate intellectual ability. The VCI is a measure of crystallized intelligence. It measures a child's ability to access and apply acquired word knowledge. The VSI measures a child's ability to evaluate visual details and understand visual spatial relationships to construct geometric designs from a model. The FRI measures a child's ability to detect the underlying conceptual relationship among visual objects and use reasoning to identify and apply rules. The WMI measures a child's ability to register, maintain, and manipulate visual and auditory information in conscious awareness. The PSI measures a child's speed and accuracy of visual identification, decision-making, and decision implementation. It provides composite scores representing the overall intelligence quotient (IQ) as well as subtests and composite scores representing intellectual functioning in specific cognitive domains [28].

Korean Version of the Social Communication Questionnaire (K-SCQ)

The SCQ is a tool that clinicians use when screening individuals for ASD. The parent or primary caregiver of the target child can easily answer "yes/no" and screen a wide range of symptoms related to autism in a short time. It was designed as a questionnaire version of Autism Diagnostic Interview-Revised (ADI-R) [29]. It is a screening tool consisting of 40 items asking parents or caregivers about their children's ASD-related symptoms (communication, reciprocal interactions, and restrictive and repetitive behaviors and interests). There are 2 forms, namely the Lifetime AutoScore Form and the Current AutoScore Form. The Lifetime Form provides an answer based on the individual's overall development, and the Current Form provides answers based on the individual's behavior in the last 3 months. The K-SCQ was translated into English and approved by the authors [30].

Social Responsiveness Scale-2 (SRS-2)

The SRS-2 is an evaluation tool used to verify the effectiveness of social interactions. This test is a questionnaire that asks parents or teachers to evaluate the characteristics of social interactions that children have displayed in the past 6 months and consists of 65 items. Each question is rated from "not at all" (0 points) to "almost always" (3 points) and can be scored on a scale of 0-195 points. The evaluation content consists of social insight, social information processing, mutual social communication ability, social anxiety/avoidance, and autistic immersion and traits. Higher scores indicate lower social functioning [31].

K-CBCL Evaluation

The K-CBCL is an evaluation tool used to verify the effects related to overall problem behavior, adaptation, and social performance. This test is a standardized checklist in which parents describe their children's behavioral and emotional problems. It consists of two parts: the Social Ability Scale and the Syndrome and Total Problems Scale [32]. The K-CBCL consists of a 132-item questionnaire, and responses are provided on a 3-point Likert scale ranging from 0 to 2. It consists of a social competence scale, school performance scale, syndrome scale, and a total problem scale [32].

K-VABS-2 Analysis

The K-VABS-2 is an evaluation tool to verify the effects related to overall problem behavior, adaptation, and social performance. This test is the Korean version of the second edition of the VABS. It measures adaptive behavior, including 4 domains (communication, daily living skills, socialization, and motor function) and 11 subdomains (receptive language, expressive language, writing, individual, family, community, interpersonal relationship, play, ability to cope, and large and small muscle areas). This was evaluated by dividing the adaptation levels into 5 and maladaptation levels into 3 [33].

Symptom Checklist-Revision (SCL-R)

The SCL-R is a symptom checklist developed by Derogatis et al. It consists of 9 symptom dimensions (somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, and additional items) with a total of 90 items [34].

CDI Evaluation

The CDI is an evaluation tool to verify the effect of improving mental health, such as relieving stress and reducing depression in children. This test measures the degree of depression in children. It is a modified version of the Adult Beck Depression Inventory (BDI) for children aged 8-13 years [35]. It consists of 27 items. The evaluation is provided in a self-report format, where the mood state of the individual is indicated in 1 of the 3 sentences describing each question [36].

RCMAS Evaluation

The RCMAS is an evaluation tool for testing mental health–enhancing effects, such as stress relief and anxiety. This tool is a children's version of Taylor's Manifest Anxiety Scale for Adults, and it is the most widely used self-report scale for the assessment of anxiety disorders in children and adolescents aged 0-19 years [37]. It is designed to evaluate various symptoms related to anxiety, and all 37 questions are asked to be answered with "yes" or "no" about how you think and feel about yourself.

Recruitment

Ethics Approval and Consent to Participate

This study was approved by the Korea National Institute for Bioethics Policy (KONIBP), a Public Institutional Review Board (P01-202202-01-017). Before participating in the study, consent will be obtained from parents and participants (children).

Participants

Setting

The intervention will be administered remotely from a treatment center for developing the social abilities of children with ASD in Korea or by self-referral through community web pages on the internet for parents with ASD.

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Screening and Inclusion Criteria

We will recruit 24 children between March 2022 through treatment centers or internet-based social networking services. Inclusion criteria for children are the following: (1) age between 7 and 12 years, (2) diagnosed with ASD, (3) sufficient cognitive abilities to understand the rules with IQ≥90 according to a standardized intelligence test, (4) children and parents fluent in Korean, and (5) no defects in motor function. Written informed consent will be obtained from all the children and parents who will participate in this study.

Exclusion Criteria

Children will be excluded from the study if they do not speak, hear, or have impaired vision; if they have been diagnosed with a history of congenital or acquired brain damage, such as cerebral palsy; or if they have difficulty in cooperating with program participants because of serious developmental delays or difficulties in controlling behavior.

Sample Size

The sample size calculation provided by the clinical trial pilot test was employed because no studies were undertaken in advance to determine the effectiveness of the peer program by conducting exploratory clinical trials [38]. The recommended sample size for such pilot studies is 12 persons per group.

Randomization and Masking

Participants will be assigned (1:1) to either the experimental or control group using permuted blocks (block size 4) and stratified by age (children aged 7-9 years and 10-12 years). An independent statistician will build the randomization list with consecutive subject numbers using the PROC PLAN method in SAS version 9.4.

Researchers providing the interventions are not blind; however, those who perform the neuropsychological assessments of the participants are blinded. Because all participants will receive the same outcome measures, assessors will not be able to identify which group a participant belongs to, based on the results. Wherever possible, if an assessor becomes unblinded, further evaluations for that participant will be completed by a different assessor (blind to the arm allocation).

Data Management

The data acquired in this study will not be viewed or leaked by anyone other than the researcher responsible for the participants' safety, and participants' data will be entered into the system when entering computerized data with security functions and kept confidential. Except for the information supplied by research institutes, data entered into the computerized data input system are inaccessible and are not accessed or leaked to anyone other than researchers licensed as accountable researchers. Furthermore, all research-related records will be kept for 3 years from the end of the study, per Article 15 of the Bioethics Act Enforcement Rules, and data relating to personal information among documents passed by the storage agency will be destroyed per Article 16 of the Personal Information Protection Act Enforcement Decree.

Statistical Analysis

All baseline variables will be summarized in a randomized group. Continuous data will be reported as means (SD) unless skewed and will be reported as medians (IQR). Before testing the effectiveness of the program, an independent sample *t* test and a Mann-Whitney U test will be performed to determine whether there are differences in demographic variables between the groups. To compare the effects of all outcomes, the analysis will be conducted using the paired *t* test and Wilcoxon signed rank test. To evaluate treatment effects in each group, ANOVA will be repeatedly performed for determining differences in variables between the baseline and posttest for the treatment and control groups, with a condition analysis using (treatment vs control) × time (baseline vs posttest). ANOVA will be performed to compare the effects of the program between the groups and to determine whether there is a significant difference between each group by judging the rejection range based on a significance level of 0.05. We plan to perform statistical analysis using Python (version 3.8.5) and R (version 4.0.4).

Results

We intend to recruit and enroll participants from March 2022. After registering the participants, the study will be conducted from March 2022 to May 2022, jointly by Yonsei University and Dobrain Co, Ltd. The recruited children will participate in internet-based programs. The results are scheduled to be published in July 2022.

Discussion

Significance of the Study

We expect that conducting the peer program on metaverse will improve the social skills of children with ASD. Studies have demonstrated that PEERS programs are significantly effective in improving the overall social skills, frequency of social engagement, and social skills knowledge, while reducing ASD symptoms. In addition, previous studies have shown the effectiveness of an additional 16-week follow-up observation, which can be interpreted as the program proving effective not only in terms of the effectiveness of the treatment but also in terms of persistence [10,39,40]. Our study is an RCT implementing "Being a Good Sportsman," which is a part of the PEERS program in the VR world called metaverse. Numerous technical trainings to improve social skills have been conducted offline for practical purposes. We believe that using this offline technology in a metaverse setting will be just as helpful in enhancing sociality as using them offline, and that ASD children who struggled to adjust to their environment during offline education will be able to do so successfully in the metaverse environment. Metaverse can increase the scalability and freedom of the program in that it can provide the characteristics of surrounding people who can help ASD youth. In addition, if the program is conducted using metaverse rather than simply delivering education on the internet, it is possible to provide not only theoretical content but also practice using actual peer groups, thus enabling interactive learning. The internet-based "Becoming a Good Sportsman" program and this study are metaverse-based education programs, which

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include only some of the PEERS programs. This research can be expanded by developing and applying educational programs based on all PEERS programs.

When conducting the “Being a Good Sportsman” program on metaverse, a wearable device will be used to measure biometric information. Based on the biometric results, it is possible not only to verify the validity of internet-based programs but also to collect the children’s biometric information in specific situations (eg, anxiety, anger) and environments (eg, first visit place, home). By collecting data, we can detect children's behavior early and predict what they will do in the future. The collected biometric data can be used to address and alleviate children's anxiety in advance, thus significantly reducing the problematic behavior of children with ASD.

Limitations

Computer equipment and internet connections can cause complications in a study using an internet-based metaverse game platform. Furthermore, because this is a pilot study, we are unable to generalize the effect of the metaverse-based social skills training program because of the small number of participants. We intend to evaluate the behaviors of the experimental and control groups shortly after intervention, because of which direct comparative tests of the metaverse-based social skills training program's long-term effectiveness will be impossible.

Acknowledgments

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Authors' Contributions

YRP is the chief investigator and is responsible for the study design and execution, and the decision to submit the results for publication. The study design was conceived and approved by JHL, TSL, SWL, JHJ, SYY, and YJC. JHL wrote the protocol manuscript with approval from all authors and developed the statistical analysis plan. TSL, SWL, and JJH designed and wrote the lead on the delivery and design of the therapy. SSY and YJC were involved in ensuring that the investigation was carried out in accordance with the Institutional Review Board (IRB) approval and plan. All the authors have critically reviewed the manuscript for important intellectual content and have read and approved the final manuscript.

Conflicts of Interest

YJC is CEO of Dobrain, and SYY is an employee of Dobrain. The remaining authors have no conflicts of interest to declare.

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Abbreviations

ASD: autism spectrum disorder
BDI: Beck Depression Inventory
CDI: Children’s Depression Inventory
FRI: fluid reasoning index
IQ: intelligence quotient
K-CBCL: Korean version of the Child Behavior Checklist
K-SCQ: Korean Version of the Social Communication Questionnaire
K-VABS-2: Korean version of the Vineland Adaptive Behavior Scale-2
K-WISC-IV: Korean-Wechsler Intelligence Scale for Children-IV
PEERS: Program for the Education and Enrichment of Relational Skills
RCMAS: revised Children’s Manifest Anxiety Scale
RCT: randomized controlled trial
SCL-R: Symptom Checklist-Revision
SCQ: Social Communication Questionnaire
SRS: Social Responsiveness Scale
SRS-2: Social Responsiveness Scale-2
VCI: verbal comprehension index
VSI: visual spatial index
VR: virtual reality
WMI: working memory index

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Protocol

Internet-Based Prevention Program of Victimization for Youth in Care and Care Leavers (EMPOWER YOUTH): Protocol for a Randomized Controlled Trial

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Abstract

Background: The global estimate of the number of children in institutional care is around 5 million, with around 1 million of these children living in Europe. In Germany, about 75,000 children and adolescents find themselves in the foster care system and about 93,000 additional children and adolescents are living in institutions. Traumatic experiences and neglect in childhood are highly prevalent among these youth in care and are related to severe long-term effects. Childhood maltreatment and abuse can increase the risk of future victimization experiences. Although youth in care are at risk of victimization or revictimization, no specific evidence-based prevention program has been designed to address these specific needs.

Objective: This study aims to evaluate the efficacy of a newly developed 6-module internet-based prevention program of victimization for youth in care, named EMPOWER YOUTH.

Methods: In a randomized controlled trial, the intervention group will be compared to a waiting-list control group with an unblinded 1:1 allocation ratio. Assessments will take place before randomization (baseline) and at follow-up 18 weeks after baseline (ie, 12 weeks after finishing the last module of the program). The primary endpoint is the number of victimization, and online and offline bullying experiences (composite score) at the 18-week follow-up. Secondary endpoints are risk-taking behavior, aggressive tendencies, empathy, prosocial behavior, depressiveness, and loneliness at follow-up. The expected outcome requires a sample size of 156 subjects to achieve a power of 80%. Assuming a 30% dropout rate at follow-up, we require 225 participants to be allocated to the trial. Participants are youth in care, that is, adolescents in foster care, adopted adolescents, or young care leavers aged 14 to 21 years.

Results: Ethical approval was granted by the Ethics Committee of the Medical School Berlin in March 2021 (MSB-2021/55). Recruitment started in September 2021 and is planned until November 2022. The results are expected to be published in January 2023.

Conclusions: Given the increased likelihood for future victimization experiences among youth in care, there is a strong need for a low-threshold intervention specifically for this high-risk age group. There are no existing nationwide mental health programs exclusively for youth in care in Germany.

Trial Registration: German Clinical Trials Register DRKS00024749; https://tinyurl.com/tjaahayw

International Registered Report Identifier (IRRID): DERR1-10.2196/34706

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KEYWORDS

foster care; youth in care; victimization; prevention; online program

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Introduction

Background

The global estimate of the number of children in institutional care is around 5 million, with around 1 million of these children living in Europe [1]. Reliable data on the number of children living in foster care or adoptive families worldwide are currently not available. In Germany, about 75,000 children and adolescents find themselves in the foster care system and about 93,000 additional children and adolescents are living in institutions [2]. Traumatic experiences and neglect in childhood are highly prevalent among these youth in care and are related to severe long-term effects on mental health [3]. Childhood abuse and neglect are associated with high levels of symptoms such as sexualized behavior, anxiety, posttraumatic stress disorder (PTSD), and depression [4]. Furthermore, an abusive or neglected caretaking setting can be a risk factor for continued and repeated negative relationships. Often, the interpersonal and intrapersonal beliefs of abused individuals are strongly negative about themselves and others, and low self-esteem in youth in care has been found in a number of studies [5]. Moreover, youth in care often show insecure and disorganized attachment behavior [6] and have long-term interpersonal difficulties, disturbances of self, and impaired affect regulation.

Consequences can be multifaceted. Youth in care have a greater risk of unintended pregnancy, ranging from 16% to 50% [7]. Moreover, risky sexual behaviors, including initiating sexual intercourse at an earlier age, having a greater number of sexual partners, inconsistently using contraception, and exchanging sex for money, have been found in this group of adolescents [7]. Stevens et al in their study with youth in care found that higher levels of anxiety and depression were related to higher rates of risky sexual activity and substance use [8]. Often, the ability of risk recognition, which is the ability to identify danger cues (eg, dangerous social situations), is decreased [9]. These factors can lead to interpersonal high-risk situations, which may hinder proper responses and may lead to future victimization. Childhood maltreatment and sexual abuse are associated with a 2 to 3 times higher risk of revictimization [10]. In conclusion, youth in care comprise a highly vulnerable group in adolescence and young adulthood. They often demonstrate poor risk recognition and are often victims of bullying (online and face-to-face), sexual assault, and maltreatment. A change in the caretaking setting via an out-of-home placement in either a foster care family [3,11] or an institution [12] does not prevent this increased chance for future maltreatment or the long-term negative mental health outcomes.

Although the majority of youth in care are at high risk of victimization or revictimization, no specific evidence-based prevention program has been designed to address these specific needs. Most interventions aimed at youth in care are multidimensional programs of a heterogeneous nature that offer a broad focus of treatment (eg, cognitive behavioral techniques, psychoeducation, case management, skill building, emotional literacy, and social support). A systematic review by Hambrick et al evaluated mental health interventions for children in foster care (aged 0-12 years) [13]. Medium effect sizes were found for decreased internalizing problems, and large effect sizes could be shown for positive parenting practices. However, only 3 of the studies were randomized controlled trials (RCTs) [13]. In a more recent systematic review, Bergström et al concluded that only 3 of 18 included interventions for youth in care had sufficient support for program efficacy [14] (Attachment and Biobehavioral Catch-Up [15], Incredible Years [16], and Take Charge [17]). The reported effect sizes were small to moderate [14]. However, none of the included programs focused on the prevention of future victimization [13,14]. Moreover, most programs target foster parents or social workers and not youth in care directly, and take place face-to-face, often in group settings, creating several challenges for feasible widespread implementation of these programs.

Only few studies have been conducted for the prevention of sexual revictimization of adolescents. DePrince et al evaluated prevention of revictimization of adolescent girls in the child welfare system [18]. The participants in the risk detection group were about 5 times less likely to report sexual revictimization compared to the nonintervention control group. A group prevention program for sexual revictimization using risk recognition, communication skills, practical knowledge teaching (ie, not leaving the party with a stranger and refusing alcohol), and problem-solving strategies could reduce the incidence of sexual assault [19]. Further, the program significantly increased self-efficacy and decreased distress at follow-up. Another revictimization program for women with a history of childhood sexual assault was based on acceptance and mindfulness-based theory but failed to find significant differences between the intervention and control groups for revictimization [20]. A computer-based program aimed at preventing dating violence and sexual victimization was examined in schools with youth aged 11 to 15 years [21]. The Me & You computer-based program was found to significantly lower the odds for perpetrating dating violence, but not to lower the odds for victimization [21].

In the past years, computer-based interventions have been developed through the integration of technology and psychological interventions. Internet-delivered interventions have a number of advantages compared to traditional face-to-face treatments for adolescents and young adults. First, this age group has a high affinity for the use of the internet, online games, and social networks. Further, face-to-face interventions are often restricted by long waiting lists, low availability of psychosocial support, and time constraints. Finally, the anonymity of the internet offers participants an alternative way to overcome their initial shame and encourages them to confront difficult themes, such as social difficulties, and to disclose feelings of shame [22]. An increasing number of e-mental health studies have been conducted in youth for a variety of psychiatric and somatic conditions. A meta-analysis [23] found an overall pooled effect size with d=0.85 for internet-delivered cognitive behavioral therapy in youth, with a large effect for psychiatric conditions (d=1.27) and a lower treatment effect for somatic conditions (d=0.49). Systematic reviews and meta-analyses showed that cognitive behavioral web-based interventions for individuals with PTSD symptoms [24] and youth with neurodevelopmental disorders, anxiety,

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depression, and even suicidal ideation had high efficacy [25-27] comparable to traditional face-to-face settings [28,29].

In summary, youth in care are in clear need of additional support to prevent future victimization. Considering the age group, a guided web-based low-threshold program is a more novel and preferred mode of delivery, given the ubiquitous digital activity in this group. An internet-based intervention has several advantages compared to traditional prevention programs conducted in a face-to-face setting [29]. So far, no program specifically targeting the prevention of several forms of victimization in youth in care has been developed, and no clinical trial is currently being conducted for examining an internet-based intervention to prevent victimization or revictimization among youth in care.

Objectives and Trial Design

We aim to evaluate the efficacy of a newly developed 6-module internet-based prevention program of victimization among youth in care, named EMPOWER YOUTH. Intervention effects will be evaluated within an RCT (German Clinical Trials Register DRKS00024749) comparing the program with a waiting control group, with an unblinded 1:1 allocation ratio. At initial assessment, participants will be blinded to their allocation status. Assessments will take place before randomization (baseline) and at a follow-up 18 weeks after baseline (ie, 12 weeks after finishing the last module of the program). The main goal of the program is to analyze the spillover effects of the prevention coaching program EMPOWER YOUTH on victimization. The primary endpoint is the number of victimization, and online and offline bullying (composite score) experiences at the 18-week follow-up. Secondary endpoints are risk-taking behavior, aggressive tendencies, empathy, prosocial behavior, depressiveness, and loneliness at follow-up. We hypothesize that the prevention program will be effective for reducing the incidence of victimization, improving coping mechanisms in problematic social situations, and increasing the recognition of risk/dangerous situations.

Methods

Research Consortium

This project is supported by a research grant (grant number FKZ 01KR1806E) of the Federal Ministry of Education and Research in Germany and is part of a research consortium called EMPOWERYOU, which is made up of the following universities and institutions (in alphabetical order): Karlsruhe Institute of Technology, Medical School Berlin, PFAD e.V. Association of Foster Care and Adoptive Families in Germany, University of Aachen, University of Bielefeld, and University of Bremen. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting clinical trial protocols [30].

Recruitment

Youth in care are defined as adolescents in foster care, adopted adolescents, or young care leavers aged 14 to 21 years. Participants will be recruited through the organization PFAD e.V. Association of Foster Care and Adoptive Families in Germany, as well as other organizations working with youth in care through which more than 13,000 foster families or young care leavers can be reached. Since many youth in care are not organized in groups or organizations, recruitment will also take place online via social media (ie, Instagram, Facebook, and TikTok). Furthermore, flyers and posters will be sent to child welfare services, as well as other welfare institutions working with youth in care in Germany.

Participants and Eligibility Criteria

Inclusion Criteria

The study flowchart is provided in Figure 1. Youth in care are defined as adolescents in foster care, adopted adolescents, or young care leavers aged 14 to 21 years. The age range 14 to 21 years is consistent with the definition for “adolescents” in the German Guidelines for Psychotherapy [31] (article A, first paragraph, point 4). Moreover, adolescents until the age of 21 years in Germany are often still either dependent on foster/adoptive parents or living in institutionalized care with some form of supervision. Hence, the entire research consortium implemented a cutoff of 21 years. Further inclusion criteria are sufficient writing and reading skills in German based on self-report and access to the internet via a desktop computer, laptop, tablet, or other mobile device.

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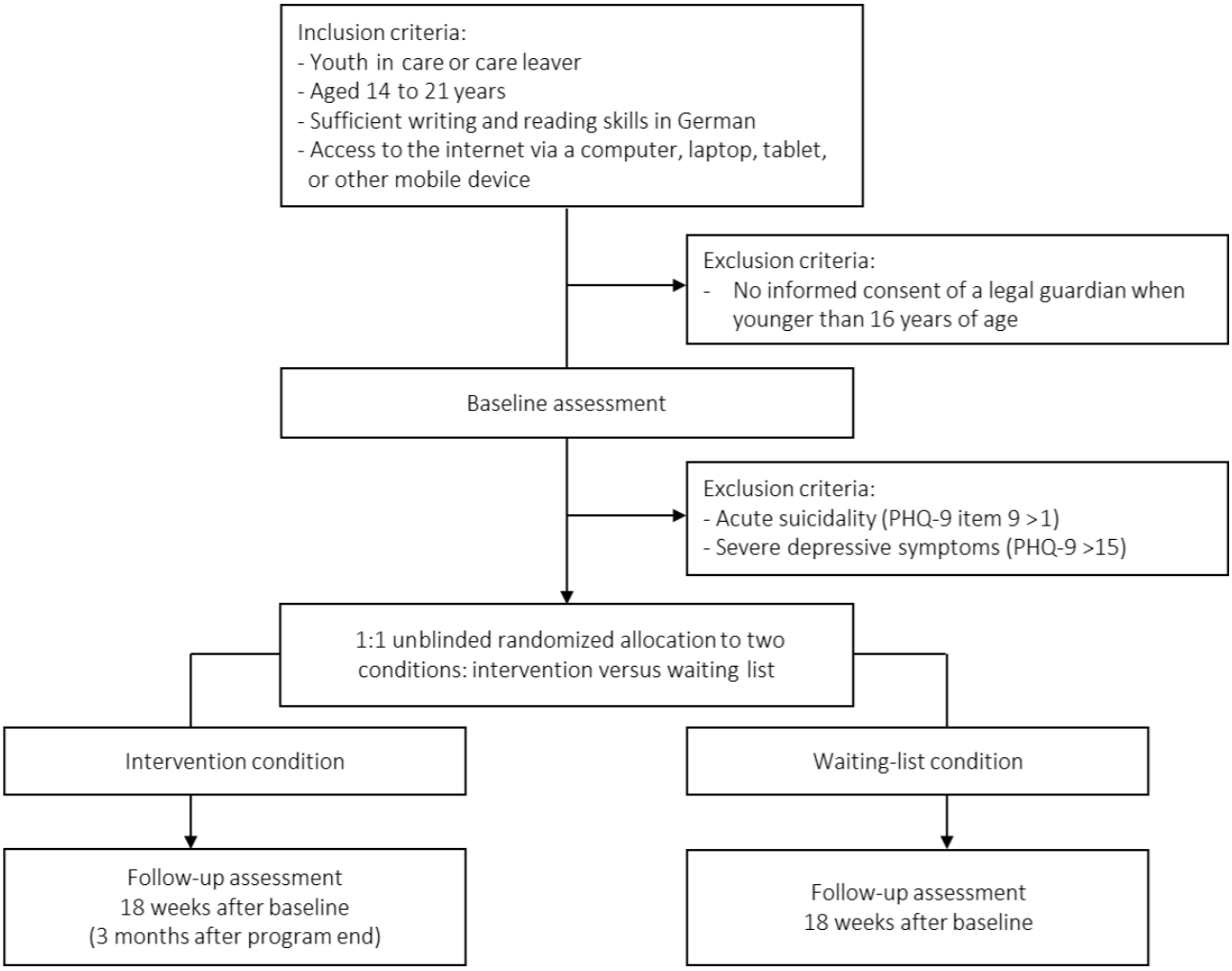
Figure 1. Flowchart of the EMPOWER YOUTH randomized controlled trial.



Exclusion Criteria

Participants are excluded from the RCT when (1) acute child endangerment is suspected; (2) they receive other psychosocial approaches aimed at victimization or revictimization; (3) severe depression symptoms are present as assessed via the Patient Health Questionnaire-9 for Adolescents (PHQ-9) [32] (PHQ-9 >15 at baseline); and (4) suicide ideation (indicated by a score of >1 on the suicidal thought item of the PHQ-9 at baseline) is present. If participants score above 1 on the suicide item, a further suicide screening will be conducted via telephone in accordance with our safety protocol. If participants do not provide a telephone number, either an email or letter by post will be sent to make contact with the participants or their legal guardians.

Intervention

Experimental Condition

The internet-based prevention program EMPOWER YOUTH for adolescents and young adults has been developed to meet the needs of youth in care and address several risk factors of victimization or revictimization. Youth in care who participate are taught theory and skills to prevent victimization in themselves and others. EMPOWER YOUTH promotes knowledge of risk situations and consequences, and strategies that help defend youth from victimization. After finishing the program, the participants receive a certificate stating they are EMPOWER YOUTH coaches. The aspect of becoming a coach and participating to help others is emphasized during recruitment and during the program participation. This program format was chosen because the results of focus groups indicated that youth in care feel stigmatized receiving a program aimed specifically at them as potential "victims." This change of perspective, that is, being a coach to help others rather than being victimized, prevents youth in care from perceiving themselves as potential victims due to the program, which would directly counteract the aim of the project. The intervention includes various multimedia features (videos, fictional audio recordings, and writing exercises). Participants will be provided with a personalized password-protected interface. Altogether, there will be 6 modules, with an approximately 45-minute workload. Mentors/psychologists will provide individual written feedback within 2 working days, along with instructions for the next module. The mentor contact should enhance compliance with the program [33]. Participants will receive up to three reminders to complete a module.

Based on the existing literature and the evaluation of 3 focus groups with adolescents and young adults in foster care, the 6 program modules focus on the following categories of psychological risk factors: (1) emotion regulation, (2) self-appraisal, (3) risk recognition, (4) offline risk recognition

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problems and coping with victimization or revictimization, and (5) online risk recognition problems and coping with victimization or revictimization. In all the modules, interpersonal relatedness and prosocial behaviors are indirectly addressed via case descriptions and the accompanying exercises. The case descriptions are partly derived from situations described by youth in care in the initial focus groups.

In the first module "What's up?", participants receive knowledge about emotions in a video (naming emotions; regulation of emotions; and the connection between emotions, thoughts, and actions/behaviors). They practice identifying emotions and thoughts in 2 case descriptions (presented as audio recordings) and are asked to reflect on potential actions that could be taken in the described situations. The module also entails an exercise on breathing, an exercise on formulating positive thoughts, and a writing exercise in which the participants describe a difficult biographical situation and identify their emotions, thoughts, and actions in that situation.

The second module "I am okay, you are okay, we are okay," teaches participants about personal rights, diversity, and self-worth in a video. This is followed by a multiple-choice exercise, in which they identify the personal rights they have recently used, and an exercise on self-care activities. The participants practice identifying personal rights and personal worth in 2 case descriptions, and are asked to reflect on actions they could take as coaches to ensure these personal rights and why these actions should be taken (eg, diversity and general worth). In another exercise, the participants are asked to reflect on obstacles they have overcome, and on their uniqueness and identity as a person. This is followed by a final writing exercise in which participants are asked to write a letter to themselves naming characteristics and past behaviors they are proud of.

In the third module "Stop!", the participants learn about recognizing (social) risk situations based on different warning signals. They are asked to reflect on the danger presented in 3 different case descriptions. Moreover, several different risk behaviors are listed, and they are asked to rate how likely it is that they would engage in these behaviors. In the final writing exercise, participants are asked to describe a risk situation they found themselves in and to identify the different warning signals they recognized or maybe missed.

After learning how to recognize risk situations, the fourth module "Your limit" deals with effectively setting boundaries in offline risk situations. Four case descriptions are used in this module. The participants practice to differentiate between behavior and emotion, and to identify if these are passive, aggressive, or assertive. In a writing exercise, they are asked to reflect on an offline risk situation they found themselves in; if and how they set boundaries; and if this was passive, aggressive, or assertive. Moreover, they are asked for advice for other adolescents and young adults who could find themselves in similar situations.

The fifth module "Like and share?" deals with setting boundaries in online risk situations. The participants learn about their rights in online situations and how to legally collect evidence and set boundaries. Four case descriptions are used. In a writing exercise, participants are asked to reflect on the module and describe their own personal take-home message that they will use to support others in the future.

In the sixth and final module "You're the expert," participants are invited to fill out 2 interactive quizzes. The first quiz consists of claims and asks if these claims are true or false (knowledge). The second quiz consists of 5 case descriptions, and participants are asked what advice, as EMPOWER YOUTH coaches, they have in these situations. Another relaxation method is presented to the participants. The final module ends with a writing exercise in which the participants are asked to reflect on all the modules: what do they take away from the program and what was most important to them?

EMPOWER YOUTH can be accessed online [34]. The development of a website, compatible with a wide variety of electronical devices, such as desktop computers, laptops, and mobile phones with different operating systems, increases program participation. The use of a mobile app would have created an unwanted selection bias.

Control Condition

For ethical reasons, a waiting-list control group has been chosen. A placebo comparator has not been chosen, because there is no evaluated similar intervention for this condition in this specific population.

Concomitant Treatment

Additional treatments can be administered on entry into the trial or at any time during the study. These will be documented at the follow-up assessment as concomitant treatments on the case report form of the participant. Concomitant treatments are allowed in the intervention group as well as the control group if they do not represent psychosocial approaches aimed at victimization or revictimization. Examples of concomitant treatments include individual psychotherapy, psychiatric consultations, and activities that serve to strengthen social-emotional, cognitive, or physical competencies.

Allocation

Randomization will take place after the baseline assessment. The randomization procedure will be conducted by employees at the University Hospital Aachen (part of the EMPOWERYOU consortium), which will not be involved in this trial otherwise. Hereby, a blind randomization process is guaranteed. Participants will be informed of their allocation status via email after baseline data collection is completed to assure that they are blind to allocation during the initial assessment. Participants will be randomized into the following 2 groups: intervention group and waiting-list control group. The allocation ratio between the 2 arms of the study is 1:1. After 18 weeks, a follow-up assessment will take place. Each assessment lasts approximately 45 minutes and is conducted online. For the online assessments, the participants will receive an invitation via email with an individual identification code (subject number and randomization number). This allows for data collection without any direct identifiers.

Outcome Measures

The primary endpoint is assessed via a composite score of the Bullying Screener [35] and the Juvenile Victimization

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Questionnaire (JVQ) [36]. The Bullying Screener is a 6-item screening tool that assesses bullying as a victim and an offender. After the respective definition of bullying type, children are asked how often these things have happened to them or how often they have done this to others in the last 3 months. Children then respond on a 4-point scale from never to a lot (at least once a week) [35]. The JVQ is a validated screening questionnaire including 34 offenses against youth and covers the following 5 areas of concern: (1) conventional crime, (2) child maltreatment, (3) peer and sibling victimization, (4) sexual victimization, and (5) witnessing and indirect victimization. It encompasses follow-up questions that also assess the frequency and perpetrators of the victimization events. Children are asked whether they were exposed to the respective event in the past 3 months (time period adaptation for this study) and respond with yes (1) or no (0), leading to a total score, with a higher score indicating greater victimization exposure [36].

The secondary endpoints are risk-taking behavior, recognition of problematic/dangerous situations, aggressive tendencies, empathy, prosocial behaviors, depressiveness, posttraumatic stress symptoms, and loneliness. The Adolescent Risk-taking Questionnaire [37] will be used to measure risk-taking behaviors and judgements. It consists of 2 sections. The first section of the questionnaire measures adolescents' judgements of riskiness for 22 behaviors, and the second part measures adolescents' frequency in engaging in these behaviors. Judgement of riskiness is made on a 5-point Likert scale, ranging from 0 (not at all risky) to 4 (extremely risky). Participation in risky behavior was also rated on a 5-point Likert scale, ranging from 0 (never done) to 4 (done very often). The total risk judgement score is obtained by adding all the items; a high score indicates a strong judgement of riskiness for the behaviors listed in the questionnaire. The total risk behavior score is obtained by adding the frequency rating of all the items; a high score indicates a high level of participation in risky activity. The items can be divided into the following 4 major factors: thrill-seeking risks, rebellious risks, reckless risks, and antisocial risks. The Cronbach α coefficient for the risk judgement scale is .97 (range .86±.96) and for the behavior scale is .99 (range .87±.96). A good test-retest reliability was found, with 1-week test-retest reliability for risk judgement being 0.79 and for risk behavior being 0.78 [37].

The following constructs will be assessed via 3 of the 4 subscales of the German Questionnaire for determining empathy, prosocial behavior, and aggression (FEPAA) [38]. There is an alternative version (versions A and B), and different versions will be used at the 2 assessment points. Cronbach α varies between .61 (prosocial behavior scale) and .79 (aggressive tendencies scale) for version A, and between .57 (prosocial behavior scale) and .77 (aggressive tendencies scale) for version B. Reliability is 0.75 for version A and 0.66 for version B. Overall, 40 items of the original 55 will be assessed.

Depressiveness will be assessed with the PHQ-9 [32]. The PHQ-9 is used to screen for the presence and severity of depression and takes less than 3 minutes to complete. The PHQ-9 achieved a Cronbach α of .89 among 3000 primary care patients. The test-retest reliability was assessed by the correlation between PHQ-9 scores obtained from in-person and phone interviews with the same patients. The correlation value obtained was 0.84 [32].

Loneliness will be assessed via the Loneliness Scale-SOEP [39], which consists of 3 items with a 5-point rating scale. The α coefficient of reliability obtained was .72 [39].

To assess the presence of any posttraumatic stress symptoms, the 8-item version of the Child Revised Impact of Events Scale [40] will be used. It consists of items with a 4-point rating scale and takes between 5 and 10 minutes to complete.

Statistical Analysis

An intention-to-treat design will be used. Missing data due to study dropout will be handled using multiple imputation. E-mental health programs for children, adolescents, and young adults with the highest rate of completion were those with therapist support, with dropout rates ranging from 13% to 17% [33]. In our trial, we anticipate a dropout rate of 30% at follow-up assessment, using a more conservative attrition rate and following the results of our pilot feasibility study. At the end of the trial, a dropout analysis will be conducted.

Primary Endpoint

The primary endpoint (number of victimizations 18 weeks after randomization) will be analyzed by analysis of covariance (ANCOVA) with baseline individual number of victimization scores, self-reported depression, severity of victimization (eg, sexual abuse), and PTSD as covariates and intervention as a factor. A significance level of 5% will be chosen. No interim analysis is planned. Conservative missing value imputation strategies will be performed if necessary.

Secondary Endpoints

Quasimetric scores of self-reported questionnaires will be analyzed in an exploratory manner and will also be evaluated by ANCOVA, if suitable, regarding the scale level and type of distribution. Otherwise, they will be transformed to fulfill the presuppositions of the method or will be analyzed by means of nonparametric methods. For categorical secondary endpoints, absolute and relative frequencies will be presented and tested by the chi-square test or Fisher exact test, as appropriate. In case significant treatment differences are observed between both arms, potential predictors of beneficial treatment outcomes (eg, sociodemographic or individual ones) will be identified using multivariable analyses (eg, logistic regression models). To investigate the predictors of beneficial protocol adherence and dropout, logistic regression models will be applied. For all primary and secondary endpoints, quartiles and, if suitable, means and standard deviations will be reported for descriptive purposes. Effect sizes will be estimated and presented with 95% CIs. Predictors of treatment outcome will be identified using multivariable analyses. For secondary analyses, neither adjustment for multiple testing nor imputation of missing values is planned. Quartiles and, if suitable, means and standard deviations will be reported for descriptive purposes.

Power

The expected outcome requires a sample size of 156 subjects (α=.05, *t* test, 1-sided) to achieve a power of 80%. These assumptions are based on the effects (*d*=0.40) of previously

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published studies [41] on follow-up change in the revictimization composite score. Assuming a 30% dropout at follow-up, we require 225 participants to be allocated to the trial. In the middle of the trial, the dropout rate will be assessed in an interim evaluation, and in case of a higher dropout rate than expected, the number of participants allocated to the trial will be increased accordingly.

Ethical Considerations

The study has been approved by the Ethics Committee of the Medical School Berlin (MSB-2021/55). Informed consent in the study will be obtained from the participants before baseline assessment via a digital double opt-in method. For participants under the age of 16 years, informed consent from a legal guardian will be obtained before baseline assessment. Participants have the possibility to leave the trial without any disadvantage at any time. The trial will be conducted in accordance with the Guidelines for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki (latest version), and international and local laws. The study has been registered in the German Clinical Trials Register (DRKS00024749). Throughout the trial, participants will be identified solely by means of an individual identification code (subject number and randomization number). Electronic case report forms will be stored in accordance with local data protection laws and will be handled with the strictest confidence. The appropriate regulations of local data legislation (ie, European General Data Protection Regulation [42]) will be fulfilled in its entirety.

Data Safety and Monitoring

Data Safety

Participants will be deidentified, including the removal of direct identifiers (eg, names and addresses) and indirect identifiers (eg, occupation). Nonelectronic data will be stored in a locked filing cabinet at the university. These data will be kept for 10 years. Electronic data will be kept on 2 password-protected servers only accessible by approved study staff members.

Data Monitoring and Auditing

An independent Data Safety Monitoring Board (DSMB) has been established. The DSMB will provide additional oversight on data safety, ethical procedures, and best clinical practice. This DSMB is independent of all investigators and the funding agency, and no member of the DSMB has direct involvement in the conduct of the study. The DSMB is composed of 3 researchers familiar with the area of the study. The type of information monitored will include recruitment, number of dropouts, and all adverse events, including study withdrawals. The DSMB will receive recruitment and retention updates on a regular basis. Before starting with the trial, a data safety concept was developed and approved by the DSMB. No external auditing is planned.

Stopping Rules

A participant may withdraw from the study at any time, at his or her own request. Upon request, all collected data (ie, from the assessments and responses in the online program) will be deleted. The responsible investigator has the right to discontinue the intervention for a participant who experiences one or more of the following incidents: (1) adverse events or serious adverse events, particularly acute child endangerment or suicidal tendency and (2) an unacceptable benefit/risk ratio. In case a family member reports aversive experiences during the trial, we will follow recommendations for the ethical treatment of participants and provide referrals for services. In cases where acute child endangerment is detected, we will report this to the appropriate services, and based on the recommendations from the DSMB, we will halt study participation. However, youth in care will still be able to complete the intervention if desired. The responsible investigator has the right to discontinue the whole trial, if information that affects the benefit/risk ratio of the trial emerges or if there are repeated serious adverse events associated with the trial. In this case, the decision of stopping the trial will be communicated to the DSMB and discussed with all principal investigators of the EMPOWERYOU consortium.

Results

Ethical approval was granted by the Ethics Committee of the Medical School Berlin in March 2021 (MSB-2021/55). Recruitment started in September 2021 and is planned until November 2022. The results are expected to be published in January 2023.

Discussion

Given the increased likelihood of future victimization experiences among youth in care, there is a strong need for a low-threshold intervention specifically for this high-risk age group. So far, there are no existing nation-wide mental health programs exclusively for youth in care in Germany. If the efficacy of the prevention program EMPOWER YOUTH is identified in the RCT, a widespread implementation and dissemination process is planned. Stakeholders have been involved in the developmental phase and will consequently be informed of the RCT results via nontechnical briefs, symposia, conference presentations, and publications. Moreover, as part of the integrated knowledge translation, social media channels will post regular updates on the project. Providing knowledge to child welfare workers, social workers, medical doctors, and psychotherapists about the issue of victimization will support the implementation of EMPOWER YOUTH as a potential prevention program. This will ultimately improve the well-being of youth in care and prevent the need for more intensive and costly service utilization for youth in care. The future use of EMPOWER YOUTH could be seen under the Prevention Act, an initiative to promote health. Health insurance could support the continuation of the prevention program after the end of funding.

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Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
DSMB: Data Safety Monitoring Board
JVQ: Juvenile Victimization Questionnaire
PHQ-9: Patient Health Questionnaire-9 for Adolescents

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PTSD: posttraumatic stress disorder
RCT: randomized controlled trial

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Protocol

The Impact of Mobile Health Use on the Self-care of Patients With Type 2 Diabetes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic diseases are a substantial public health issue worldwide and affect an individual's quality of life. Due to the alarming rise in type 2 diabetes, health care that was primarily focused on diagnosis and treatment of the disease is increasingly focused on prevention and self-care. Patients who adhere to a constant and strict treatment regimen (physical activity, diet, medication) and regularly monitor their health are more likely to maintain self-care and health, prevent the exacerbation of the disease, and avoid the complications of diabetes (retinopathy, diabetic feet, etc). In recent years, many innovative devices that have become increasingly present in inpatient health care, such as mobile apps, are available to help patients maintain consistency in monitoring their health status. Mobile apps make it easier for individuals to monitor their self-care and illness and follow instructions regarding disease control.

Objective: This study aims to determine the impact of mobile app use on self-care in patients with type 2 diabetes. We will evaluate and test the usefulness of the *forDiabetes* app as a tool to improve the self-care of individuals with type 2 diabetes.

Methods: We will perform a double-blind randomized controlled trial. The study will include individuals aged over 18 years diagnosed with or have regulated type 2 diabetes who are treated in family medicine practices. Additionally, the individuals included in the study should not have any acute complications due to the consequences of type 2 diabetes. They will use an Android or iOS mobile phone and a blood glucose meter during the investigation. With the help of simple randomization, individuals will be divided into the intervention and control groups. Individuals in the intervention group will use the *forDiabetes* mobile app to monitor their self-care for type 2 diabetes. Individuals in the control group will not receive a particular intervention. Data will be collected using the *Self-care of Diabetes Inventory* questionnaire and *Brief Illness Perception Questionnaire.* Blood sugar, blood pressure, glycated hemoglobin (HbA_{1c}), and weight measurements will be monitored using calibrated instruments during the study by the nurses employed at the family medicine practice. Data will be collected at the beginning of the study and after a patient visits the family medicine practice.

Results: In the first half of 2020, we have prepared a translation of the mobile app that will be used by the participants of the intervention group, as well as more detailed instructions for using the app. We have also prepared a translation of the questionnaires in Slovene. The research results will be published in 2023.

Conclusions: This research contributes to greater visibility and usability of mobile apps for the self-care of patients with type 2 diabetes and raises awareness of the possible use of innovative methods.

Trial Registration: Clinicaltrials.gov NCT04999189; https://clinicaltrials.gov/ct2/show/NCT04999189

International Registered Report Identifier (IRRID): PRR1-10.2196/31652

(JMIR Res Protoc 2022;11(6):e31652) doi:10.2196/31652

KEYWORDS

diabetes; mobile application; disease management; self-care

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Introduction

Background

Type 2 diabetes is a complex chronic disease [1,2] with an enormous global burden that has substantial implications for human health [3]. The consequences of the disease cause substantial economic and social responsibilities [4] and pose a growing public health problem [5,6]. Preventing and limiting the progression of the disease is an urgent task worldwide [7] and remains an important challenge for individuals and society [8]. The self-care of type 2 diabetes is key to containing the disease [9,10], reducing disease complications, and improving quality of life [11]. By supporting patients with type 2 diabetes in healthier self-care behaviors, we can influence the outcome of the disease [5]. The constant monitoring of diabetes and lifestyle factors can contribute to better health [12]. Many complications are the result of uncontrolled disease [13].

The current COVID-19 pandemic affects the direction of and interrupts health care, disrupting long-term conditions including type 2 diabetes [14,15]. The need of self-care for patients with type 2 diabetes is increasingly present [16]; therefore, mobile technology has become an essential tool for promoting self-care [17]. The optimal use of mobile technologies is necessary to achieve benefits and optimal cost efficiency [18]. A mobile app strengthens self-care and contributes to better information, health education, and self-confidence in dealing with the disease [19]. Knowledge of mobile apps has been identified as an essential factor enabling independent disease management and self-care [20]. The use of new technology is one way to bridge the gap between patient needs and providing health care [21]. A mobile health app for patients with type 2 diabetes affects their knowledge of the disease, improves blood glucose control [22], and positively affects self-care [23]. In the future, mobile apps will represent an essential part of the health care system, so research in this area is needed [24]. Mobile apps show potential for disseminating self-care education [4]; improving motivation [25], disease symptom management, and patient experience [26-28]; helping patients with strict treatment requirements [29] and the adoption of a healthy lifestyle [30]; and reducing care costs [31-33].

As a guide to the self-care of individuals with type 2 diabetes using the mobile app, we will use the Middle-Range Theory of Self-Care of Chronic Illness. Self-care is a general concept built from 3 key ideas: self-care maintenance, monitoring, and management. Maintaining self-sufficiency (or self-care maintenance) refers to an individual's behaviors to improve well-being and maintain health and stability. Self-care monitoring refers to the process of observing oneself due to changes in signs and symptoms. Self-care management is defined as responding to signs and symptoms when they occur [34,35].

Objectives and Hypotheses

Objective 1 is to assess the impact of using the mobile app on the assessment of patient self-care. Hypothesis 1 states that in the intervention group of patients with type 2 diabetes, the self-sufficiency assessment at the first control visit will increase compared to the control group that did not use the mobile app.

Objective 2 is to assess the impact of mobile app use on disease perception. Hypothesis 2 states that in the intervention group of patients with type 2 diabetes, perception at the first control visit will improve compared to the control group that did not use the mobile app.

Objective 3 is to assess the impact of mobile app use on blood sugar and HbA_{1c} levels. Hypothesis 3 states that in the intervention group of patients with type 2 diabetes, blood sugar and HbA_{1c} levels at the first control visit will decrease compared to the control group that did not use the mobile app.

Objective 4 is to assess the impact of using the mobile app on the patient's body weight. Hypothesis 4 states that in the intervention group of patients with type 2 diabetes, the body weight at the first control visit will decrease compared to the control group that did not use the mobile app.

Objective 5 is to assess the impact of mobile app use on the patient's blood pressure values. Hypothesis 5 states that in the intervention group of patients with type 2 diabetes, the blood pressure value at the first control visit will decrease compared to the control group that did not use the mobile app.

Methods

Randomized Controlled Trial Design

To determine the effectiveness of using the mobile app on the self-care of patients with diabetes, we will conduct a double-blind randomized controlled trial. The study will include people aged over 18 years diagnosed with type 2 diabetes who are treated in family medicine practices in Slovenia. It will also include patients who have already been given some form of treatment to manage the disease and do not have chronic complications due to the disease (retinopathy, diabetic foot, nephropathy, neuropathy, etc). We will ensure this by receiving information on the patient's health status from the medical staff. The patients will use a mobile phone and a blood glucose meter during the research period. Individuals will use the *forDiabetes* [36] mobile app in the intervention group. *forDiabetes* [36] is an existing app designed for diabetes self-care and allows the tracking and monitoring of crucial diabetes data (physical activity; high-carbohydrate foods consumed; blood glucose, blood pressure, and HbA_{1c} levels; weight; medications; etc). Before selecting the mobile app, its quality was assessed by 2 nurses using the Mobile Application Rating Scale: user version [37]. The mobile app was rated as high quality and suitable for patients (mean 4.54, SD 0.33; on a scale out of 5) by the nurses. In accordance with the American Association of Diabetes Educators, we also assessed whether the mobile app includes self-care behaviors [38]. The mobile app contains behaviors from the awareness of the social determinants of health, integration of technology into self-care, and role of the diabetes care and education specialist.

In the control group, individuals will not use any diabetes technologies to guide the self-care of their disease, but they will be using a blood glucose meter. The control group patients will manage their disease as before and attend scheduled checkups.

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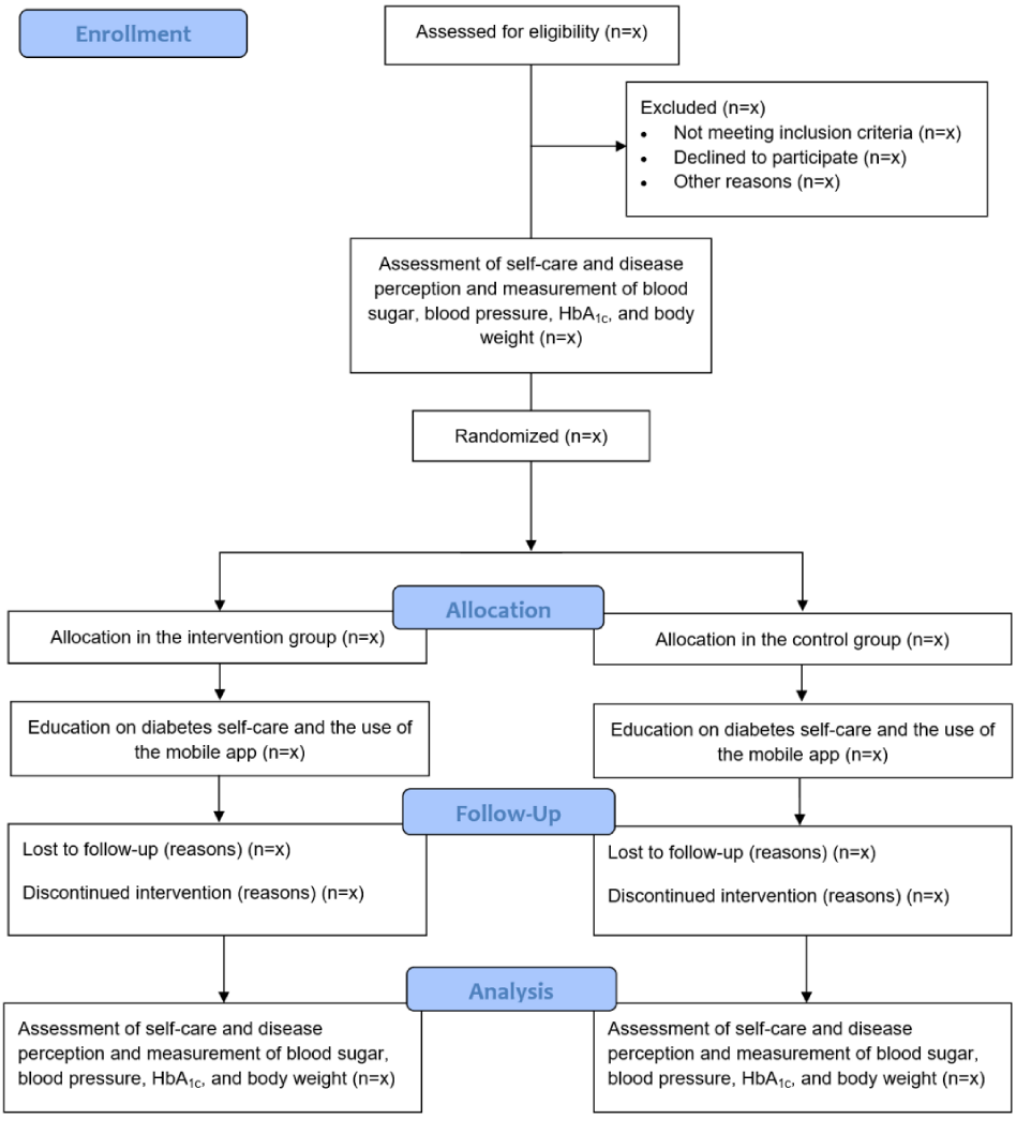
Before the start of the study and at the follow-up visit to the family medicine practice after using the mobile app, we will perform assessments of self-care and disease perception using the *Self-care of Diabetes Inventory* (SCODI) [39] and *Brief Illness Perception Questionnaire* (Brief IPQ) [40] instruments, respectively. A nurse employed at the family medicine practice will also monitor blood sugar, blood pressure, and glycated hemoglobin (HbA_{1c}) levels and body weight in the intervention and control groups with standardized, validated instruments. The nurse will use the standardized calibration devices according to the guidelines for each measurement. Data will be recorded at each inspection. We will also collect the data that the patients will enter daily into the mobile app (physical activity; high-carbohydrate foods consumed; blood glucose, blood pressure, and HbA_{1c} levels; weight; medication; etc) in real time.

The research will be carried out in family medicine practices where individuals with type 2 diabetes are treated throughout Slovenia. The study will cover at least one private and one public family medicine practice from each regional unit in Slovenia. We will use a simple randomized approach to select the family medicine practices for cooperation from a preprepared list of family medicine practices. Before conducting the research, we will obtain the necessary consent from all institutions where the study will take place to enter the family medicine practices. We will also get the required permits from the individuals involved. At the beginning of the randomized controlled trial, we will obtain the written or oral consent of the institutions to participate in the research and enter their environment. The institutions will be provided with all necessary information and the research purpose. In the introductory part of the research, the participants in the study will be informed about the purpose and goal of the study, ensuring the anonymity of the participants, the voluntary nature of participation, and the possibility of withdrawing from participation. The survey will run for 1 year. Figure 1 presents a graphical illustration of the research process.

Figure 1. Protocol for conducting a randomized controlled trail. HbA_{1c}: glycated hemoglobin.



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Mobile App Translation

The mobile app *forDiabetes* [36] includes the required self-care behaviors according to the American Association of Diabetes Educators [38] and is suitable for maintaining self-care in individuals with type 2 diabetes. Before starting the research, we have obtained written consent to use the mobile app. *forDiabetes* [36] is an existing app translated from English into Slovene before the research was conducted. The text was translated by 2 researchers who have the necessary knowledge in self-care and English. In the case of wording deviations, there was a discussion between the researchers to find a Slovene word as close as possible to the meaning of the English word and used as professional terminology in the Slovenian language.

Randomization and Blinding

Through simple randomization, the participants will be divided into the intervention and control groups, thus providing all participants with the same opportunity to be selected into any group in the study [41]. The randomization process will be blinded, as this will avoid the possibility of choice bias [42,43]. Blinded group assignment will be enabled using a group assignment software, which will allow a general random selection of the individual groups. The researcher involved in the randomization process and the patients themselves will not know to which group the patients were assigned. The medical staff will be informed about the start of the research and use of the mobile app by the individuals in the intervention group. The only difference between the intervention and control groups will be the use of the *forDiabetes* [36] mobile app, which the intervention group will use from the beginning of the study until the first control visit. Both groups will receive instruction regarding type 2 diabetes and the related self-care.

Data Collection

The initial part of the questionnaire consists of questions about the patient's demographic data and data on the patient's support from the medical staff. The first part of the questionnaire will cover the assessment of self-care. Self-care in patients with type 2 diabetes will be assessed using the SCODI instrument [39]. The tool consists of 40 assumptions classified into 4 dimensions: self-care maintenance (12 assumptions), self-care implementation (8 assumptions), self-care monitoring (9 assumptions), and self-confidence (11 assumptions). The instrument is assessed using a Likert scale, where a higher score represents better self-care [39]. We will also use the Brief IPQ scale [40] to assess disease perception. The questionnaire rapidly assesses disease perception and measures the patients' cognitive and emotional representations of their disease. The questionnaire contains 8 questions graded on a 10-point scale and 1 open-ended question. There are 5 questions that assess the cognitive perceptions of the disease: consequences (point 1), timeline (point 2), personal control (point 3), treatment control (point 4), and identity (point 5); 2 questions that assess emotional representation: care (point 6) and emotions (point 8); and 1 question that estimates the comprehensibility of the disease (point 7). The assessment of causal representation is based on an open response that requires the patients to indicate the 3 most important causal factors in their disease (point 9) [40]. The nurses employed at the family medicine practices will use standardized, calibrated devices according to the guidelines to measure blood sugar, blood pressure, and HbA_{1c} levels and body weight. Data will be recorded at each control check.

The questionnaires were translated using the reverse translation method into English. This ensured the adequacy and consistency of the translated questionnaire. It was first translated from English into Slovene independently by 2 translators. One of the translators involved had expertise in nursing, and the other had the necessary knowledge of the standard English language. Thus, we obtained 2 translation versions, which were merged in the next step through review and consultations. In the last step, 2 experts with the necessary English knowledge translated a standard Slovenian questionnaire into English and combined it into a familiar form. Thus, we obtained 2 translated questionnaires in English, which we subsequently incorporated into a standard format [44,45]. The final version of this translated questionnaire will need to be preconfirmed and tested on a small sample, and the subsequent corrections will be tested on a large representative sample of respondents [46]. We will carry out the validation of the questionnaire. To analyze the reliability of the questionnaire, we will calculate Cronbach α and perform confirmatory factor analysis. Cronbach α measures intrinsic reliability among multiple elements and assesses how reliable the questionnaire responses are [47]. If the Cronbach α value is low (close to 0), it means that some or all of the items do not measure the same dimension [47-49]. The content validation process will consist of the following steps: the preparation of a content review form, selection of an expert review team, implementation of content review, review of domains and elements, determination of the rating for each item, and calculation of Content Validity Index (CVI) [50]. The content validity will be assessed by a nurse employed at the family medicine practice with knowledge of type 2 diabetes self-care. To assess the substantive validity of the questionnaire, we will use the index of substantive validity for individual statements (Item-CVI) and the entire questionnaire (Scale-level CVI). We will use a 4-point scale for evaluation [50]. Item-CVI results higher than 0.78 from 3 or more experts in assessing an individual statement represent good substantive validity [51]. Scale-level CVI results of 0.80 or more indicate good substantive validity [52].

Inclusion Criteria

A randomized controlled trial will be conducted in family medicine practices where individuals with type 2 diabetes are treated throughout Slovenia. There are 10 regional units of the Health Insurance Institute of Slovenia, with 241 private and 656 public health institutions [53]. The research will cover 1 family medicine practice from each regional unit. According to the data from January to September 2018, there were 28,593 treatments of individuals in connection with type 2 diabetes conducted in family medicine practices [54]. This number was used to calculate the sample size, which was calculated using a sample size calculator (Raosoft) [55] that has been used in many similar health research studies [56-59]. We used a power analysis and entered the necessary data with a 95% error rate and 5% confidence level. The required minimum sample size is 380 participants. We will include individuals aged over 18 years with type 2 diabetes who have already been given

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treatment. Additionally, there should be no acute complications due to the consequences of type 2 diabetes in the individuals included in the study. They must use a mobile phone and a blood glucose meter during the research period.

Statistical Analysis

The sample will be described with descriptive statistics, and the explanatory variables will be presented with frequencies and percentages. In contrast, the numerical variables will be presented with the mean value, SD, and minimum and maximum values. To test the relationship between different variables, we will use the Mann-Whitney *U* test in the case of an uneven distribution of variables or the *t* test of independent samples in an even distribution of variables. The significance level of α=.05 will test the hypotheses.

Ethics Approval

We received permission from The Republic of Slovenia National Medical Ethics Committee (03/5R-2021) for the primary research. We will also obtain the necessary consent from all institutions and participants in a randomized controlled trial. We will obtain permits from the institutions to enter the family medicine practices to conduct the research. We will also obtain consent from the participants to participate in the study. Before starting the analysis, we received written authorization to use the mobile app *forDiabetes* [36]. We also obtained permission from the authors to use and translate the questionnaires SCODI [39] and Brief IPQ [40]. In the introductory part of the research, the research participants will be acquainted with the purpose and goal of the study, ensuring the anonymity of the participants, voluntary nature of participation, and possibility of withdrawing from participation. Participants who submit a completed questionnaire will consent to the research and use of their data. The data will be securely stored and used only for research and publication, and only the researchers involved will have access to the actual data. The data will be kept for 10 years. We will ensure the anonymity of the participants throughout the research; it will not be possible to identify a person and institution or other demographic data from the results presented. The study does not pose a risk to the participants and represents a minimal burden. We will also consider the principles of legality, fairness, proportionality, accuracy, and timeliness of the data during the research

Results

Before the current phase of the research, we have prepared a translation of the mobile app that will be used by the participants of the intervention group, as well as more detailed instructions for using the app. We have also prepared a translation of the questionnaires in Slovene. The research results will be published in 2023.

Discussion

Expected Findings

Adherence to chronic management measures is essential for maintaining good health outcomes [60]. By 2045, the number of patients with diabetes will rise to approximately 629 million [61]. Mobile apps provide motivation and support for self-care in these patients [62], but there is still a lack of knowledge about their actual use [63].

Based on the described methodological process, we will perform a randomized controlled trial to determine the effectiveness of a mobile app and its impact on patients with diabetes. The research represents a unique opportunity to use and integrate mobile apps in the treatments of individuals with type 2 diabetes to solve challenges and achieve better self-care. We will enable the use of an efficient and evidence-based mobile app that is suitable for users' needs and includes the concept of self-care in the framework of mobile health. The research will help to gain new knowledge in integrating mobile technology into the life of an individual with type 2 diabetes.

Limitations

The main limitation is that we will only include patients with controlled and managed type 2 diabetes in the study, which means that we will examine only a specific part of the population. The study will also have only patients treated in family medicine practices, which may prevent the possibility of generalization to all people with type 2 diabetes.

Having both control and intervention groups at the same family medicine practices may provide bias, as this will not conceal the allocation of an intervention in a randomized controlled trial. Researchers will know in which group the participants were assigned, as these participants will carry out the necessary training for the use of the mobile app and other interventions. The research will use a questionnaire to assess the participants' self-care and perception of the disease, which can provide socially expected and desirable answers.

Our study contains the following assumptions. People with type 2 diabetes have deviations or shortcomings in each concept of self-care. The app will affect a patient's self-care with type 2 diabetes and other critical clinical measures. Self-care and disease perception are measurable and that the translated questionnaire will be helpful in our research. Medical professionals, employees in family medicine practices, and individuals with type 2 diabetes will be willing to participate in the study. People with type 2 diabetes will actively use the mobile app and monitor their health through data entry. The results expected during the study are changes in self-care; disease perception; blood sugar, blood pressure, and HbA_{1c} levels; and measured body weight.

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Conflicts of Interest

None declared.

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Abbreviations

Brief IPQ: Brief Illness Perception Questionnaire
CVI: Content Validity Index
HbA_{1c}: glycated hemoglobin
SCODI: Self-Care of Diabetes Inventory

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Protocol

OptimalMe Intervention for Healthy Preconception, Pregnancy, and Postpartum Lifestyles: Protocol for a Randomized Controlled Implementation Effectiveness Feasibility Trial

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Abstract

Background: Reproductive-aged women are a high-risk population group for accelerated weight gain and obesity development, with pregnancy recognized as a critical contributory life-phase. Healthy lifestyle interventions during the antenatal period improve maternal and infant health outcomes, yet translation and implementation of such interventions into real-world health care settings remains limited.

Objective: We aim to generate key implementation learnings to inform the feasibility of future scale up and determine the effectiveness of intervention delivery methods on engagement, experience, acceptability, knowledge, risk perception, health literacy, and modifiable weight-related health behaviors in women during preconception, pregnancy, and postpartum periods.

Methods: This randomized hybrid implementation effectiveness study will evaluate the penetration, reach, feasibility, acceptability, adoption, and fidelity of a healthy lifestyle intervention (OptimalMe) implemented into, and in partnership with, private health care. Individual health outcomes associated with implementation delivery mode, including knowledge, risk perception, health literacy, self-management, and health behaviors, are secondary outcomes. A total of 300 women aged 18 to 44 years, who are not pregnant but wish to conceive within the next 12 months, and with access to the internet will be recruited. All participants will receive the same digital lifestyle intervention, OptimalMe, which is supported by health coaching and text messages during preconception, pregnancy, and postpartum periods. We will use a parallel 2-arm design to compare telephone with videoconference remote delivery methods for health coaching. Methods are theoretically underpinned by the Consolidated Framework for Implementation Research and outcomes based on the Reach, Engagement, Adaptation, Implementation and Maintenance framework.

Results: The study was approved on August 16, 2019 and has been registered. Recruitment commenced in July 2020, and data collection is ongoing. Results are expected to be published in 2022.

Conclusions: The study's design aligns with best practice implementation research. Results will inform translation of evidence from randomized controlled trials on healthy lifestyle interventions into practice targeting women across preconception, pregnancy, and postpartum periods. Learnings will target consumers, program facilitators, health professionals, services, and policy makers to inform future scale up to ultimately benefit the health of women across these life-phases.

Trial Registration: Australian and New Zealand Clinical Trial Registry ACTRN12620001053910; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378243&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/33625

(JMIR Res Protoc 2022;11(6):e33625) doi:10.2196/33625

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KEYWORDS

preconception; pregnancy; postpartum; weight; obesity prevention; womens health; intervention; implementation

Introduction

Background

Obesity is a major global public health and economic burden. In an increasingly obesogenic environment, young women are a high-risk population group with suboptimal lifestyle behaviors [1], accelerated weight gain, and rising obesity prevalence across early to middle adulthood [2,3]. Prior to pregnancy, excess weight affects fertility [4] and independently increases the risk of adverse maternal and neonatal outcomes [5]. During pregnancy, up to 50% of women exceed international gestational weight gain recommendations [6], which increases their risk of complications, such as gestational diabetes, cesarean section delivery, and having a large-for-gestational-age infant, compared with those whose weight gain is within recommendations [6,7]. Independent of maternal prepregnancy BMI, excessive gestational weight gain increases subsequent childhood [8,9] and maternal obesity by 3-fold [10]. Excessive gestational weight gain superimposed on preexisting overweight or obesity further exacerbates risks and perpetuates a cycle of weight gain in women across their reproductive lifespan [11].

Pregnancy is a critical window in which maternal health behaviors and lifestyle should be optimized to benefit the future health of both mother and child [11]. Consequently, most research to date has concentrated on efficacy-based antenatal lifestyle interventions for improving outcomes [12,13]. A recent systematic review and meta-analysis [12] by the US Prevention task force of 68 trials that involved a total of 25,789 women reported a reduction in gestational weight gain after behavioral lifestyle interventions (mean difference −1.02 kg, 95% CI −1.30 to −0.75; 55 studies; n=20,090), with an associated reduction in gestational diabetes (relative risk 0.87, 95% CI 0.79 to 0.95; 43 trials; n=19,752) and emergency cesarean delivery (relative risk 0.85, 95% CI 0.74 to 0.96; 14 trials; n=7520) risks [12]. This level 1 evidence on antenatal healthy lifestyle intervention efficacy is supported by findings of cost-effectiveness and potential cost savings [14], mandating translation into policy and practice [12,15].

However, vital implementation gaps remain [16]. Weight management guidelines for preconception and pregnancy periods lack quality, consistency, and translation of effective intervention strategies into practice with extended reach that is in line with real world experience [17]. Barriers in the preconception period include identifying and engaging women who intend to become pregnant and who are, otherwise, not regularly engaged with the health care system [18]. In pregnancy, identifying broad reach, feasible intervention delivery methods, including remote delivery options, remains unclear [12,13]. Barriers in the postpartum period include engagement, penetration, and uptake of healthy lifestyle interventions with very limited reach and impact to date [19]. To leverage the substantial investment in efficacy trials and deliver health impacts, these barriers must be addressed.

We previously designed a low-intensity, low-cost healthy lifestyle program, called HeLP-her, that has engaged thousands of reproductive-aged women and has an extensive evidence base [16,20-24]. The program effectively prevents progressive weight gain in reproductive aged women [22,23], estimated to be between 0.625 kg and 1.2 kg per year [25], depending on the population studied [2,26]. During pregnancy, HeLP-her optimized gestational weight gain (intervention: mean 6.0, SD 2.8 kg; control: mean 6.9, SD 3.3 kg; $P<.05$) and postpartum weight retention (intervention: mean 0.51, SD 4.48 kg; control: mean 1.96, SD 5.74 kg; $P<.05$) overall, with the greatest efficacy demonstrated in nonobese women [20,21,27]. HeLP-her is theoretically underpinned and improves self-management behaviors through health coaching supported by intervention resources and self-management tools. It has been contextually adapted successfully across delivery methods, settings, and life stages, retaining core components to ensure fidelity [16,20,21,23].

Our formative work has included extensive evidence synthesis to systematically evaluate the efficacy of lifestyle interventions incorporating diet, physical activity and weight- and self-management behaviors during preconception [28], pregnancy [13], and postpartum [19] periods, to integrate key intervention components and inform study design. We have developed and integrated health-related content based on best practice clinical guidelines [29,30] and have identified facilitators and barriers to healthy lifestyle– and weight-related behaviors, information preferences, and health professional engagement across these life stages [31-34]. We have engaged consumers and health professionals to iteratively adapt our evidence-based intervention for broader reach, with translation of the intervention content, resources, and tools to a dedicated web-based digital platform, and have performed extensive consumer testing to evaluate and iteratively optimize acceptability, relevance, and engagement of intervention content in a representative target population of women.

Overall Aim

Applying a hybrid effectiveness-implementation study, we aim to generate key implementation learnings to inform the feasibility of future scale up and determine the effectiveness of intervention delivery methods on engagement, experience, acceptability, knowledge, risk perception, health literacy, and modifiable weight-related health behaviors in women during preconception, pregnancy, and postpartum periods.

Specific Objectives

Our objectives are as follows:

1. Determine implementation feasibility with 1) process evaluation (ie, measure of process used to implement the program and any variation experienced; facilitators and barriers to intervening events impacting implementation), 2) the RE-AIM framework to assess Reach, Effectiveness, Adoption, Implementation and Maintenance of the intervention and 3) cost effectiveness analysis.

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2. Evaluate intervention participation (ie, engagement and adherence to program) and engagement (ie, degree of online module completion, frequency, and duration of time spent on the platform).
3. Determine intervention effectiveness on health related outcomes measured at the individual level including health knowledge, health literacy, and self-management behaviors.
4. Determine any discrepancy according to the health coaching delivery method.

Hypotheses

We hypothesize as follows:

1. The intervention will be feasible to implement and can effectively reach and engage women prior to pregnancy through co-designed strategies that are acceptable to women and the implementation partner with demonstrated cost-effectiveness.
2. Participation and engagement with intervention resources will be greater for participants who complete the intended intervention dose compared with those who do not.
3. The intervention will improve preconception and pregnancy health knowledge and self-management.
4. Phone and videoconference health coaching delivery will be equally feasible and cost-effective, yet engagement, adherence, and effectiveness will be greater with videoconference compared with phone-based health coaching.

Methods

Implementation

Design

OptimalMe is a type 3 hybrid effectiveness-implementation study [35] with an active intervention phase (2 years) and a passive observation phase (up to 5 years). Type 3 hybrid implementation designs are those in which implementation outcomes are primary, and individual or population outcomes are secondary [35]. The primary outcome of the project includes overall intervention penetration and reach and the feasibility, acceptability, adoption, and fidelity of the delivery of OptimalMe. Secondary outcomes include evaluation of individual health outcomes associated with implementation delivery mode, including knowledge, risk perception, health literacy, self-management, and health behaviors. The study design is a parallel, two-arm, randomized trial at the level of the individual utilizing a pragmatic philosophy, working within real-world conditions to assess overall effectiveness. All individuals will receive the same evidence-based lifestyle intervention, and implementation delivery methods will be compared.

Setting

The Australian health care system is government supported via Medicare, which provides universal free care to Australian citizens and residents (and others who are eligible) and is supported by a subsidized private health system. Private health insurance, paid by the individual, allows patients to choose hospitals and health care providers from outside of the public system, with a 12-month waiting period before some, or all, of the cost of hospital treatment is reimbursed. Overall, approximately 54% of Australian adults have a form of private health insurance [36], and 27% of births in Australia occur in private hospitals [37]. Women who give birth in private hospitals attend ambulatory private obstetric care and have limited contact with hospitals prior to delivery.

Women who upgrade private insurance to include, or join with, pregnancy and birth coverage, comprise a unique population, prospectively signaling future intention for a pregnancy. In a sample of 294 women who had recently upgraded or obtained insurance for pregnancy and birth coverage, 41% intended to conceive within the next 12 months [33].

The implementation partner in this research program is Medibank Private, which is one of Australia's largest insurers (funding approximately 20,000 births annually). Feasibility scoping shows approximately 7800 women join with, or upgrade to, pregnancy and birth coverage with this insurer nationally each year.

Framework

This implementation research is underpinned by the Consolidated Framework for Implementation Research [38], which provides a pragmatic framework, informed by *translation into practice* theories, that is designed to guide complex implementation projects and generate knowledge across settings and studies [38]. The framework consists of 5 domains [38]: Domain 1 consists of the unadapted intervention to be implemented and assumes the intervention is composed of core or fundamental components, essential to efficacy, surrounded by peripheral components that are adaptable to the local context, without altering the integrity of the intervention. The adaptable components are informed by domain 2 (the outer setting, ie, policy, guidelines, population needs), domain 3 (the inner setting, ie, the organization's structure, culture, readiness to change), and domain 4 (the individuals within the outer or inner setting involved in the intervention as influencers of implementation. The implementation process (domain 5) works across all domains to achieve implementation through an iterative change process of executing and evaluating implementation activities [38].

The fundamental core components of our intervention include theoretical underpinning; simple diet; physical activity and self-management messages; low-intensity delivery format; individual health coaching sessions focused on goal setting, problem solving, and self-management delivered by a qualified health professional; and ongoing intervention support via text messaging (Domain 1). Core components were informed by our extensive intervention evidence base [16,20,21,23] and were consistently applied to setting, population, intervention tools, resources, and delivery method and format. The integration of peripheral intervention components was undertaken to incorporate best practice clinical guidelines and systematic review lifestyle intervention evidence (Domain 2) and using an intervention co-design process with the implementation partner, Medibank Private (Domain 3) experts in obstetric and lifestyle delivery and reproductive women in this life stage (Domain 4). This included the incorporation of health education resources

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within the intervention and the development of a consumer-tested web-based digital platform for remote delivery and comanaged participant engagement. The efficacy of health coaching delivery methods (phone and videoconference) will be compared. A governance process has been established to enable responsive and pragmatic adaptations to peripheral components in partnership with the implementation partner (Medibank Private), yet designed and managed by the clinician academic research group (Monash University). The primary outcomes form Domain 5, which includes overall intervention feasibility, reach, acceptability, and adoption as well as fidelity of the delivery of OptimalMe as planned.

Study

Design

The study will be conducted in accordance with Consolidated Standards of Reporting Trials [39] and Template for Intervention Description and Replication frameworks [40].

Eligibility Criteria

The target intervention population will include Medibank Private members who have joined or upgraded with pregnancy and birth coverage within the 3 months prior to recruitment (to align with likely planned conception based on insurance uptake and wait times). Eligibility criteria focus on inclusiveness and includes those who are not pregnant, who wish to conceive within 12 months of recruitment, who are aged 18 to 44 years, with any BMI, who read and speak English, and who have access to an internet-capable device will be included.

Sample Size

Given the implementation effectiveness study design, sample size has not been powered on a clinical outcome because the primary outcome is to determine implementation learnings to inform feasibility. Available funding enables intervention delivery to approximately 300 women, which is approximately 10% of the eligible population with intention to conceive, based on our formative research [33].

Randomization

Participants will be randomized to receive health coaching either by telephone or via videoconference. An external senior statistician will provide computer-generated randomization codes to the research coordinator only, who will sequentially allocate all participants but will have no role in intervention delivery. Researchers involved in intervention delivery and data collection will be blinded to the allocation sequence; however, due to the nature of the intervention, they will not be blinded to participant allocation. Researchers responsible for data analysis and reporting will be blinded to both allocation sequence and participant allocation. Randomization performed external to the implementation setting is designed to reduce bias. Due to the nature of the intervention, participants will not be blinded to group allocation.

Recruiting Strategy

A co-designed process, using an opt-in design, was developed with the implementation partner to facilitate Australia-wide recruitment. We will use direct email communication (approximately 500 members every month, to be varied based on response rates and historical trends in email engagement observed during specified periods, including seasonal holiday periods) to recruit women (randomly selected to receive a targeted invitation by system generated mailing lists) who meet initial eligibility criteria (insurance coverage and age) with a link to the landing page of the web-based intervention platform. The page contains introductory information about the healthy lifestyle intervention, including a video. Individuals who wish to take part will be required to confirm remaining eligibility criteria, including pregnancy status and intention to conceive within 12 months, provide informed consent electronically, and register via a digital interface. The researcher coordinator will then contact the Medibank-managed integrated voice recognition system to confirm the potential participant's membership (using first and last name, membership ID, date of birth, and postal code) and pregnancy and birth coverage status to confirm eligibility. An email with an activation link to an account for the intervention will be sent to participants, at which time, they are randomized to 1 of the 2 coaching delivery methods. Recruitment will continue until target numbers (n=300) are reached. This pragmatic approach enables management of participant flow into the intervention and will not disqualify those who may be unaware of pregnancy status at point of recruitment or who may re-evaluate their intention to become pregnant after recruitment (Multimedia Appendix 1).

Intervention

Theoretical Underpinning

This intervention is based on our previous healthy lifestyle program—HeLP-her [16,20-23,27]). HeLP-her is a low intensity, behavior change program, grounded in social cognitive theory [41]. HeLP-her is nonprescriptive and provides health coach–delivered simple messages on healthy lifestyle behaviors aligned with national dietary and physical activity guidelines [30,42,43]. These are reinforced by behavior change strategies including identifying individual health priorities and facilitators and barriers for change. Realistic achievable goals are prioritized and developed by participants, and a behavioral action plan that outlines goals and timeframes is established. Individual barriers, strategies for change, and social supports are identified and discussed, and self-monitoring is practiced and encouraged [27].

Delivery

Co-design of intervention delivery with the implementation partner prioritized remote delivery to ensure equitable accessibility to the intervention across Australia by using a dedicated web-based digital platform, supported by health coaching (delivered via phone or videoconference), with ongoing text message support (Figure 1).

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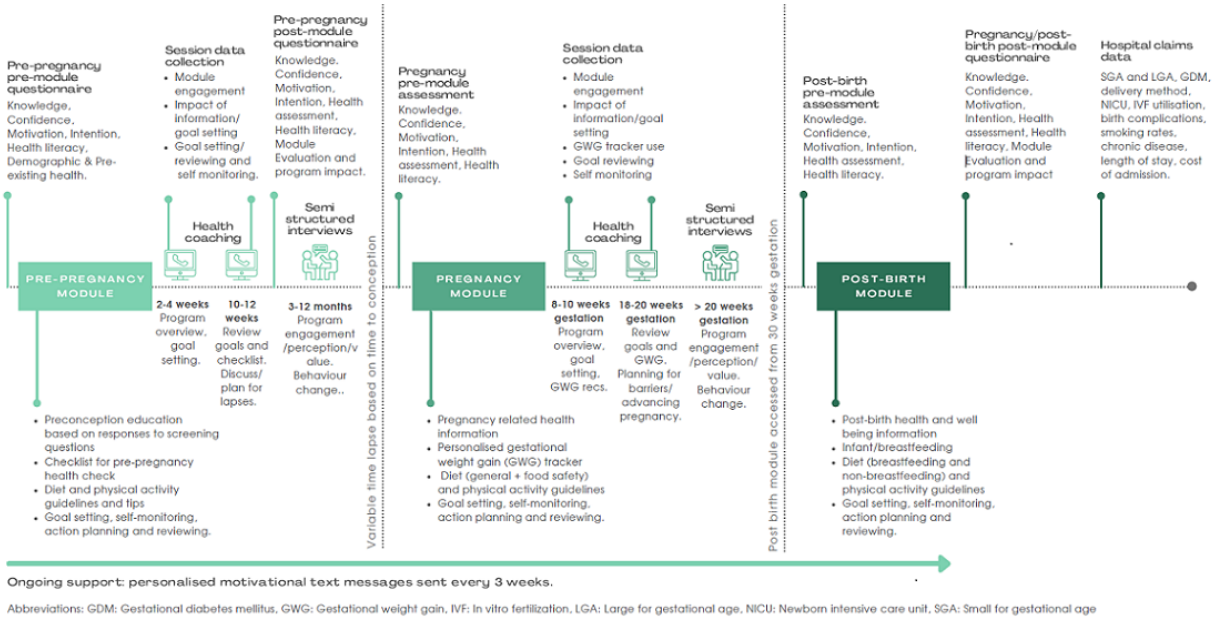
Figure 1. OptimalMe program design and delivery.



Abbreviations: GDM: Gestational diabetes mellitus, GWG: Gestational weight gain, IVF: In vitro fertilization, LGA: Large for gestational age, NICU: Newborn intensive care unit, SGA: Small for gestational age

Platform

The secure web-based platform can be accessed via desktop and mobile apps. The platform contains preconception, pregnancy, and postpartum modules. Participants are provided access to the preconception module at the outset from the dashboard (Figure 2). The pregnancy module is accessible to participants when they update their personal profile on the dashboard (pregnancy status and estimated due date). In addition to the 3 modules, the dashboard contains an interactive BMI (and gestational weight gain, if pregnancy is reported) calculator, a checklist, and activities to review behavioral action plans.

All modules have a similar format—each has a health information (education) section and a healthy lifestyle behavior change (self-management) section. The health information section contains health, medical, and screening information and the healthy lifestyle section contains diet and physical activity recommendations, as well as an interactive behavior change section. Health, medical, and screening information are presented as a suite of fact sheets specific to each reproductive phase (Multimedia Appendix 2). Information provided is based on the Royal Australian College of General Practitioners Red Book [29], Australian Government Clinical Practice Guidelines for Pregnancy [30], and our formative research [33,34]. A series of health screening questions at module commencement based on these guidelines will inform the presentation of fact sheets according to relevance. For example, preconception participants will be asked when their last cervical screen was completed. If a participant indicates a cervical screen outside of a guideline-specified timeframe, the relevant cervical screening fact sheet will be presented under *Essential information* at the top of the screen. Conversely, if a participant indicates a cervical screen within a guideline-specified timeframe, the fact sheet will be presented under *Other recommended reading*. This design feature ensures that participants are directed to the information that is most relevant to their health needs (based on their responses to screening questions) while minimizing the burden of information, which has previously been identified as a barrier to receiving health information [31].

Fact sheets have a similar structure—each fact sheet has 3 to 4 key messages, followed by detailed topic information and links to other websites for additional evidence-based information. Each fact sheet is supported by an interactive component that enables the user to populate a checklist item summarized on the platform dashboard (Figure 2). For example, opening a fact sheet about cervical screening will populate the *Check my cervical screening status with my GP* item. Health literacy is tested at the top of each fact sheet with a true or false question, with corresponding information that explains the correct answer.

Healthy lifestyle resources include fact sheets related to weight gain prevention and infographics that are based on Australian adult pregnancy [30] and breastfeeding [42] dietary guidelines and physical activity guidelines [43]. Additional resources include information on how to read food labels, how to estimate food portion sizes, healthy snack and food substitution ideas, and calories consumed using various food choices versus those burned from walking. Behavior change is supported by an interactive goal-setting section that guides the user to develop a personalized goal through action planning, which includes an activity to self-select modifiable health behaviors for improvement (eg, packaged or convenience food consumption, alcohol intake, physical activity, fruit and vegetable intake, and sleep). Areas of relevance are selected and prioritized by each participant (ie, areas are ranked in order of importance). Participants are guided through goal-setting using free text to specify what they would like to achieve identify motivating factors and social support pathways, barriers to behavior change and specific strategies to overcome barriers that are time dependent and identification. An action item to review goals will be automatically added to the digital platform, which is encouraged 2 weeks after goal planning and commitment (Figure 2).

The platform was consumer-tested using a quantitative survey for functionality (ie, ease of navigation across the platform),

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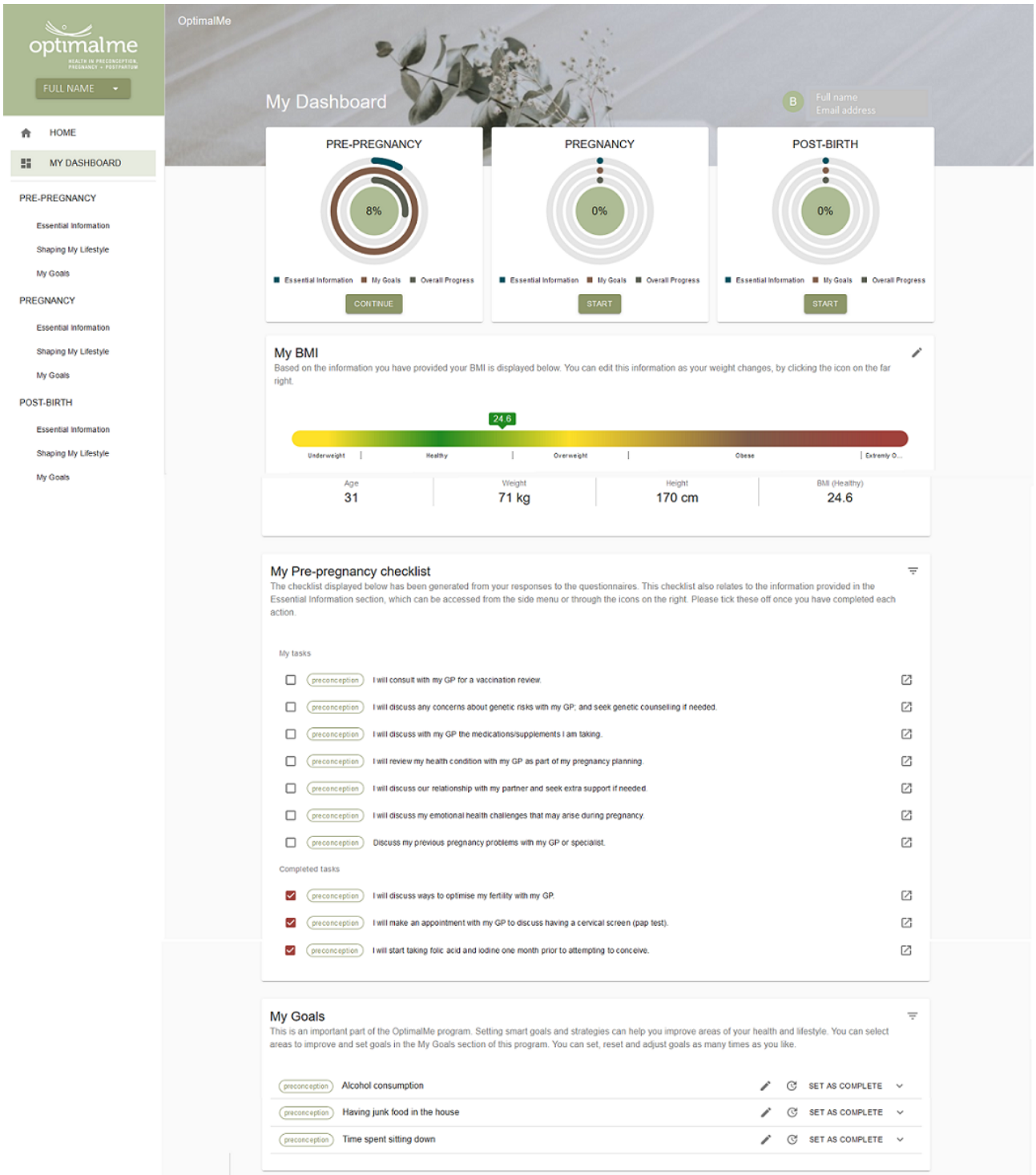
acceptability (ie, usefulness of the information, presentation and aesthetics, ease of understanding content) and relevance (ie, appropriateness of information, potential for the platform to assist in optimizing health behaviors, peer recommendation). The survey contained a series of statements requiring response on a 5-point Likert scale that ranged from strongly disagree to strongly agree, with an opportunity to provide free text. Responses were transformed to a binary representation (0, disagree and neutral; 1, agree). Overall, 36 women were recruited from the community with advertisements across all modules using both computer (19/36, 53%) and mobile phone or tablet (17/36, 47%) devices. Women were aged between 25 and 38 years old, and the majority were university educated (33/36, 92%). Most women agreed that they could navigate to different areas of the platform and return to the dashboard with ease (23/30, 77%); they found the platform to be aesthetically appealing (25/36, 69%), and the amount of information to be appropriate (28/36, 78%) and easy to understand in its presentation (29/30, 97%). The majority believed that the information would assist them in improving their health-related behaviors (25/30, 83%) and considered the platform relevant to recommend to women of the same life stage (24/36, 67%).

Figure 2. Platform user dashboard.



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Health Coaching Sessions

Health coaches with a tertiary qualification in health sciences (ie, dietetics, nutrition, exercise physiology, or allied health) will deliver the program and aim for continuity wherever possible to maintain rapport. The purpose of the individual health coaching sessions is to build rapport with participants, reiterate program objectives, enhance engagement, practice goal setting and self-management skills, support participants with lifestyle modules, and provide personalized feedback on behavior change. Any module components that have not been accessed or completed by participants at the point of health coaching will be flagged for completion by the participant during or after the session.

All participants will be offered 2 personalized preconception health coaching sessions (approximately 20 minutes in duration, delivered either be phone or videoconference according to randomization) 2 to 4 weeks after program entry and 6 weeks later.

During pregnancy, 2 additional 20-minute health coaching sessions will be scheduled (8-10 weeks gestation or 1-2 weeks after starting the pregnancy module commencement and 19-20 weeks gestation).

Ongoing Program Support

SMS text messages will be sent every 3 weeks as a reminder to practice healthy behaviors.

Fidelity

Intervention fidelity will be maintained by facilitators using a checklist after health coaching sessions to reduce potential reporting bias. The checklist will include planned discussion points, deviation in delivery of session with reasons, and duration of session. Coaching sessions will be periodically recorded with participant consent to monitor fidelity.

Intervention facilitators will complete program-specific training on the intervention, including health coaching delivery. Facilitators will be required to have a sound knowledge of evidence-based practice; an understanding of health behaviors, nutrition, and physical activity; and a tertiary qualification in a health-related discipline. Program-specific training includes both theory and practical components and motivational interviewing techniques [20-23,44].

Outcome Measures

Outcome measures (Table 1) are underpinned by the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance [45]). Both quantitative (recruitment and intervention delivery fidelity checklists [46]) and qualitative (semistructured interviews) data collection methods will be used (Multimedia Appendix 1 and Multimedia Appendix 2).

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Table 1. Description of outcome measures.

Outcome	Description
Implementation feasibility (primary)	Program evaluation and feasibility for future scale up
Reach	• Proportion of the target population that were invited and participated in the program and intervening factors
Implementation fidelity	• Delivery according to design and any variation experienced • Facilitators and barriers: identification and description of intervening events
Adoption of the program by the implementation partner	• Contextual events or factors influencing implementation within the setting, variation in any co-design implementation component
Cost-effectiveness	• To answer questions about overall feasibility of implementation
Intervention effectiveness (secondary)	Exploratory evaluation of the effectiveness of intervention delivery across preconception and pregnancy (Figure 1)
Participation	• Adherence and engagement measures to intervention dose including health coaching sessions and web-based platform interaction including degree of module completion, frequency and duration of time spent on the platform
Acceptability	• A set of questions relating to the influence of the program in changing health behaviors, the usefulness and relevancy of the information provided, valuable aspects of the program and areas for improvement • Qualitative data analysis of insights, participation factors, intervention reach, adoption and maintenance of behavior change, intervention delivery format, and areas for improvement until thematic data saturation
Effectiveness	• On individual health behaviors including self-reported weight, health literacy [47], self-management [48], diet [49], and physical activity [50] using validated questionnaires • Collected at the start of the intervention, after preconception health coaching sessions and module, and at the start of the pregnancy module
Pregnancy and birthing outcomes	• In vitro fertilization utilization (restricted to only hospital component visibility of this process such as retrievals and transfers); gestational diabetes diagnosis, delivery type (ie, vaginal or cesarean section), birth complications and neonatal intensive care unit admission, length and cost of hospital stay and ancillary utilization (ie, physiotherapy, dieticians, dental) • Captured via encrypted data linkage with Medibank Private for health outcomes up to and including 5 years after the start of the study as observational study phase data

Statistical Analysis

Deidentified quantitative and qualitative databases will be maintained on encrypted Monash University servers and managed by research staff involved in data collection. We will use descriptive approaches to evaluate primary outcomes measures. Quantitative data collected for secondary outcome measures will be exported to STATA (version 17.0; StataCorp LLC). Descriptive statistics (means with standard deviations or frequencies with ranges) will be used to characterize intervention effectiveness and the recruited sample by demographic characteristics (age, BMI, country of birth, education, socioeconomic status, and parity), preexisting health, and health-related behaviors (ie, self-management, diet, and physical activity). Logistic and linear regression models will be used to explore associations between before and after the intervention. Additionally, factors known to influence secondary outcomes, including weight, such as diet, physical activity, breastfeeding status, and parity will be adjusted for a priori. Mixed-effects regression models, with the individual specified as the random effect, will be investigated to account for repeated measures. Missing data will be examined, and multiple imputation will be used to generate complete data, if data are not found to be missing at random. Sensitivity analyses will be performed to explore robustness. A P value <.05 will be considered statistically significant.

Transcripts of semistructured interviews will be independently analyzed and coded by 2 researchers using NVivo software (version 12; QSR International). Data will be searched for concepts in relation to participatory factors and program evaluation, with codes generated and grouped into themes using an inductive approach. Quantitative data will be analyzed first, to inform thematic analyses. The definitions of themes will be determined by consensus (between 2 researchers).

Economic Evaluation

The economic evaluation will be designed to identify the costs associated with implementation, and the net costs to health care funders. Costs of the OptimalMe implementation package will

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be identified from the trial data, including the costs of platform maintenance, staff time (in providing the coaching sessions), and SMS text messages. Fixed and variable costs will be identified, allowing cost per woman to be estimated at different scales of the intervention. The net costs to health care funders will be identified by quantifying the costs associated with birth type, birth complications, neonatal intensive care unit admissions, hospital stay, and ancillary utilization. Costs to Medicare Benefits Schedule will be identified based upon item numbers [51] associated with birth type and complications. Costs to private health insurers associated with hospital stay will be identified directly from the study. Costs to public hospital funders from neonatal intensive care unit admissions or any public hospital transfers will be identified from the National Hospital Cost Data Collection produced by the Independent Hospital Pricing Authority [52]. The total cost per woman will be calculated, and generalized linear models will be utilized to identify differences in costs between delivery methods. We will use these models to estimate the net cost impacts to different funders at different levels of the population reached.

Ethical Approval

The Monash Health Human Research and Ethics Committee approved the study (RES-19-0000291A), and the study has been registered (using predefined study description classifications; as such, the trial was registered as an efficacy trial in the absence of a feasibility study descriptor) on the Australian and New Zealand Clinical Trial Registry (ACTRN12620001053910).

Results

The project is supported with funding from Medibank Private Ltd. Recruitment commenced in July 2020 with results expected to be published in 2022.

Discussion

Prevention of weight gain and obesity is a global health priority. Increased emphasis is placed on high-risk populations [53,54], including reproductive-age women with accelerated preconception, pregnancy, and postpartum weight gain [6]. Lifestyle interventions can be used to optimize weight and reduce maternal and neonatal adverse outcomes [12,55], yet translation of effective interventions into real-world settings remains critically limited. We address this gap and leverage extensive investments in efficacy research by undertaking implementation research to inform feasibility, acceptability, applicability, effectiveness, and sustainability of an evidence-based weight gain prevention intervention for preconception, pregnancy, and postpartum periods. Implementation research leverages investment in efficacy-based randomized trial knowledge to study methods that promote the systematic uptake of evidence-based interventions into practice and policy to improve health [35].

Our study design aligns with best practice implementation research; focuses on system-level outcomes; and is underpinned by evidence from efficacy trials, systematic reviews, meta-analyses, and guidelines. Additional health information, specific to preconception, pregnancy, and postpartum life stages, has been integrated, with checklists and resources. Evidence on core and peripheral components has been integrated to adapt the intervention with stakeholders across women, multidisciplinary clinicians, and partners. Novel delivery strategies, including sophisticated digital platform and remote health coaching delivery methods, while retaining core intervention features including low-intensity individual health coaching and ongoing text message support. This work has integrated, and been supported by, robust implementation and intervention frameworks and theories.

We anticipate that the OptimalMe intervention will demonstrate feasibility and directly provide evidence to inform scaled intervention delivery. Learning will not only inform future implementation design but translation of evidence targeting consumers, program facilitators, health professionals, services, and policy makers to inform future scale up of healthy lifestyle interventions to ultimately benefit the health of women.

Acknowledgments

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Medibank Private Limited provided in-kind support to enable study recruitment, which would not have otherwise been possible. We gratefully acknowledge the assistance of Josphin Johnson, for project coordination and support; Grace Xie, Alex Hu, and Susanne Baker, for information technology programming and development; Steven White and David Young, for information technology security expertise and guidance; Jacqueline Boyle, for obstetrics/gynecology expertise; Lisa Moran, for dietetics expertise; and Jo Zhou, for expertise on dietary data collection.

Authors' Contributions

CLH and HT conceptualized the trial. CLH, BRB, RG, and HT provided intellectual input into the trial design and methodology. CLH, BRB, and RG designed and wrote the intervention content. CLH and BRB implemented the trial. CLH, RG, and BRB designed the evaluation methodology and data collection. CLH drafted the manuscript. All authors reviewed the manuscript for intellectual content and approved the final version.

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Conflicts of Interest

None declared.

Editorial Notice

This feasibility randomized study was not registered, explained by authors that this is part of an efficacy randomized study that is registered. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials, because the risk of bias appears low and the study for which this protocol is reported was considered formative. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness.

Multimedia Appendix 1
Co-designed recruitment strategy.
[PNG File , 158 KB - resprot_v11i6e33625_app1.png]

Multimedia Appendix 2
OptimalMe health-related content (fact sheets) within preconception, pregnancy, and postpartum modules.
[PNG File , 146 KB - resprot_v11i6e33625_app2.png]

Multimedia Appendix 3
CONSORT eHEALTH Checklist (V 1.6.1).
[PDF File (Adobe PDF File), 736 KB - resprot_v11i6e33625_app3.pdf]

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Abbreviations

BMI: body mass index

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Protocol

The Efficacy of Virtual Reality Game Preparation for Children Scheduled for Magnetic Resonance Imaging Procedures (IMAGINE): Protocol for a Randomized Controlled Trial

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Abstract

Background: It is known that magnetic resonance imaging (MRI) procedures generate fear and anxiety. Children may become restless during scanning, which results in movement artifacts requiring the MRI procedure to be repeated with sedation. Few studies seem to have looked at the effect of immersive virtual reality (IVR) on anxiety in children scheduled for MRI scans and how to identify which children are more responsive.

Objective: The aims of this study are 3-fold: develop an algorithm of predictability based on biofeedback, address feasibility and acceptability of preprocedural IVR game preparation for anxiety management during MRI procedures, and examine the efficacy of IVR game preparation compared with usual care for the management of procedural anxiety during MRI scans.

Methods: This study will have 2 phases. We will first conduct a field test with 10 participants aged 7 to 17 years to develop a predictive algorithm for biofeedback solution and to address the feasibility and acceptability of the research. After the field test, a randomized controlled trial will be completed using a parallel design with 2 groups: an experimental group (preprocedural IVR game preparation) and a usual care group (standard care as per the radiology department's protocol) in an equal ratio of 49 participants per group for 98 participants. Recruitment will be carried out at a hospital in Quebec, Canada. The experimental group will receive a preprocedural IVR game preparation (IMAGINE) that offers an immersive simulation of the MRI scan. Participants will complete a questionnaire to assess the acceptability, feasibility, and incidence of side effects related to the intervention and the biofeedback device. Data collected will include sociodemographic and clinical characteristics as well as measures of procedure-related anxiety with the French-Canadian version of the State-Trait Anxiety Inventory for Children (score 1-3) and the Children's Fear Scale (score 0-4). Physiological signs will be noted and include heart rate, skin conductance, hand temperature, and muscle tension. Measures of the level of satisfaction of health care professionals, parents, and participants will also be collected. Analyses will be carried out according to the intention-to-treat principle, with a Cronbach α significance level of .05.

Results: As of May 10, 2022, no participant was enrolled in the clinical trial. The data collection time frame is projected to be between April 1, 2022, and March 31, 2023. Findings will be disseminated through peer-reviewed publications.

Conclusions: Our study provides an alternative method for anxiety management to better prepare patients for an awake MRI procedure. The biofeedback will help predict which children are more responsive to this type of intervention. This study will

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guide future medical practice by providing evidence-based knowledge on a nonpharmacological therapeutic modality for anxiety management in children scheduled for an MRI scan.

Trial Registration: ClinicalTrials.gov NCT04988516; https://clinicaltrials.gov/ct2/show/NCT04988516

International Registered Report Identifier (IRRID): PRR1-10.2196/30616

(JMIR Res Protoc 2022;11(6):e30616) doi:10.2196/30616

KEYWORDS

virtual reality; children; video games; magnetic resonance imaging; anxiety; pediatrics; patient collaboration; patient preparation; biofeedback

Introduction

Background

Magnetic resonance imaging (MRI) is a technique that is considered noninvasive and safe because it does not use any radiation or x-rays unlike positron emission tomography scans or computed tomography scans. MRI technology, instead, uses a magnetic field to generate images of the tissues and organs. For MRI procedures to work as intended, the patient must remain still while lying down within a confined space for a certain amount of time.

The scan environment may be a source of anxiety for some patients. This can be due to the claustrophobic nature of a narrow space. MRI procedures have been known, for almost 40 years, to generate fear and anxiety caused by claustrophobia [1]. In addition, MRI scanners generate loud clicking sounds while running. These loud acoustic noises may be as loud as 100 dB, the equivalent of a snowmobile next to the patient [2]. Not surprisingly, up to 30% of the patients undergoing MRI procedures had anxiety-related reactions of varying degree of intensity [3]. Interviews performed with younger children and their parents revealed that MRI procedures caused anxiety in children because of their size, design, and sound [4]. Hence, this environment is difficult to tolerate, especially for children. Often, anxious children may become restless during the examination, leading to uncontrolled movements resulting in undiagnostic images. As a consequence, this may result in a premature termination of the procedure itself, requiring the examination to be repeated ulteriorly, thus causing subsequent episodes of anxiety [4-6].

As a result, it is becoming common practice in radiology departments in many hospitals to require conscious sedation, as the frequency of repeated MRI scans is higher in the pediatric population [5-7]. However, sedation is not without any risk or consequences. Emerging evidence suggests that sedation in children might have long-term neurocognitive side effects, in addition to the short-term procedure-related risks [8]. As some authors also pointed out, its use is also related to an increased amount of fear in children and their parents and will require extended hospital stays for monitoring, adding to the cost burden [9].

Similar to any medication, there is always a risk of adverse reactions. Therefore, several efforts have been directed into the development of nonpharmacological methods to reduce fear and anxiety in children requiring MRI scans. Many interventions ranging from music and artwork to video games have been used and deemed useful to relieve anxiety in children during an MRI examination [10,11]. Interventions performed before the scan have also been investigated. Among these, preprocedural patient education has been shown to decrease anxiety and enhance comprehension of MRI examinations, which in turn, can serve to increase patient collaboration [12]. However, different education material can have different effects on reducing anxiety levels [13]. Mock MRI scanners, which involve using a full-size replica scanner for a 5-minute training session to lie still, have been used to help explain to children what the procedure involves and what to expect in an age-appropriate manner. This preparation has been reported to reduce MRI examination–related procedural anxiety, rate of motion artifacts, need for sedation, overall duration of the study, as well as a decrease in heart rate during the procedure [14,15]. However, a shortcoming of the use of mock replicas is that there is limited availability in hospitals, because the mock MRI machine would require a room to be stored in, as well as additional resources, including staff and time, to organize these sessions.

Physical mock sessions before MRI scans have shown promising results. Therefore, virtual reality (VR) used to replicate an MRI environment can also be used as patient preparation [16]. Preprocedural VR education has been studied in different medical procedures, including chest radiography, dental procedures, anesthesia, and surgeries [5,17,18]. These studies show that VR preparation helps improve procedural experience among pediatric patients by reducing anxiety, distress, and procedure time while increasing parents' satisfaction. VR is a novel technology gaining popularity in pediatric hospitals worldwide for a variety of reasons. It is a distraction method that has proven effective in reducing pain and anxiety in children in different settings such as phlebotomy, wound care, chemotherapy, dental procedure, and bone pins removal [19-23].

To the best of our knowledge, very few studies have looked at the effect of VR on anxiety in children scheduled for an MRI scan specifically and how this intervention could help identify which children are more responsive to VR. As VR technology is becoming progressively more accessible, we believe that incorporating a VR preparation tool ahead of time to familiarize children before the MRI procedure would help decrease anxiety; increase patient collaboration; decrease the need for sedation; and improve satisfaction for the patient, family, and health care professionals.

Aims of the Study

The aims of this study are 3-fold: (1) develop an algorithm of predictability based on biofeedback, (2) address feasibility and

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acceptability of a preprocedural immersive VR (IVR) game preparation before an MRI procedure for children's anxiety (field test phase), and (3) examine the efficacy of a preprocedural IVR game preparation compared with usual care for the management of procedural anxiety in children undergoing an MRI examination (by conducting a randomized controlled trial [RCT]).

Hypothesis (for Scientific Validation)

We believe that an IVR intervention in the form of an interaction-enabled video game to prepare participants before an MRI examination is easy to use and could help decrease MRI examination–related procedural anxiety in children aged 7 to 17 years. We believe that a patient who follows instructions well, without any signs of anxiety detected by physiological parameters, will have better results in the MRI procedure than a patient who has difficulty following instructions or who shows signs of anxiety through their physiological parameters.

Objectives

The primary research question concerns whether preprocedural interaction-enabled IVR game preparation will decrease MRI examination–related procedural anxiety for children undergoing an MRI procedure. The secondary objectives of the scientific clinical validation phases are as follows:

1. To determine whether preprocedural IVR game preparation is a feasible and acceptable nonpharmacological method to decrease MRI examination–related procedural anxiety.
2. To determine whether children experiencing preprocedural IVR game preparation will have a slower heart rate before and during the MRI procedure than children not exposed to the IVR game preparation.
3. To determine whether children experiencing preprocedural IVR game preparation will require lower need for sedation than children not exposed to the IVR game preparation before an MRI examination.
4. To determine whether children experiencing preprocedural IVR game preparation will require rescheduling of the examination less often than children not exposed to the IVR game preparation before an MRI examination.
5. To evaluate the occurrence of side effects with preprocedural IVR game preparation in comparison with children not exposed to the IVR game preparation before an MRI examination.
6. To compare satisfaction levels of health care professionals between preprocedural IVR game preparation and usual care groups.
7. To compare satisfaction levels of children and parents between preprocedural IVR game preparation and usual care groups.
8. To compare overall procedure time required for an MRI examination between preprocedural IVR game preparation and usual care groups.
9. To develop a predictability algorithm that will help identify which children will have better results in the MRI procedure after the IVR game preparation.

Methods

Design

This study will have 2 phases. We will first conduct a field test with 10% (10/100) of the total sample size calculated to initiate the development of a predictive algorithm for biofeedback solution requiring actual participants and to address the feasibility and acceptability of the VR intervention and research process. The field test phase will follow the steps indicated in this protocol. Any changes needed will be made between the end of the field test and the start of the RCT. No changes will be made once the RCT starts. After the field test, we will proceed to a scientific clinical validation based on an RCT design using a parallel design with 2 groups: an experimental group (preprocedural IVR game preparation) and a usual care group (standard care as per the protocol of the radiology department) in an equal ratio of 49 participants per group for a total of 98 participants, including a correction for an attrition rate of 24.9% (48/193) that allows for delays and repetitions of procedures, established according to the 2020 radiology records at the study setting.

Sample and Setting

Recruitment will be carried out at Centre Intégré Universitaire de Santé et de Services Sociaux de l'Est de l'Île de Montréal, Quebec, Canada, a general care hospital with a pediatric unit and services. Participants will be identified through the radiology information system as having an appointment for an upcoming MRI procedure. A research nurse will be notified by the radiology technologist and will proceed to contact the parents for recruitment ahead of time before their arrival at the radiology department. On the day of the appointment, parents will be approached to sign the consent if they still agree to the study. Assent from the child will also be obtained on the same day. Of note, owing to the COVID-19 sanitary crisis, availability of recruiting personnel, and the difficulty of movement between units and departments, recruitment will be limited to the radiology department. According to the statistics in 2020, a total of 145 MRI procedures were prescribed for children aged 7 to 17 years at this setting, but in reality, 193 procedures were carried out because of delays and repetitions of procedures. Thus, an attrition rate of 24.9% (48/193) was considered in the calculation of the sample size.

Inclusion Criteria

Children and their parents will be invited to participate in the study if they meet the following inclusion criteria: (1) aged 7 to 17 years; (2) required to undergo an MRI procedure; and (3) accompanied by a consenting parent or legal guardian who can understand, read, and write either French or English.

Exclusion Criteria

Participants will be excluded from the study if they (1) are diagnosed with epilepsy or any other condition preventing them from playing a VR game or (2) cannot tolerate a sitting or semiupright sitting position (Fowler position) during the preparation because the VR gear requires an angle of at least 30° for head tracking. Participants who received anxiolytics (eg, benzodiazepines) in the last 24 hours before the MRI

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procedure will not be excluded, but the names and dosages of the medication and time of administration will be documented in the data collection form.

Interventions

Standard preparation as per the radiology department's protocol will serve as the control (usual care) group.

Preprocedural IVR game preparation will serve as the intervention group.

Control Treatment

The usual care group will only receive the standard preparation, which comprises of an explanation of the MRI procedure given by the radiology technician as per the radiology department's protocol. The research nurse will be able to complete any information should they find it incomplete or substandard.

Experimental Treatment

The preprocedural IVR game preparation (IMAGINE) was developed by Paperplane Therapeutics (an intervention development team). IMAGINE is an IVR simulation game intended for young patients aged 7 to 17 years who will undergo an MRI examination. It aims to reduce anxiety and phobic reactions of young patients and to better prepare them for this examination. As the game is a preparation, it is a no-success game and is independent of the child's ability and previous experience with video games. IMAGINE is designed to be supported by stand-alone VR headsets such as Oculus Quest and Pico Neo II. This preprocedural IVR game preparation offers an immersive and fun simulation that aims to desensitize young patients to MRI procedures and transform an anxiety-inducing experience into a fun play session. From a game point of view, the patient takes a seat aboard a spaceship. The child will have to complete various quests to activate the MRI machine, which is portrayed as a very useful device for the crew members as it will enable them to promulgate the appropriate medical care. The participant will learn about the main principles of MRI procedures and experience a very realistic simulation of the MRI examination. It is developed with personalized care content tailored to children to maximize the feeling of immersion and minimize cybersickness. The preprocedural IVR game preparation is approved by a team of health care professionals in pediatric care.

IMAGINE includes an interaction-enabled VR replica of the inside and outside environment of the scanner, including visual and audio effects of an actual MRI examination, to allow the child to be exposed to the MRI journey in a fun and interaction-enabled way before the examination using the Pico Neo II VR Helmet. This will allow children to prepare for the MRI scanner by enabling them to experience the process of undergoing an MRI examination beforehand, thereby improving their understanding of upcoming events and eventually prevent, decrease, or control preprocedural and MRI examination–related procedural anxiety. The simulation already contains a cursor in the center of the patient's field of view and follows the head movements. A round target inside the replica of the MRI device tells the patient how to place their head in the neutral position and gives positive feedback when done. During the simulation, head movement information will be extracted from the positioning cameras, accelerometer, and gyroscopes already available in the headset. A VR tour session will be available in the waiting area for patients and parents before the MRI procedure. An approved and validated device (such as Thought Technology [24]) will also be used during the simulation to continuously record biofeedback data such as heart rate, skin conductance, hand temperature, and muscle tension. We will also ask participants to undertake the IVR experience and complete a questionnaire to assess the acceptability, feasibility, and incidence of side effects related to the intervention and the biofeedback device. In the likely event of an episode of dizziness, nausea, or vomiting, the child will be provided with proper care in accordance with the unit's protocol and will immediately be removed from the IVR. According to the results obtained, we will adjust the protocol and then proceed to the scientific clinical validation to evaluate the efficacy of this preprocedural IVR game preparation in the management of MRI examination–related procedural anxiety in children and to develop a predictability algorithm. The VR intervention will last for 15 to 20 minutes, which is considered an adequate amount of time to maintain a child's attention and allow for a complete experience of the MRI procedure, including the room's environment and audiovisual stimuli. While the child plays with the interaction-enabled IVR game preparation, there is also the option to allow parents to observe what the child is viewing through their headgear on a separate screen. Unfortunately, due to lack of physical space within the preparation room, only 1 parent will be able to assist during the VR session.

Study Time Points

Sociodemographic and clinical characteristics will be assessed in the waiting room to establish baseline at T0. Measures of procedure-related anxiety with the State-Trait Anxiety Inventory for Children, French-Canadian version (STAIC-F; score 1-3) and also the Children's Fear Scale (CFS; score 0-4) will be taken before the intervention (T0), immediately after the intervention (T1), and after the MRI procedure (T2). A measure of the level of satisfaction of health care professionals, parents, and participants through a questionnaire developed and pretested by the team will also be collected at T2. Physiological signs such as heart rate, skin conductance, hand temperature, and muscle tension through an electromyogram will be collected throughout the simulation. Data will be collected on the occurrence of side effects throughout the study. Clinical monitoring will be performed by an independent nurse from the research team.

Ethics Approval

Ethics approval (2022-2554) was obtained in March 2022 by the Ethics Board of the CIUSSS de l'Est-de-l'Île-de-Montréal.

Measures and Outcomes

Sociodemographic and Clinical Questionnaire

Demographic and clinical characteristics will be assessed with parent reports filled out by the research nurse using the case report form and will include data on age, sex, ethnicity, reason for MRI imaging study, and history of imaging studies, including MRI, computed axial tomography scans, and x-ray

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examinations. Data such as name, dosage, and time of administration of anxiolytics taken 24 hours before the MRI examination will be collected. The questionnaire will also include a section describing the context of the procedure including adherence to the intervention, total procedure time, use of other nonpharmacological interventions, and the occurrence of side effects.

Criteria for Feasibility Assessment

The field test phase will be assessed for feasibility using the CONSORT (Consolidated Standards of Reporting Trials) checklist for pilot studies to determine whether proceeding to the full study is possible. Any modification needed to the collection process will be carried out at this stage. No modification will be carried out once the RCT starts.

Primary Outcome

The primary outcome will be the mean difference in State anxiety at T2 for both study groups as measured by the S scale of the STAIC-F.

Measures of Primary Outcomes

The level of State anxiety (primary outcome) will be assessed using the State Scale of the STAIC-F questionnaire [25,26]. The STAIC-F (Multimedia Appendix 1 [25,26]) is a self-report instrument inspired by the State-Trait theory extended by Spielberger [27] that measures a momentary state of anxiety (state) and a stable tendency to experience anxiety (trait). The same author obtained internal consistency of coefficients of 0.87 for girls and 0.82 for boys [25]. The first 20 items constitute the situational (State) anxiety scale. The response "almost never" is graded 1, the response "sometimes" is graded 2, and the response "always" is graded 3, for a total score varying between 20 and 60 [26]. The next 20 items deal with Trait anxiety. The quotation is identical. A table is provided, which presents the average scores by age and sex. A score can be considered high when the child is ≥1 SD from the mean. It is typically completed in 8 to 12 minutes for initial evaluation, and subsequent evaluations typically require 5 to 7 minutes. The scale was developed specifically for use for children aged 9 to 12 years but can be used in younger children if the scale items are read out loud to them, as well as for older children [25]. Participants will rate their State-Trait anxiety with the French-Canadian version 40-item questionnaire (STAIC-F) in the waiting room (T0). The first 20 items, which correspond to situational anxiety, will be reassessed after the intervention (T1) and after the MRI examination (T2). Psychometric studies of the STAIC-F show excellent internal consistency coefficients of the State-Trait Anxiety Inventory for Children (STAIC) scales, with Cronbach α values of .89 and .88, respectively, and the test-retest reliabilities after a 6-month period were also similar to those of the original version, and the concurrent validity, assessed by the correlation with the Revised Children's Manifest Anxiety Scale, was also found to be good [26]. A study investigated MRI examination–related anxiety in children using the English shortened-version of the STAIC scale for children aged 8 to 15 years [28], and 2 other studies examined MRI examination–related anxiety using the standard English STAIC scale for its robust psychometric properties for children aged 8 to 17 years and 12 to 18 years [29,30]. Considering the French-speaking population targeted in this study, the psychometrically sound properties of the French-Canadian version, and previous studies using the STAIC questionnaire to evaluate MRI examination–related procedural anxiety, we believe that it is justified to use this questionnaire in this study for children aged 7 to 17 years to evaluate their levels of anxiety.

The level of anxiety will be also assessed using the CFS [31] at baseline before the preprocedural IVR game preparation or usual care intervention (T0), immediately after the intervention (T1), and after the MRI procedure (T2; Multimedia Appendix 2). The CFS is a self-reported measure of anxiety adapted from the Adult Faces Anxiety Scale [32] for specific use in children undergoing painful experiences. It consists of 5 faces ranging from 0 (*no fear or anxiety*) through 4 (*extremely fearful or anxious*). The child is asked to indicate which face shows best how they felt during the procedure. Test-retest reliability has been established with children aged 5 to 10 years during painful procedure (r_s=0.76) and concurrent validity with the Children Anxiety and Pain Scale (r_s=0.73) [33]. We chose the CFS because of its psychometric qualities and because it is a 1-item self-measure of anxiety and fear. Moreover, "although fear tends to decrease with age in general, medical fears may be an exception" [34]. In addition, "age-related differences in fear ratings have not been found" [35]. Furthermore, this scale has been used with children aged 8 to 18 years for procedural fear related to venipuncture [36] and children aged 11 to 13 years for fear of, and anxiety regarding, vaccination [37].

Secondary Outcomes

The secondary outcomes were (1) mean difference in the sense of presence and engagement (immersion) into the VR game between groups (T1), (2) the presence of head deviation during the intervention, (3) changes in physiological signs through biofeedback during the intervention, (4) satisfaction levels of parent (T2), (5) satisfaction levels of children (T2), (6) satisfaction levels of health care professionals (T2), (7) occurrence of side effects, (8) mean difference in total procedure time and frequency of rescheduling MRI examinations between groups, and (9) mean difference in Trait anxiety levels between groups.

Measures of Secondary Outcomes

The secondary outcomes were measured as follows:

1. The sense of presence and engagement (immersion) in the VR game will be assessed using the Graphic Rating Scale (GRS) [38-40], a 7-item Likert-type scale tailored for VR interventions. Convergent validity among pairs of scores of the GRS with children aged 8 to 17 years was *r*=0.84 and test-retest reliability was 0.91 [40].
2. The head deviation during the simulation will be measured continuously for the entire duration of the intervention through the positioning cameras, accelerometer, and gyroscopes in the headset.
3. Physiological signs and biofeedback (heart rate, skin conductance, hand temperature, and muscle tension via an electromyogram) will be measured using the biofeedback device that will continuously capture and record

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physiological signs. The research nurse will note the heart rate measures at T0; immediately after T1; and at 1, 5, 10, and 15 minutes of the MRI procedure. Increased heart rates may indicate physiological arousal or may be a consequence of "positive stress" [41].

4. Satisfaction levels of the parent will be assessed using a 0 to 10 numerical scale to answer the following question as recommended by Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) [42]: "Considering anxiety relief, side effects, and emotional recovery, how satisfied were you with the treatments your child received for anxiety?"
5. Satisfaction level of the children will be assessed using a 0-to-10 numerical scale to answer the following questions: "How fun is the game?" "Did the game help you feel less scared during the MRI examination?" and "Will you recommend this game to other children who have to go through the same examination as you?"
6. Satisfaction level of the health care professional will be assessed using a tailored questionnaire with a 4-choice response scale from strongly agree to strongly disagree for 7 items related to their level of satisfaction with the intervention and its effects on the procedure.
7. Occurrence of side effects will be assessed and documented from enrollment until discharge.
8. Procedural time and number of rescheduled MRI examinations will be noted in the clinical questionnaire.
9. Trait anxiety level will be measured using the T scale of the STAIC-F.

Sample Size and Statistical Analysis

Sample Size Consideration

Primary analysis will involve the comparison of 2 group means. In addition, no interim analysis will be conducted. Therefore, group sample sizes of 37 (ie, 74 in total) are necessary to achieve 80% power to reject the null hypothesis of equal means when the population mean difference for State anxiety score is 5 with an SD for both groups of 7.47 [28] and a significance level (Cronbach α) of 5% using a 2-tailed *t* test. The SD for both groups varied from 4.61 to 7.47 [28]. To be conservative, we chose 7.47. On the basis of data from the medical imaging registry, the attrition rate was approximately 24%. Assuming a similar attrition rate, 98 participants (49 per group) will be required. The sample size calculation was performed using PASS Software (version 12.0; NCSS Statistical Software).

Statistical Analysis

Analyses will be conducted using SAS statistical analysis software (version 9.4; SAS Institute Inc). Descriptive statistics will be conducted for sociodemographic and clinical variables and presented by treatment group.

Primary Outcome Analyses

An analysis of covariance (ANCOVA) adjusted for age, sex, baseline (T0) Trait anxiety score measurement, and baseline State anxiety score measurement will be used to assess the mean difference in State anxiety scores on the STAIC-State between the experimental and the control groups at T2. Analyses will be carried out according to the intention-to-treat principle, with a significance level (Cronbach α) of .05.

Secondary Outcome Analyses

An ANCOVA adjusted for age, sex, and baseline anxiety score measurement will be used to assess the mean difference in anxiety scores on the CFS, between the experimental and the control groups at T2. To assess the mean difference in the sense of presence in VR and engagement into the game (GRS), between the experimental and the control groups at T1, an ANCOVA adjusted for age and sex will also be conducted. We will use a linear mixed model to estimate the effect of the treatment on the changes in heart rate over all assessment time points. This analysis will be adjusted for age, sex, and baseline heart rate. Differences between arms for levels of satisfaction of parents, children, and health care professionals (T2) as well as the overall procedure time will be assessed using (2-tailed) *t* tests or nonparametric Mann-Whitney *U* tests if data are nonnormal. A chi-square test or Fisher exact test will be conducted to compare dichotomous variables including the occurrence of side effects, the number of rescheduled MRI examinations, and the use of sedation in each group.

Adverse events and serious adverse events (if any) will be reported using the Medical Dictionary for Regulatory Activities terminology, and their proportions will be compared between the groups.

To help develop the predictability algorithm, the head deviations and other physiological data will be analyzed. An algorithm based on those deviations will be developed prospectively as the study progresses to evaluate the success of the MRI procedure in the intervention context and offer useful predictability inputs in preparation for the real MRI examination. No existing algorithms specific to the study were found. The physiological data will also help create a time sequence that could be matched with the information that will be extracted from the intervention. At the end of the session, it will be possible to see if, for example, a movement of the patient is generally triggered by an increase in stress as captured by the sensors. The result of the examination will then be compared with the data obtained during the intervention. The team will attempt to determine which variables correlate with the real-life outcome. Our hypothesis is that a patient who can follow the instructions well without any signs of anxiety captured by physiological parameters will have better results in the MRI procedure than a patient who has difficulty following the instructions or who shows signs of anxiety expressed through their physiological parameters.

Study Proceedings (Clinical Validation Phases)

Participants will be identified through the radiology information system as having an appointment for an upcoming MRI procedure. Either the physician prescribing the MRI examination or the radiologist will have indicated certain patients as not needing sedation during the MRI examination and thus identified as eligible for this study. The research nurse will be notified by the radiology technologist and will contact the parents for recruitment a few days before the procedure. On the day of the appointment, parents will be approached to sign the consent if

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they still agree to the study. The child's assent will also be obtained on the same day. Participants are informed of their assignment to either the preprocedural IVR game preparation or usual care group after randomization. Before initiation of the procedure, the research nurse will explain the intervention to the patient and install the IVR game preparation and start the video game program. Baseline measurements of anxiety will be taken before the interventions in the waiting room (T0).

The research nurse will log in 10 minutes before the IVR video game preparation or usual care interventions to obtain the group allocation of the participant if they meet all eligibility criteria. Given the nature of the interventions, the participants and personnel cannot be blinded to the interventions. However, to minimize observer bias given the subjective measures of outcomes, parents and children will only be informed to which group they are assigned 10 minutes before the intervention. Data will be collected on paper forms and then the information will be transferred into REDCap (Research Electronic Data Capture; Vanderbilt University) by a research nurse. Data on game completion by the child will be recorded but no data will be collected on specific game inputs. Furthermore, although a separate screen allows research staff and parents to watch the child's perspective, none of it will be recorded. The paper copies of the data forms will be kept locked. The data will be reviewed by a data manager to check for possible errors. The informed consent, assent, and baseline data collection will require approximately 10 minutes. After randomization, the IVR game preparation intervention will last for 15 to 20 minutes. Postintervention data collection will require approximately 10 minutes. In total, the duration of the intervention period, from recruitment to discharge, will be 30 to 40 minutes for each participant. Time has been allocated to the clinical workflow to allow for the research nurse to clean the VR technology before the arrival of each new patient.

Data collection forms of the participants will be stored under a double lock at one of the principal investigators' office at the research center and will be kept for 7 years after the end of the trial. As this is an open-label clinical trial and no prior data suggest that any of the 2 interventions are associated with side effects, a data monitoring committee is not required. However, the occurrence of any side effects will be reported to the ethics committee. VR technology such as a head-mounted display (eg, Pico Neo II VR Helmet) has the potential to cause motion sickness, including discomfort, disorientation, and nausea. To overcome this issue, the development team specialized in immersive technology had previously developed a game that fully maximizes the experience of immersion and the sense of being in a virtual environment while minimizing motion sickness. During a previous pilot study using this VR game, no participant reported motion sickness symptoms while using IVR [43].

Privacy and Confidentiality

A consent form will be presented by a research nurse to participants and their parents or legal guardian to clearly explain the use of the VR technology, its expected benefits and adverse effects, and any necessary information that may be collected for research purposes.

Results

Recruitment began in April 2022. As of May 10, 2022, only 1 participant for the field test was recruited. No participant for the clinical trial has been recruited as yet. The data collection time frame is projected to be between April 1, 2022, and March 31, 2023. The study period will end in April 2024. The findings will be disseminated through peer-reviewed publications.

Discussion

Feasibility of the Study

The feasibility and acceptability of the research protocol will be addressed in the field test phase, which will be followed by a parallel design RCT with 2 groups. The development of a VR game preparation tool can help increase patient collaboration by distracting and calming children before entering the MRI examination room, which in turn will decrease the number of failed tests and repeat tests and hence increase the efficiency of the radiology department. We believe that the use of VR in the pre–MRI examination setting in the form of a fun and interaction-enabled video game can help reduce MRI examination–related anxiety in children by familiarizing them with the MRI environment. Very few studies in the field have investigated the effect of VR preparation for MRI scans for children, but the use of a VR-environment education tool before radiotherapy in adults has shown promising results such as improved education, reduced anxiety, and improved patient-reported satisfaction by improved comprehension of the medical procedure [12]. Other studies have also used VR exposure as a preparation tool for elective day-care surgery in children, and results suggest lower levels of anxiety, pain, and emergence delirium compared with control groups receiving care as usual [17]. Similarly, children often fear and apprehend dental visits. Researchers are investigating the use of IVR as a familiarization tool before dental visits to improve the experience of children. It is expected that by using a VR tool, children will become less fearful by becoming more familiar with what to expect, which in turn can decrease the number of missed dental visits [44]. As demonstrated by most up-to-date breakthrough studies, VR game preparation is a promising venue and this ideology resonates with the aim of this study, which is to broaden and confirm the beneficial use of VR game preparation in anxiety-related MRI procedures.

Clinical Trial

Our study's field test phase followed by a larger RCT aims to transpose and demonstrate the beneficial effect of VR game preparation for MRI procedures because its use has already been shown to improve patient satisfaction in other anxiety-related medical procedures (as previously mentioned). To our knowledge, no algorithm has been developed to identify children who are more likely to be responsive to VR intervention. The study team aims to develop this innovative biofeedback algorithm through data collection and analysis. This is a scientific breakthrough, in that the development of such an algorithm can potentially identify modifiable participant factors that future research studies can address to potentialize future use of VR interventions in the medical field. Furthermore, this

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project will provide evidence-based knowledge on a nonpharmacological method for anxiety management for patients required to undergo MRI studies through an innovative intervention. Our study provides an alternative method to manage anxiety and better prepare patients for an awake MRI procedure. The preprocedural IVR game preparation can potentially decrease the need for sedation by educating the child about the MRI procedure. The biofeedback will also help predict which children are more responsive to this type of intervention. It is expected that the experimental group, as demonstrated in other studies, will experience less procedural anxiety after VR game exposure, which will be featured in this study with analogous physiological parameters (eg, slower heart rate), and a smaller number of terminated MRI studies as increased patient collaboration will reduce anxiety-related movement artifacts. Positive participant and health care worker satisfaction levels will also encourage the use of VR game preparation in other anxiety-related medical procedures in the future. As opposed to physically bulky replica scanners that can be used only on the day of the procedure to help prepare children for MRI studies, our intervention is more versatile and user friendly. As VR technology is becoming more accessible to the public, our VR game preparation can be experienced using portable VR goggles at home before the day of the MRI procedure. As most patients requiring an MRI examination come from an outpatient setting, the portability of our intervention requires less on-site time and staff to organize and operate the replica scanner on the day of the imaging study. Thus, the VR game preparation that our team developed can increase patient turnover in the radiology department, shorten the waitlist for other patients requiring MRI examinations, and facilitate medical access. Participants will have an increased comprehension of the MRI study, and this positive association with medical equipment can further benefit and improve children's experience with hospital settings.

Benefits for Study Participants

We strongly believe that IVR is an innovative intervention that could be offered to most of the children scheduled for a medical imaging procedure. For children eligible to use VR, and their family, it provides a more immersive preparation and could decrease their anxiety by exposing them to a better preparation to the intervention ahead of time. It is an easy-to-use intervention that could be set up in a few minutes and that does not require an additional resource to make it work.

Preprocedural IVR game preparation may help reduce MRI examination–related procedural anxiety in children receiving care, increase satisfaction rate of families whose children receive care and reduce intervention time or repeats required for MRI studies. As for medium- to long-term impact, there is reduced fear in the hospital environment, reduced anticipation of the recurring imaging study procedures, and improved quality of care for children.

Challenges and Limitations

Recruitment of the necessary sample size of patients may be difficult to estimate because cases requiring MRI examinations happen randomly. Furthermore, the game used during this study was designed by the intervention development team to be engaging for our target audience, to be easy to use within the parameters necessary to the completion of the study, and to minimize cybersickness. As a result, conclusions from this study may be difficult to extrapolate outside of our own controlled setting and may need the same game or another one designed with the same parameters in mind.

Conflicts of Interest

None declared.

Multimedia Appendix 1
French-Canadian version of the State-Trait Anxiety Inventory for Children (STAIC-F).
[DOCX File , 23 KB - resprot_v11i6e30616_app1.docx]

Multimedia Appendix 2
Children's Fear Scale.
[DOCX File , 45 KB - resprot_v11i6e30616_app2.docx]

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Abbreviations

ANCOVA: analysis of covariance
CFS: Children's Fear Scale
CONSORT: Consolidated Standards of Reporting Trials
GRS: Graphic Rating Scale
IVR: immersive virtual reality
MRI: magnetic resonance imaging
PedIMMPACT: Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
RCT: randomized controlled trial

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REDCap: Research Electronic Data Capture
STAIC: State-Trait Anxiety Inventory for Children
STAIC-F: State-Trait Anxiety Inventory for Children, French-Canadian version
VR: virtual reality

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Protocol

Impact of a Papillomavirus Vaccination Promotion Program in Middle School: Study Protocol for a Cluster Controlled Trial

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Abstract

Background: On Reunion Island, incidence and mortality for uterine cervical cancer is high, yet coverage rate for human papillomavirus (HPV) vaccination is low.

Objective: The main objective of the study is to evaluate the impact of a health promotion program promoting HPV vaccination on the proportion of middle school girls who complete the full HPV vaccination schedule (2 or 3 doses) by the end of school year.

Methods: This study is a cluster controlled intervention study using a superiority design. A combined health promotion program will be offered containing information to students and parents, training of general practitioners, and free school-based vaccination (in a "health bus"). Children who attend this program will constitute the intervention group and will be compared to children from another middle school who will not attend the program constituting the control group.

Results: Recruitment began in October 2020. In the intervention school, of 780 students, 245 were randomly selected in the 12 classes. In the control school, 259 students out of 834 were randomly selected.

Conclusions: In this study, we explore the impact of a health promotion program combining information toward students, parents, and general practitioners with free school-based vaccination. We expect a significantly higher HPV vaccination coverage in the intervention school as compared to the control school, whether it be among girls or boys. The final implication would be an extension of this program in all middle schools on the Island and thus an increase in HPV vaccination coverage.

Trial Registration: ClinicalTrials.gov NCT04459221; https://clinicaltrials.gov/ct2/show/NCT04459221

International Registered Report Identifier (IRRID): DERR1-10.2196/35695

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KEYWORDS

HPV vaccine; vaccination program; middle school; school; student; women's health; sexual health; cervical cancer; vaccination; papillomavirus; vaccine; public education; patient education; community education; promotion; program; youth; children; protocol; mortality; uterine cervical cancer; cancer; HPV; health promotion; girls; school; intervention; parent; training

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Introduction

Background

On Reunion Island, a French territory located near the eastern coast of Madagascar in the Indian Ocean, uterine cervical cancer is the fourth most common cause of cancer in women, similar to worldwide [1]. However, the standardized incidence rate in 2016 was 8.8 in 100,000 women, 2 times higher than in metropolitan France. The standardized mortality rate follows a similar trend: on Reunion, it accounts for 4.8 in 100,000 women, whereas the metropolitan rate was 1.7 in 100,000 women [2,3].

Cervical cancer results from human papillomavirus (HPV) infection, which is the most common viral sexually transmitted infection. There are more than 100 types of HPV, some of which are high-risk oncogenes, such as HPV 16 and HPV 18, which are responsible for 70% to 80% of invasive cervical cancers [4]. On Reunion Island, most frequent HPV genotypes are HPV 16, HPV 52, HPV 33, and HPV 31, all contained in the nonavalent HPV vaccine [5].

Indeed, prevention of cervical cancer is mainly based on screening by cervical HPV test and on HPV vaccination, which has proven to be effective in reducing the prevalence of HPV transmission but also in reducing the incidence of condyloma and intermediate grade dysplasia [6,7]. Since HPV is mainly transmitted sexually, it is important to vaccinate before the beginning of sexual life.

Because HPV infections can also lead to vulvar, vaginal, penile, anal, or throat cancers, some countries (eg, United States, Canada, Australia, Germany, Austria, Belgium, Italy) recommend gender-neutral vaccination in order to promote herd immunity and reduce circulation of the virus in the general population [6,8]. In France, since December 2019, it is recommended that HPV vaccination should be offered to all children, regardless of their gender, aged 11 to 14 years (2 doses), with catch-up vaccination possible for adolescents aged 15 to 19 years not yet vaccinated (3 doses). Before December 2019, vaccination was only recommended for girls. High levels of vaccination coverage are obtained in countries that vaccinate in schools [9-11].

On Reunion Island, the HPV vaccination coverage rate is the lowest in France, estimated at 8.1% among girls aged 16 years in 2018, while the national average is already low (23.7%) [12].

This low coverage rate on Reunion Island may have several explanations. First, inhabitants seem to be poorly informed about the existence of this vaccine [13]. Moreover, vaccination coverage rates depend on the socioeconomic level of the population. In France, lower rates of HPV vaccination uptake were observed in adolescents with universal health insurance coverage (French equivalent of the US Medicaid program) compared with those not receiving such insurance [14]. Reunion Island is one of the French departments with the highest rates of inhabitants covered by this universal health insurance. Finally, not only is there vaccination hesitancy in general but also most specifically against HPV vaccine, among patients and also among physicians [13]. A total of 41% of Reunion inhabitants hold unfavorable opinions about vaccinations, with the HPV vaccine being among the most frequently cited. Among patients not vaccinated against HPV, 37% stated that the vaccine had not been suggested to them by their doctor, and 7.3% were confronted with doubts expressed by their doctor concerning vaccination in general [13]. However, a systematic review of 79 studies in 15 countries showed that the most important factor influencing HPV vaccination was physician recommendation [15,16]. Indeed, 89.3% of the Reunion population fully trusts their doctor [13]. Therefore, interventions targeting health professionals and especially general practitioners appear to be paramount, especially when combined with interventions targeting the population to be vaccinated [17].

Thus, given the epidemiological situation on Reunion Island (high incidence and mortality for cervical cancer, very low coverage rate for HPV vaccination), we aimed to study the impact of a prevention program against sexually transmitted infections, including pathologies related to HPV, with a program promoting HPV vaccination among young students in middle school.

Objectives

Hypotheses were as follows: (1) clear and appropriate information for the target population of the vaccination (middle school students aged 9 to 17 years) as well as for their parents will improve their knowledge about HPV vaccination and thus increase their adherence to this vaccination regimen, (2) combining information with vaccination in the school setting will improve coverage, as it will reduce any material obstacles that may prevent the vaccination process, and (3) raising awareness among general practitioners will enable them to better understand the benefits and risks of HPV vaccination and thus encourage families, who naturally trust them, to adhere to the program.

The main objective of the study is to evaluate, in a population of middle school girls on Reunion Island, the impact of a health promotion program on the proportion of middle school girls who complete the full HPV vaccination schedule (2 or 3 doses) by the end of school year.

The program, conducted during school year, will combine: (1) sexual health promotion (students and parents) during classes at school at the beginning of school year, (2) training of general practitioners (who practice in a perimeter of 5 km around the middle school) on HPV vaccination at the beginning of school year, and (3) free school-based vaccination (in a “health bus”) during the academic year.

Secondary objectives in the study population at the end of school year are as follows:

- Assess the impact of the combined health promotion program on the proportion of middle school girls who initiated HPV vaccination (at least 1 dose)
- Assess the acceptability of the HPV vaccination program among middle school boys
- Describe the barriers to HPV vaccination for both girls and boys
- Assess the acceptability of HPV vaccination in the school setting

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- Assess the value of setting up a sexual health information point through a health bus
- Evaluate the satisfaction of students, parents, and school workers with the measures put into place
- Evaluate vaccination coverage for different mandatory vaccines according to the current national vaccination calendar

The aim of this study was to evaluate whether a health promotion program combining information and free school-based vaccination could raise HPV vaccination coverage.

Methods

Trial Design

This study is a cluster controlled intervention study using a superiority design. Children who will attend the combined health promotion program will constitute the intervention group and will be compared with children who will not attend the program (as is currently the case in all French middle schools), who will constitute the control group.

Study Setting

This trial will concern Reunion Island in order to investigate the particular epidemiological situation of HPV on the island, even if the results of this study are expected to be applicable to other French regions.

The 2 arms of the trial will be designed to have the most comparable populations and to avoid any risk of contamination between the 2 arms or having general practitioners taking care of children in both schools.

We have thus chosen to carry out a cluster trial. The 2 groups (intervention group and control group) will be selected from a middle schools located in each of 2 cities. In each of the schools, we will randomly draw 3 classes in each grade level (6th, 7th, 8th, and 9th grade) to have a balanced number of students in each arm (see sample size). Thus, 12 classes will be selected for each school.

Provided that there is a relationship between socioeconomic status and vaccination coverage, it was decided to focus the study only on middle schools in priority education zones, which theoretically enroll a population in which HPV vaccination coverage is the lowest. On Reunion Island, 21 middle schools are classified as priority education zones, spread over 7 cities. In agreement with the head of the academy and the school directors, 2 schools have been designated among the abovementioned middle schools: the intervention school will be Paul Hermann Middle School, located in St Pierre, and the control school will be Plateau Goyave Middle School, located in St Louis.

These choices are based on the schools' ability to participate in this research, their geographical location, and the ability to park the health bus at or in the immediate surroundings of the school of the intervention group. The health bus will be provided by the Association d'Education Thérapeutique et d'Intervention Sociale (ASETIS, or Association for Therapeutic Education and Social Intervention), existing since 1996 and recognized as being of public interest.

Eligibility Criteria

Inclusion criteria are as follows: enrolled in one of the classes randomly selected in the 2 middle schools designated, affiliated with or benefiting from a social security system, who will agree to participate in the study and whose parents or holders of parental authority will sign a free, informed, and written consent. Exclusion criteria (intervention group only) are as follows: hypersensitivity to the active substances or to one of the excipients of the vaccine (Gardasil 9), a permanent contraindication to vaccination, pregnant or breastfeeding (based on self-reporting), already initiated HPV vaccination (complete or incomplete schedule), or eligible to participate for collection of data but not for vaccination in the health bus; students with an incomplete vaccination schedule will be referred to their general practitioner to complete the missing doses. Vaccinations will be performed by a junior doctor under the supervision of a senior doctor.

Intervention Description

Intervention Group

Meetings with parents in the intervention middle school will be scheduled at the beginning of school year to inform parents about HPV vaccination and explain this study to them. Consent forms will be collected during these meetings. If assemblies are forbidden by the government because of COVID-19, information meetings for parents will be cancelled. Instead, 6 interventions will be planned.

August-September: Program Information Sent Home to Parents via Students

Written information adapted to student age about HPV vaccination, and documents outlining objectives, interventions, constraints, foreseeable risks and expected benefits of the research, and the rights of the participants in this research context will be sent with children to give to their parents. Consent form to participate to the study to be signed by both parents or holders of parental authority and a sociodemographical questionnaire with questions about HPV knowledge will also be included.

October-November: Contact With Parents and Return of Information to School

Investigation team will call each authority holder individually by telephone to inform them about HPV vaccination, the study, its objective, nature of the constraints, and foreseeable risks and expected benefits of the research. The team will also remind them of the rights of participants in research and will check the eligibility criteria. Finally, when possible, the team will collect their oral consent. Parents will be asked to place the documents (consent form and sociodemographic questionnaire) in an envelope and seal it before returning it to the main teacher for reasons of data confidentiality. Documents will then be collected by the investigation team.

November-December: Data Collection and Student Information Sessions About Sexual Health and Vaccination

Children in the selected classes will be asked to bring in their health record on a specific date, along with the above mentioned documents, for those who forgot to return the envelope to the

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main teacher previously. On that day, an investigator will collect data necessary for the study in the health records (especially vaccination data) for children for whom consent form was signed by the parents. During this time, an information session about sexually transmitted diseases and vaccination will be given in class, lasting approximately 1 hour and adapted to the level of understanding (according to grade and age), in partnership with teachers. Health records will be immediately returned to the students.

November-December: General Practitioner Information Dissemination

A total of 88 general practitioners working in a radius of 5 km around Paul Hermann Middle School will be sent an information leaflet about HPV vaccination and cervical cancer prevention, including the latest literature review, and information about this study. If meetings are forbidden, general practitioners will be invited to a video conference call, "Around HPV," at the beginning of school year.

December, February, and May (3 Campaigns): HPV Vaccination in the Health Bus

Free HPV vaccination will be offered in a health bus for girls and boys. The bus will be parked in the playground, inside the school grounds, allowing students to go there during breaks, lunchtime, or after school. Vaccination periods will be predefined, so that the recommended HPV vaccination schedules can be followed.

Vaccinations will be performed by the medical staff of the University Hospital of Reunion Island (a junior doctor under the supervision of a senior doctor) after informed consent to vaccination signed by either parents or holders of parental authority, who are invited to come along into the bus with their child.

Vaccination will be performed with nonavalent HPV vaccine. The proposed schedule is the one recommended by the marketing authorization: children aged 9 to 14 years (girl or boy): 2-dose schedule (intramuscular), with the second dose to be administered between 5 and 13 months after the first dose; children aged 15 years and older (girl or boy): 3-dose schedule (intramuscular), with the second dose to be administered at least 1 month after the first and the third at least 3 months after the second, with all 3 doses to be administered within 1 year. The vaccine label data will be documented in the health record.

Before vaccination, absence of contraindications will be checked. In case of high fever or acute illness, the vaccination will be postponed and offered at a later date. Vaccinated persons will be monitored for at least 15 minutes after vaccination in the presence of medical staff because of adverse effects that may occur in the direct aftermath of the injection (rare anaphylactic reactions, syncope (fainting) sometimes associated with falls) or psychogenic reaction to needle injection (neurological signs such as transient blurred vision, paresthesias, and tonic-clonic movements of the limbs during the recovery phase). During campaigns in February and May, the first dose of vaccination can be offered, although children will be asked to return to their general practitioner for subsequent doses.

The health bus system will be implemented as part of this study. Two students will be able to be vaccinated at a time. A child will never be left alone with an adult inside the bus; there will always be a minimum of 2 adults present. Students can take advantage of this special time on the bus to receive personalized information on sexuality and obtain free condoms.

June: Data Collection in Randomly Selected Classes

At the end of school year (June), an investigator will collect data from health records at a specific time during class. In particular, the researcher will look for the presence of de novo HPV vaccination performed by general practitioners outside of the health bus. Signed consent of parents or holders of parental authority will be collected before any intervention in the study (ie, before data collection and before school vaccination is carried out).

Vaccination data, even if not collected at the time of the intervention, can be collected either during the vaccination campaigns, or during the intervention at the end of school year, especially for children whose parents have agreed to participate but not to be vaccinated in the health bus. Indeed, since vaccination dates appear in the health record, it will be possible afterward to know whether pupils were vaccinated before the interventions under study in order to have the vaccination rate at the very beginning of the study.

July-September: Evaluation of Satisfaction and Barriers to Vaccination

Research staff will meet with students, parents, members of school staff, and general practitioners who volunteered, and semidirected interviews will be conducted to understand their satisfaction about the study and determine barriers to vaccination.

Control Group

In the control middle school, the study will take place at the end of school year (May-June) in 2 stages.

Parent Information About the Study

We will organize parent meetings to inform them of the study. If no parental meeting is possible due to the COVID-19 pandemic, parents of children in selected classes will be sent an envelope containing written information about HPV vaccination and information about the study, the sociodemographical questionnaire, and the objection form to participate to the study (data collection of health record). Thus, if the form is returned to a teacher, the investigation team will not be able to access the child's health record. On the other hand, if no form is returned, it will be considered that parents do not object to data collection.

Data Collection and Student Information About Sexual Health and Vaccination

Children in the selected classes will be asked to bring in their health record on a specific date, along with the completed sociodemographic questionnaire and signed informed consent for data collection from parents. On that day, an investigator will collect data necessary for the study (especially vaccination data) in the health records for children for whom no objection form was returned. During this time, an information session

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about sexually transmitted diseases and vaccination will be given in class, lasting approximately 1 hour and adapted to the level of understanding (according to grade and age), in partnership with teachers. Health records will be immediately returned to the students concerned.

Participant Timeline

Participant timeline is displayed in Figure 1. In case assemblies are forbidden due to COVID-19 pandemic, parental meetings will be cancelled and an alternative participant timeline is displayed in Figure 2.

Figure 1. Initial participant timeline. HPV: human papillomavirus.

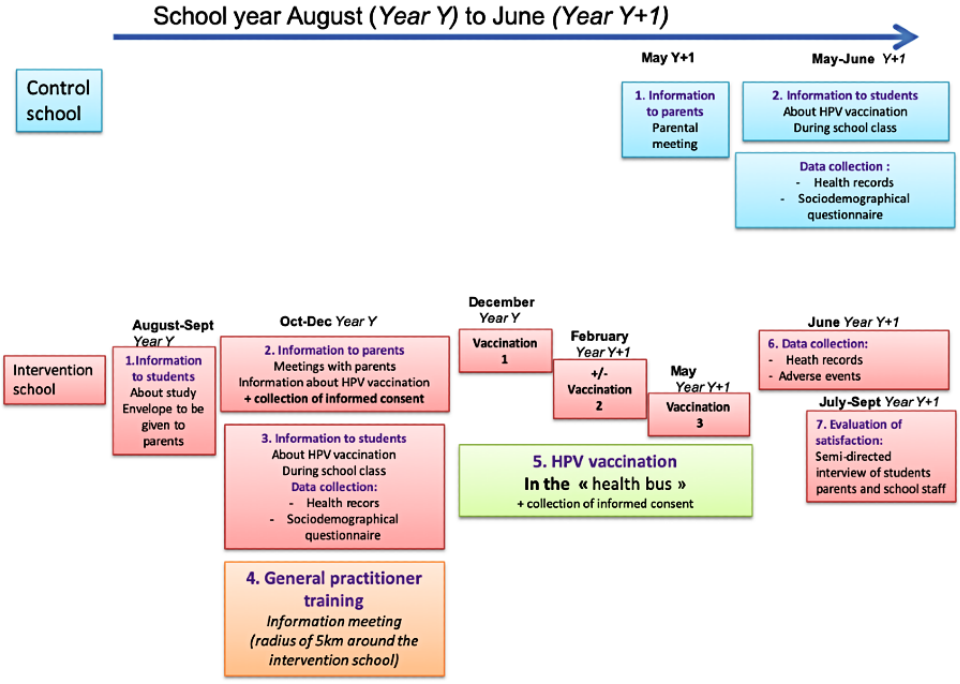
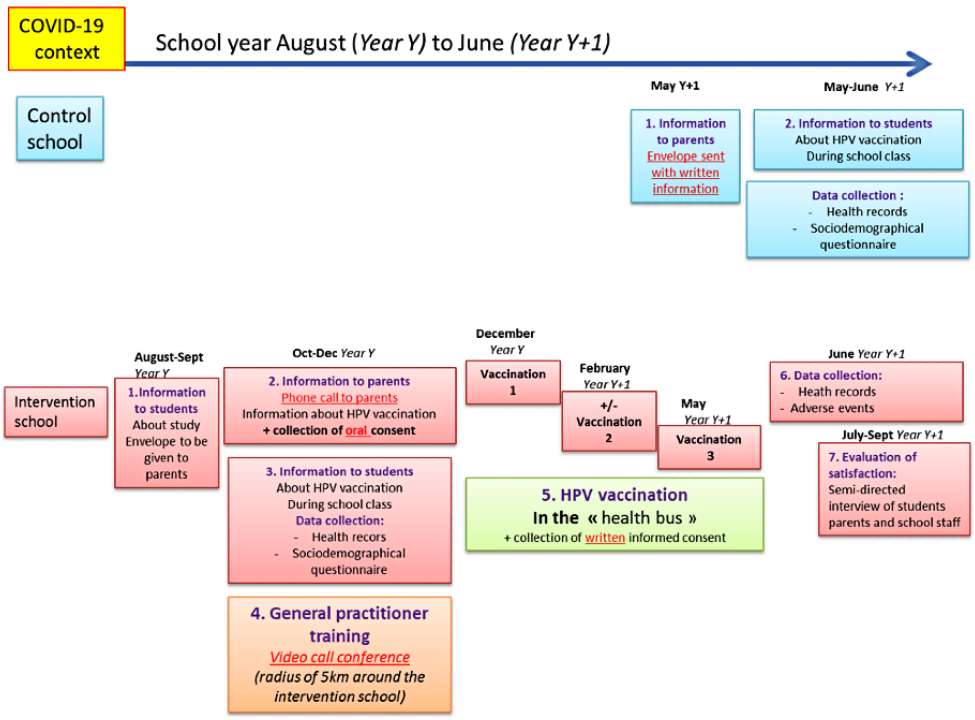


Figure 2. Participant timeline in the context of COVID-19, with meeting restrictions. HPV: human papillomavirus.



Data Collection and Management

Data will be collected in a paper observation book after consent is signed by parents or holders of parental authority and by students. Data will be collected in the form of self-questionnaires (parents and children). Data concerning vaccination status at inclusion and at the end of the study were checked in the health record by the investigation team.

Data will be collected in paper format and will be entered into an electronic case report form (Ennov Clinical) by a clinical

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study technician. Data will be saved daily. A data validation plan, defined jointly by the principal investigator and the Methodology and Data Management Center (from the University Hospital of Reunion Island), will be developed and the controls to be performed will be described in detail for each variable. Once data entry is completed, the data will be checked for consistency. Inconsistencies will be reported in the CS Test module of Ennov Clinical. The data freeze/unfreeze process will be performed according to the procedure set up in the Methodology and Data Management Center.

Plans for Storage of Vaccine

University Hospital of Reunion Island will be in charge of purchasing the vaccine doses and providing them, via the central pharmacy, to the ASETIS health bus at the intervention college. There will be no change in product packaging, which was identical to the packaging at the time of purchase: 0.5 mL glass prefilled syringes with needles. Labeling (in accordance with current regulations and good clinical practice) referring to use in clinical research will be affixed to the boxes of vaccines intended for the study. The products will be brought by a staff member of the ASETIS association on the days of school vaccination.

The products will be transported, respecting conditions of conservation of the vaccine (kept between 2 °C and 8 °C and protected from light). Expiration date will be checked before any injection. Accounting and traceability of the doses given will be documented by the doctors administrating the vaccination. The health bus has the capacity to store the vaccine doses in the appropriate conditions in a refrigerator.

The products will be stored at the central pharmacy in University Hospital of Reunion Island and in the health bus on vaccination days. The unused doses during the first school vaccination campaign (first dose) will be returned to the hospital central pharmacy to be used during the following campaigns. At the end of the vaccination campaigns, the unused or expired doses will be destroyed according to the regulations in force.

Statistical Analyses

Sample Size

To our knowledge, there are no recent studies that have evaluated the impact of school-based vaccination on HPV vaccination coverage rates. An experimental catch-up vaccination program (diphtheria, tetanus, poliomyelitis, pertussis, measles, mumps, rubella, meningococcus C, hepatitis B, and HPV) in schools in the Vosges (Eastern France) [18] showed a participation rate ranging from 42.9% in the first year to 29% in the second year.

The calculation of the study size is based on the expected proportion of vaccination among girls, as this is the main objective of this study and we have no data for vaccination among boys at this time. Statistical assumptions were as follow:

- Proportion of schoolgirls who have had a complete HPV vaccination schedule at the end of school year of 6% in the control group for all students (compared to the 8.1% expected at age 16 years [12])
- Proportion of schoolgirls with a complete HPV vaccination schedule at the end of the school year of 20% in the intervention group

Thus, 87 girls in each group would need to be included to demonstrate this 14% difference at α=.05 and power ($1-\beta$=0.80). Assuming 15% nonanalyzable data (lost to follow-up, nonresponse), a total of 103 female students per group would need to be included. As there are roughly as many girls as boys in each class, we would need to include 206 students per group. In order to have an equal representation of each age group, the sampling will be stratified in the grades: 6th, 7th, 8th, and 9th grade. Thus, 52 students per grade and per group should be included.

If we consider that the classes contain an average of 22 students each, a minimum of 3 classes per grade should be randomly selected in each of the 2 middle schools to ensure the minimum necessary recruitment. Thus, randomly selecting 3 classes per grade in each of the 2 middle schools will make it possible to include approximately 132 female students per group and thus to ensure the minimum necessary recruitment. A total of 528 students are expected to be recruited (264 girls [132 per group] and 264 boys [132 per group]). The calculation of the number of subjects required was performed with PASS (version 15, NCSS) software.

Sequence Generation

In priority education schools, there are classes called Sections d'enseignement general et professionnel adapté (SEGPA; adapted general and vocational education sections): these classes, from 6th to 9th grade, are integrated into the middle school. They welcome young people who have significant school difficulties that cannot be resolved by academic assistance and support. There is only a small group of students (16 maximum) in each class in order to individualize each student's progress. SEGPA classes should enable students to access at least a professional qualification.

In the Paul Hermann Middle School, there are 9 classes in each grade, including 2 classes of SEGPA per grade. In the Plateau Goyave Middle School, there are 9 classes in 6th grade and 9th grade and 10 classes in 7th and 8th grade, including 2-3 classes of SEGPA per grade. In each of the selected middle schools, 12 classes will be randomly selected in order to have a balanced number of students in each arm.

In order to have an equal representation of each age group, the sampling will be stratified on the grade (6th, 7th, 8th, and 9th grade), and in order to take into account the specificities of SEGPA classes, we decided to stratify on SEGPA classes as well. As the main point in this comparative trial was similarity of the 2 groups compared, we decided to randomly select 1 SEGPA class per grade and 2 non-SEGPA classes per grade. Thus we will include in this trial 256 students from Paul Hermann Middle School (intervention group) and 255 students from Plateau Goyave Middle School (control group).

Statistical Methods for Primary and Secondary Outcomes

The aim of this study is to compare clinical outcomes between classes from a middle school sensitized to HPV vaccination

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through a combined health promotion program (intervention group) and a middle school without any specific action (control group). The null hypothesis is that there is no difference in the groups. For descriptive analyses, qualitative variables will be described in terms of frequencies and percentages with their 95% confidence intervals; quantitative variables will be expressed in terms of means, standard deviations, and 95% confidence intervals or in terms of medians and IQRs (25th and 75th percentiles).

Comparability of groups at inclusion will be checked: bivariate comparisons of categorical variables will be performed by the chi-square test or Fisher exact test, depending on the conditions of application. Bivariate comparisons of means will be performed by the Student *t* test or Mann-Whitney *U* test, depending on the conditions of application. For the analysis of the primary outcome: the proportion of schoolgirls who will have completed the full HPV vaccination regimen at the end of the school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, according to validity conditions.

Concerning secondary outcomes analysis: the proportion of schoolgirls who initiated HPV vaccination (1 dose) by the end of school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test according to validity conditions. The proportion of boys who will have completed the full vaccination schedule at the end of school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, according to validity conditions. The proportion of boys who will have initiated the vaccination scheme at the end of the school year will be compared between the 2 groups (intervention and control) by the chi-square test or Fisher exact test, depending on the conditions of validity.

The analysis of barriers to vaccination will describe the causes of nonvaccination reported for students who did not initiate the vaccination schedule. Analyses will be performed for girls and boys separately. We will also compare sociodemographic data, medical history, and health care utilization data between students who initiated HPV vaccination at the end of the school year and those who did not in the intervention group. Bivariate comparisons of percentages will be performed by the chi-square test or Fisher exact test depending on validity conditions. For continuous variables, comparisons will be made using the Student *t* test or the Mann-Whitney *U* test, depending on the conditions of validity. A multivariate analysis by logistic regression will be carried out in order to take into account confounding phenomena: the variable to be explained will be the fact of having initiated vaccination at the end of the school year, and the explanatory variables entered in the model will be the variables for which the significance threshold in bivariate analysis will be ≤.20.

To be determined in the intervention group: among students who initiated HPV vaccination at the end of school year, the proportion of students who used the health bus to initiate this vaccination. Among students who completed the full vaccination schedule at the end of school year, we will determine the proportion who completed all injections on the health bus.

In the intervention group, the proportion of students who used the health bus for sexual health information will be evaluated. In the intervention group, positive and negative points reported by students, their parents, and school staff about this program will be described. Proportion of students up to date for each type of vaccine (according to current vaccination calendar) at the end of school year, in the entire study population as well as in each of the 2 groups (intervention and control), and comparison of these proportions between the 2 groups by the chi-square test or Fisher exact test will be determined, according to validity conditions.

Analyses comparing control group to intervention group will all be performed on an intention-to-treat basis. All hypotheses will be tested with bilateral tests and α=.05 and confidence interval calculated at 95%. Analyses will be performed using SAS (version 9.4, SAS Institute Inc) software.

Ethical Considerations

The sponsor and investigators agree that this research will be conducted in accordance with the law no. 2012-300 of March 5, 2012, relating to research involving human persons; Good Clinical Practices (version 4 of November 9, 2016, and decision of November 24, 2006); and the Declaration of Helsinki [19]. The research is conducted in accordance with this protocol. Except in emergency situations requiring the implementation of specific therapeutic procedures, the investigators undertake to comply with the protocol in all respects, in particular with regard to the collection of consent and the notification and follow-up of serious adverse events.

This research has received the favorable opinion of the research ethics committee (Comité de Protection des personnes (CPP); ethics committee for the protection of individuals) of Ouest II of Angers (No. 20.05.14.35227; 2020/46) and the authorization of the Agence nationale de la sécurité du médicament (ANSM), the French equivalent of the US Food and Drug Administration. The University Hospital of Reunion Island, promotor of this research, has taken out a civil liability insurance policy with the hospital insurance company Société hospitalière d'assurance mutuelle (no. 158958) in accordance with the provisions of the public health code.

The data recorded during this research are subject to computerized processing at the University Hospital of Reunion Island, responsible for data processing in compliance with the law no. 78-17 of January 6, 1978, relating to data processing, files, and freedoms modified by the law 2004-801 of August 6, 2004 and modified by the law no. 2018-493 of June 20, 2018. This research falls within the framework of the reference methodology (RM-001) in application of the provisions of Article 54 paragraph 5 of the amended Act of January 6, 1978, relating to information, files, and freedoms. This change was approved by decision of January 5, 2006, updated on July 21, 2016. The University Hospital of Reunion Island, responsible for data processing, has signed a commitment to comply with this reference methodology. The research sponsor undertakes to carry out the research in compliance with the General Data Protection Regulation of April 27, 2016, implemented on May 25, 2018. This research is registered in the ANSM European Union Drug Regulating Authorities Clinical Trials Database

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[73-2020] and at ClinicalTrials.gov [NCT04459221]. Authors obtained consent to participate in the study from participants and their parents (or holders of parental authority). Written, informed consent to participate was obtained from all participants.

Availability of Data and Materials

The following documents relating to the research are archived by the investigator in accordance with Good Clinical Practice for a period of 15 years following the end of the research (research involving drugs, medical devices, or in vitro diagnostic medical devices or research not involving a product mentioned in article L.5311-1 of the public health code): the protocol and any amendments to the protocol, observation notebooks (copies), the source files of participants who have signed a consent form, and all other documents and letters related to the research.

Original copies of signed informed consents from participants and authority holders will be archived for a period of 30 years following the end of the research. All of these documents are the responsibility of the investigator for the regulatory archiving period. No movement or destruction will be made without the sponsor's approval. At the end of the regulatory retention period, the sponsor will be consulted for destruction. All data, documents, and reports are subject to audit or inspection.

Within 1 year of the completion or termination of the research, a final report will be prepared and signed by the sponsor and investigator. This report will be made available to the competent authority. The sponsor will transmit the results of the research to the CPP and, if necessary, to the ANSM in the form of a summary of the final report within 1 year of the end of the research. The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Results

This study was funded in September 2019. Recruitment began in October 2020 (Figure 3). Concerning vaccination, recruitment was completed by June 2021. Concerning evaluation of satisfaction of participants and evaluation of barriers to HPV vaccination, completion of recruitment was completed by December 2021.

In the intervention school, of 780 students, 245 were randomly selected in the 12 classes. In the control school, 259 students out of 834 were randomly selected. Analyses are still ongoing, though it seems that this health promotion program offering information to students, parents, and general practitioners and free school-based vaccination had a positive impact on the intervention school and drew many students into the health bus for HPV vaccination.

Figure 3. Intervention screenshots.

Discussion

Principal Findings

In this study, we expect significantly higher HPV vaccination coverage (full vaccination or first dose) in the intervention school as compared to the control school, whether it be among girls or boys.

Comparison With Prior Work

Previous studies have already shown the benefits of school-based educational sessions to improve adolescent knowledge and behavior regarding HPV prevention and increase the likelihood of the students to become vaccinated [20,21]. Education interventions represent a simple yet potentially effective strategy for increasing HPV vaccination, especially when targeting groups influential to the HPV vaccination behaviors of adolescents: parents [22], school staff [23], and

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health care professionals [24]. Indeed, knowledge was associated with recommendation intention and behavior.

Strengths and Limitations

This protocol is submitted more than a year after recruitment began, since sanitary COVID-19 condition was in constant change and evolution and it was difficult to know whether we could continue the process of the trial. Amendments were made and submitted to the ethics committee, facing prohibition of meetings with more than 6 people. This protocol is the result of our constant adaptation to these different obstacles.

Having different exclusion criteria for participants in the intervention and control arms m ay introduce a selection bias by design. However, we wanted to include as many children as possible in the control group to have a representative sample of the population, and the groups may still be comparable. The sample size calculation has not taken into account correlation between participants in the same cluster. As such, the sample size is likely to be too small. However, one limit is the price of the vaccine, which limited our ability to include more students, with regard to the funds allocated.

On Reunion Island, specificities regarding economic and societal development are as follows: high rate of universal health insurance coverage where the high cost of HPV vaccine may be a barrier, mixed culture with religious faith incompatible with premarital sex and racist biopolitical mistrust of the West from which the vaccine comes from, and the particular weight of the antivaccine leagues which casted a negative halo around the subject [25]. Thus we expect a strong veto from parents.

Future Directions

Analysis of satisfaction and specific barriers to vaccination in this school-based design will help us improve our program. Maybe on Reunion Island, with a population with early sexual life and a high rate of adolescent pregnancy (5%) [26], the target age of HPV vaccination should be reconsidered. The final implication would be an extension of this program in all middle schools on the island and an increase in HPV vaccination coverage. These results are promising and may be a stepping stone to expand this program to the whole Reunion Island and hopefully someday decrease the burden of cervical cancer.

Acknowledgments

Members of medical research unit of University Hospital of Reunion Island: Lucie Auzanneau, Mélanie Begorre, who provided substantial help in protocol submission to competent authorities, and Julie Ruiz, for data collection. ASETIS association, with its health bus and prevention animators, in whom children trusted to ask for information concerning sexuality and vaccination: Maryse Picard, Stéphanie Gonthier, Julianna Danessinga, Pierre Riviere, Fabrice Fontaine. Junior Doctors Xavier Gilhard, Morgane Humbert, Julien Sitthisone, and Eva Mondon, who vaccinated children in the health bus. Agence de Santé Océan Indien provided a grant to cover all the costs related to this study, including vaccine purchase. The funding body did not play any role in the design of the study, collection, analysis, interpretation of data, or writing the manuscript.

Authors' Contributions

PLT is the chief investigator, she conceived the study, obtained financing, and led the proposal and protocol development. EC assisted in protocol development and was the lead trial methodologist. MB assisted in the development of the proposal. AB contributed to the study design and substantively revised the protocol. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report.
[PDF File (Adobe PDF File), 154 KB - resprot_v11i6e35695_app1.pdf]

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Abbreviations

ANSM: Agence nationale de la sécurité du médicament
ASETIS: Association d'Education Thérapeutique et d'Intervention Sociale
CPP: Comité de Protection des personnes
HPV: human papillomavirus
SEGPA: Sections d'enseignement general et professionnel adapté

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Protocol

Effectiveness and Cost-effectiveness of Online Brief Mindfulness-based Cognitive Therapy for the Improvement of Productivity in the Workplace: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Numerous studies have demonstrated the effectiveness of mindfulness-based programs (MBPs) among both clinical and nonclinical populations. These data document positive impacts in the workplace, including reducing perceived stress and burnout and increasing well-being. However, the effectiveness for productivity, which is of most interest to managers and administrators, is still unclear. In addition, MBPs in the workplace tend to be modified by reducing the number of the program sessions or delivering content online to improve accessibility. To date, however, the impact of MBPs that feature these modifications on productivity in the workplace has not been investigated.

Objective: The study aims to investigate the effectiveness and cost-effectiveness of online-delivered brief mindfulness-based cognitive therapy (bMBCT) for improving productivity and other work-related outcomes among healthy workers compared to the waitlist control.

Methods: We will conduct a 4-week randomized controlled trial (RCT) with a 6-month follow-up. Employees are included in the study if they (1) are between the ages of 20 and 65 years and (2) work longer than 30 hours weekly. Employees are randomly allocated to either the bMBCT group or the waitlist control group. The primary outcome of the study is the mean difference of productivity measured by the World Health Organization Health and Work Performance Questionnaire (WHO-HPQ) between the groups at 4, 16, and 28 weeks. Secondary outcomes include several clinical outcomes and health economics evaluation.

Results: We started recruiting participants in August 2021, and the intervention began in October 2021. A total of 104 participants have been enrolled in the study as of October 2021. The intervention is scheduled to be completed in December 2023. Data collection will be completed by the end of January 2024.

Conclusions: The novelty of the study is that (1) it will investigate bMBCT's effectiveness on productivity, which is still unclear, and (2) samples are recruited from 3 companies in different industries. The limitations of the study are that (1) all measures assessed are in self-report format and (2) we lack an active control group. This study has the potential to provide new data on the relationship between MBPs and occupational health and productivity.

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Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000044721; https://tinyurl.com/4e2fh873

International Registered Report Identifier (IRRID): DERR1-10.2196/36012

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KEYWORDS

mindfulness-based cognitive therapy; mindfulness; cognitive therapy; occupational health; workplace; randomized controlled trial; cost-effectiveness; cost; online; internet-based; eHealth; mental health; heath outcome; work; stress; burnout; productivity; employee

Introduction

Background

Mindfulness-based programs (MBPs) are defined as interventions featuring systematic and sustained training in formal and informal mindfulness meditation practices; this training is recognized as central to both the therapeutic approach and the underpinning theoretical model [1]. Numerous clinical trials have demonstrated the effectiveness of MBPs in clinical populations, including patients with depression [2-4], anxiety [5-11], cancer [12-15], and pain [16-20]. These results have been affirmed by the findings of several meta-analyses [21-25].

However, it should be noted that the effectiveness of MBPs is not restricted to clinical populations. MBPs have been shown to be effective in nonclinical populations as well. Existing evidence indicates that MBPs are efficacious for the improvement of stress, sleep, quality of life, and subjective well-being in healthy individuals [26-38]. This is also applicable in the context of occupational health. In their latest meta-analysis of 23 randomized controlled trials (RCTs), Bartlett et al [39] endorsed the effectiveness of MBPs in the workplace for the improvement of numerous clinical factors, such as perceived stress, psychological distress, depression, anxiety, burnout, well-being, and sleep.

Rationale for the Study

Regarding productivity, which is of most interest to managers, Bartlett et al [39] concluded that productivity was assessed too inconsistently and infrequently for related results to be included in their meta-analysis; thus, they reported the results narratively. Three previous studies have indicated that absenteeism and presenteeism post-MBP intervention show a positive but nonsignificant tendency [35,40,41]; however, one study indicated no effect in that regard [42,43]. Regarding work engagement, although 1 study showed null results [42,43], another study revealed a significant positive effect of MBPs on work engagement [44]. As the inconsistency of the results of previous studies indicates, the effect of MBPs on productivity in the workplace is still unclear. In addition, certain aspects of MBPs, including the delivery mode (eg, online delivery) and the number of sessions, tend to be modified when applied in the workplace to improve accessibility. These modifications are likely to be applied more frequently because of the effects of the COVID-19 pandemic. However, in 85% of the studies included in the meta-analysis by Bartlett et al [39], the interventions were delivered face-to-face and the average number of sessions offered was not necessarily small (7). Thus, the effectiveness of MBPs delivered online and in a small number of sessions for improved accessibility has not been sufficiently investigated, especially in terms of productivity in the workplace.

Therefore, we developed a brief mindfulness-based cognitive therapy (bMBCT) program, which consists of four 1.5-hour sessions, to evaluate the effectiveness and cost-effectiveness of online bMBCT for the improvement of productivity and other work-related indicators compared to the waitlist control.

Aim

The aim of this study is to investigate the effectiveness and cost-effectiveness of online bMBCT for the improvement of productivity and other work-related outcomes among healthy workers compared to the waitlist control.

Methods

Participants

We started recruiting participants in August 2021. The intervention is ongoing and is scheduled to be completed in December 2023. The study is being conducted at the Keio University Center for Stress Research in Tokyo, Japan. The participants are being recruited from among the employees of 3 companies in different industries: Daiwa Securities Group Inc (security), Kumon Institute of Education Co, Ltd (education), and Nichirei Corporation (processed foods). Participants are eligible for the study if they meet the following criteria: (1) aged between 20 and 65 years, (2) work longer than 30 hours weekly, (3) have no history of sick leaves longer than 1 month due to mental disorders or have recovered for longer than 6 months after a sick leave, (4) have physical illnesses but are judged fit to participate in the research by the investigators, (5) score 8 or less in the absolute presenteeism item of the World Health Organization Health and Work Performance Questionnaire (WHO-HPQ), (6) can participate in the intervention and respond to the questionnaires via the internet, and (7) can provide written informed consent. Eligible participants are excluded if they (1) have previously participated in a mindfulness-based intervention for 8 weeks or longer, (2) are unlikely to participate during the research period (eg, they plan to move/relocate), and (3) are judged by the investigators as unfit to participate in the intervention due to physical conditions and other reasons (eg, unstable internet connection). Candidates who score higher than 8 on the WHO-HPQ absolute presenteeism item are allowed to participate in the intervention

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but will not be included in the RCT. The obtained data will be included in the multivariable analysis described later.

Enrollment

Prospective participants, who applied for the study via recruiting announcements delivered at each company, received a link to the web screening from the research cooperator at each company. If they passed the web screening, an announcement of the video group orientation was made. In the online group orientation, the research investigators provided written and oral explanations of the study, which included full descriptions of the purpose, significance, and methods of the study; the risks and benefits of participation; and the requirements for consent. Prospective participants were also offered an opportunity to ask questions. The investigators recorded the method, content, and date of the explanations provided. After the online group orientation, individual video interviews were held and the research investigator evaluated whether the participants met the inclusion criteria. Since obtaining written informed consent via online sessions was not feasible, all included participants provided informed consent verbally. The records were converted into PDF files, saved in an electronic storage medium, and stored in a lockable cabinet at the Stress Research Center.

Baseline Assessment

The included participants completed the questionnaires administered for the collection of demographic and psychosocial data. The psychological assessment tools to be utilized include the WHO-HPQ, the Five Facet Mindfulness Questionnaire (FFMQ), the 9-item Utrecht Work Engagement Scale (UWES-9), the Satisfaction With Life Scale (SWLS), the Flourishing Scale (FS), the Scale of Positive and Negative Experience (SPANE), the Experiences Questionnaire (EQ), the Perceived Stress Scale (PSS), the Investigating Choice Experiments Capability Measure for Adults (ICECAP-A), Team Psychological Safety (TPS), and the Credibility/Expectancy Questionnaire (CEQ). The details of each scale are presented later in the Instruments section.

Randomization

Eligible participants were randomly allocated to either the bMBCT or the waitlist control group (in a 1:1 ratio). The participants were assigned a computer-generated random number stratified according to company and the baseline WHO-HPQ absolute presenteeism score. The Project Management Office at the Keio Center of Clinical Research, which is an institution independent from the study group, managed the randomization process. The flow of participant recruitment is shown in Figure 1.

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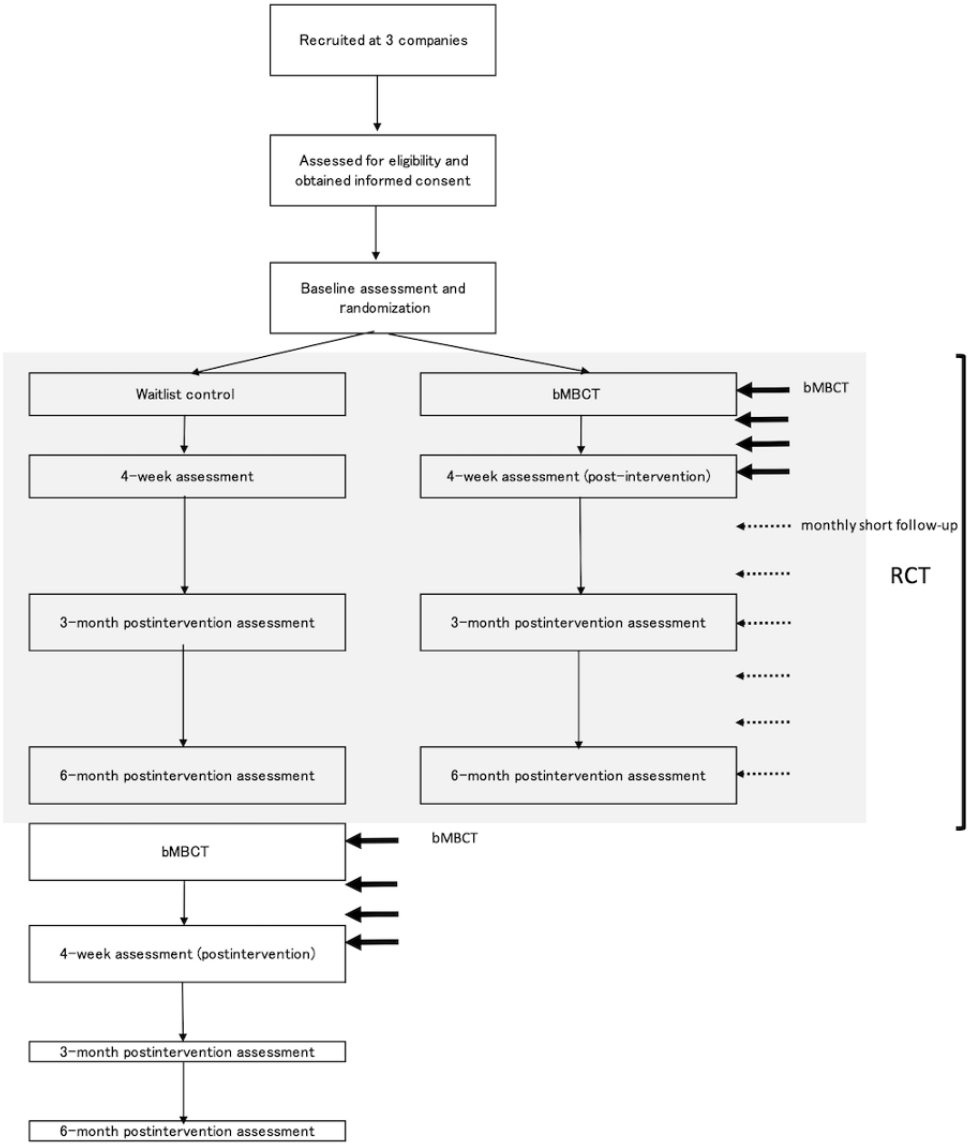
Figure 1. Flowchart of the study. bMBCT consists of four 1.5-hour-long sessions (only session 1 lasts for 2 hours). The follow-up session lasts for 1 hour and consists of a short meditation, experience sharing, and a question-and-answer session. bMBCT: brief version of mindfulness-based cognitive therapy; RCT: randomized controlled trial.



Blinding

Due to the nature of psychological interventions, both the participants and the therapists were not blinded to randomization statuses. Since all measurements obtained during the study are self-reported, there were no assessors for the evaluation of the statuses of participants.

Interventions

Brief Mindfulness-Based Cognitive Therapy

The included participants were offered a bMBCT program, which is a modified version of the original MBCT developed by Segal et al [45]. The modifications followed Crane et al's [1] specifications of "warp" (essential ingredients) and "weft" (flexible ingredients) of MBPs. To retain the essential ingredients of MBPs, we included practicing all mindful meditations except mindful movement and walking meditation (provided as homework via a delivery instruction movie). In contrast, considering the difference in the delivery setting (clinical setting vs workplace) and the target population (ie, patients with depression vs healthy individuals), some modifications were made. The first is the structure of the program. With the aim of improving accessibility to the program in the workplace, the duration of each session was shortened (from 2 hours to 1.5 hours), except session 1, and the total number of sessions was reduced (from 8 sessions to 4 sessions). To reflect the difference in the target population, the lecture relevant to depression was deleted, and activity records (ie, pleasant, unpleasant, appreciation events, and nourishing and depriving activities) were introduced to enhance the improvement of participants' well-being. The specific program contents are listed in Table 1. In the program, participants learned both cognitive approaches and mindfulness practices (eg, raisin exercise, body scan, sitting meditation, exploring difficulty, and 3-step breathing space). The participants were asked to practice meditation daily for approximately 20 minutes by listening to the pre-recorded meditation guide audios and record some activities as homework (theme depends on the session). Monthly follow-up sessions (lasts for 1 hour) will be

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provided to the participants for 6 months. No regular homework will be assigned during the follow-up period. During the follow-up period, the participants can access the mindfulness website developed by the research team from a smartphone or a personal computer (PC) and easily stream/download the meditation instructions.

In addition, the participants were encouraged to send their mindfulness experiences in daily life to the research team. The research team posted and shared them on the website. The research team also posted relevant articles to support participants in continuing the therapy. Participants were encouraged to meditate depending on their needs. In addition to encouraging individual participants to continue meditation, we encouraged them to develop voluntary groups to regularly meditate together outside the program. The bMBCT sessions and follow-up sessions are delivered live outside working hours via a videoconference platform.

The first, third, and fourth authors lead the sessions. The first author is a qualified mindfulness-based stress reduction teacher at the University of Massachusetts, with 12 years of experience in mindfulness practice. The other 2 authors have been practicing mindfulness for more than 5 years and have administered MBCTs 5 times under the supervision of the first author.

Table 1. Themes and contents of the program.

Session	Theme	Content
1	Doing mode and being mode/wondering mind	• Meditation: raisin exercise/body scan • Exercise: What is mindfulness? • Homework: mindfulness in a daily activity/body scan.
2	Sensation continues to change/thoughts are not fact	• Meditation: mindful movement/breath and body meditation/3-step breathing space • Exercise: scenario exercise (thought and feeling exercise) • Homework: body scan or breath and body meditation/mindful movement/pleasant-event calendar/3-step breathing space
3	Thoughts are a phenomenon in the mind/thought-body-behavior-mood are connected	• Meditation: sound and thought meditation/3-step breathing space • Exercise: nourishing activity • Homework: sound and thought meditation/unpleasant-event calendar/nourishing activity/3-step breathing space
4	Exploring difficulty	• Meditation: exploring difficulty/3-step breathing space • Exercise: reflection of the course (“Why am I here?” exercise) • Homework: no regular homework (encouraged to practice depending on their need)

Control Group

Participants in the control group will wait until the intervention group has completed the intervention. During this waiting period, they have been requested not to attend other mindfulness or meditation activities. After the waiting period is completed (ie, 7 months after allocation), the participants in the control group will be offered the same bMBCT but without monthly follow-up sessions.

Outcomes

Primary Outcome

The primary outcome of this study is the mean difference in absolute presenteeism (measured using the WHO-HPQ) between the intervention and the waitlist control (ie, before bMBCT offered) groups at 4 weeks, 3 months, and 6 months postintervention.

Secondary Outcomes

The secondary outcomes are the mean differences in the FFMQ, UWES-9, SWLS, FS, SPANE, EQ, PSS, ICECAP-A, TPS, and SEC scores at 4 weeks, 3 months, and 6 months postintervention.

Evaluation of Health Economics

Cost-effectiveness was measured by calculating the incremental cost-effectiveness ratio, which is the incremental cost divided by the incremental effectiveness between the groups. Incremental effectiveness was evaluated using quality-adjusted life-years, calculated from the weighted ICECAP-A scores. The analyses were conducted from a company’s perspective (ie, direct cost). Cost benefit will be evaluated using the net monetary benefit, which is calculated by subtracting the incremental cost needed for the intervention from the net monetary benefit of incremental productivity, weighted by the WHO-HPQ score.

Multivariable Analysis

To investigate factors that predict or mediate clinical outcomes, multivariate analysis will be conducted using factors obtained during the study. The details of the analytical methodology will be presented separately.

Instruments

World Health Organization Health and Work Performance Questionnaire

The WHO-HPQ is a self-report instrument designed to estimate the workplace costs of health problems in terms of self-reported sickness absences and reduced job performance (presenteeism). Presenteeism is assessed using the following questions: “On a scale of 0-10, where 0 is the worst job performance anyone could have at your job and 10 is the performance of a top worker, how would you rate the usual performance of most

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workers in a job similar to yours?" and "Using the same 0-10 scale, how would you rate your overall job performance on the days you worked during the past 4 weeks?" A low presenteeism score indicates poor performance [46].

Five Facet Mindfulness Questionnaire

This tool is a self-report questionnaire used to assess dispositional mindfulness. It includes 5 factors, which are extracted based on a factor analysis of 5 mindfulness questionnaires developed independently. The 5 facets are observing, describing, acting with awareness, not judging one's inner experience, and not reacting to one's inner experience. Total scores range from 39 to 195. Higher scores indicate greater levels of dispositional mindfulness [47].

The 9-Item Utrecht Work Engagement Scale

The UWES-9 is a 9-item self-report questionnaire that is widely used to measure work engagement across countries. It is hypothesized to assess 3 aspects of work engagement: vigor, dedication, and absorption. Each aspect includes 3 items. The scores range from 0 to 54. Higher scores indicate higher work engagement [48].

Satisfaction With Life Scale

This is a 5-item self-report questionnaire used to evaluate the cognitive aspects of subjective well-being. Scores for each subscale range from 1 (*strongly disagree*) to 7 (*strongly agree*). Total scores range from 5 to 35, with higher scores indicating higher satisfaction [49].

Flourishing Scale

This scale includes 8 items relevant to significant aspects of human functioning, ranging from positive relationships to feelings of competence, meaning, and purpose in life. Responses to each item are rated on a scale of 1-7, ranging from *strong disagreement* to *strong agreement*. Possible total scores range from 8 (*strong disagreement* with all items) to 56 (*strong agreement* with all items). High scores indicate that respondents view themselves positively in important areas of functioning [50].

Scale of Positive and Negative Experience

This measure is a 12-item scale that assesses positive experiences (6 items) and negative experiences (6 items). Owing to the generality of the items included in this scale, it can assess pleasant and unpleasant feelings that are the focus of most scales and can also reflect other conditions, such as interest, flow, positive engagement, and physical pleasure. Positive (SPANE-P) and negative (SPANE-N) scale scores range from 6 to 30. Higher scores indicate a higher positive or negative affective status. Subtraction of the negative score from the positive score yields the SPANE-B score, which is between −24 and 24 [50].

Experiences Questionnaire

The EQ is a 20-item self-report measure based on a 5-point Likert scale that ranges from 1 (*never*) to 5 (*always*). The total score ranges from 20 to 100. The scale focuses on decentering, defined as the ability to view the self as separate and different from its own thoughts, the capacity for nonreacting to negative experiences, and the ability to be self-compassionate. The EQ has been found to be reliable, and convergent and discriminant validities have been established for both general and clinical samples. The EQ is also internally consistent, with temporal stability over a 1-month period and good convergent validity [51,52].

Perceived Stress Scale

The PSS was developed to assess the degree to which situations in one's life are appraised as stressful. The scale has 2 versions: the 14-item version (PSS-14) and the 10-item version (PSS-10), which is similar to the 14-item version but with 4 items removed. We used the PSS-10 in this study. This scale is used to assess perceived stressful experiences or stress responses in the previous month. Each item is rated on a 5-point Likert scale ranging from 4 (*never*) to 0 (*very often*) to identify positive experiences or responses. Total scores range from 0 to 40. Higher scores indicate higher stress levels [53].

Investigating Choice Experiments Capability Measure for Adults

ICECAP-A was developed to measure capability well-being in adults, which the existing health-related quality-of-life scales have not been able to adequately capture. It is a scale of 5 attributes, each with 4 levels. It provides a single index value for well-being utility, either 0 or 1. A higher score indicates better well-being status [54].

Team Psychological Safety

The TPS is a scale developed for the assessment of a shared belief held by members of a team that the team is safe for interpersonal risk taking. This is a 8-item tool with a 7-point Likert scale. A higher score indicates that the respondent feels better psychological safety in the team [55].

Credibility/Expectancy Questionnaire

The CEQ is a quick and easy-to-administer scale used to measure treatment expectancy and rationale credibility in clinical trials. It consists of 6 items rated on a 9-point Likert scale, with 1 being *not at all* and 9 indicating *very logical/useful/confident/much*. Total scores range from 9 to 54. Higher scores represent higher credibility and expectancy for treatment. This scale is derived from 2 predicted factors: cognitive credibility and relatively more affective expectancy. These 2 factors are confirmed to be stable across different populations [56].

Homework Engagement/Qualitative Data

Daily formal meditation time and the answers to open-ended questions are collected at the end of each session. The questions include the following: (1) What did you notice in this session? (2) Did you experience any difficulties in this session? (3) Do you have any comments to improve the sessions?

The validity and reliability of the original versions of all these scales have been confirmed [46-56]. Regarding the Japanese versions of the scales, the validity and reliability of all scales and questionnaires, except ICECAP, the TPS, and the CEQ, have been confirmed [57-62]. For ICECAP-A, the Japanese version of the ICECAP officially accepted by the University of Birmingham was used [63]. We adopted the Japanese version

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of the CEQ, which was translated by Ito et al [64] through a rigorous back-translation procedure with the permission and support of the original developer of the questionnaire. Regarding the TPS, we used the TPS questionnaire cited in the Japanese edition of *The Fearless Organization: Creating Psychological Safety in the Workplace for Learning, Innovation, and Growth* by Edmondson [65].

Schedule for Assessments

In addition to the baseline assessment, we requested that the participants respond to these self-report assessments at 4 weeks, 3 months, and 6 months postintervention. A range of ±2 weeks from the scheduled dates for the baseline and postintervention assessments and ±4 weeks for the 3- and 6-month postintervention assessments were allowed. All assessment data were collected using the electronic patient-reported outcomes (ePRO) system. The assessment schedules are presented in Tables 2 and 3.

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Table 2. Assessment schedule for all participants.

Process/assessment	Screening period	Intervention period				Follow-up period					
		Week 1	Week 2	Week 3	Week 4	1 month	2 months	3 months	4 months	5 months	6 months
Screening	A[a]	N/A[b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Informed consent	A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
bMBCT[c]	N/A	I[d]	I	I	I	F[e]	F	F	F	F	F
Waitlist	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
WHO-HPQ[f]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
FFMQ[g]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
UWES-9[h]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
SWLS[i]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
FS[j]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
SPANE[k]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
EQ[l]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
PSS[m]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
ICECAP-A[n]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
TPS[o]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
CEQ[p]	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
Health service use	A	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
Homework engagement/qualitative data	N/A	A	A	A	A	A	A	A	A	A	A

[a]A: assessment.

[b]N/A: not applicable.

[c]bMBCT: brief mindfulness-based cognitive therapy.

[d]I: intervention.

[e]F: follow-up.

[f]WHO-HPQ: World Health Organization Health and Work Performance Questionnaire.

[g]FFMQ: Five Facet Mindfulness Questionnaire.

[h]UWES-9: 9-item Utrecht Work Engagement Scale.

[i]SWLS: Satisfaction With Life Scale.

[j]FS: Flourishing Scale.

[k]SPANE: Scale of Positive and Negative Experience.

[l]EQ: Experiences Questionnaire.

[m]PSS: Perceived Stress Scale.

[n]ICECAP-A: Investigating Choice Experiments Capability Measure for Adults.

[o]TPS: Team Psychological Safety.

[p]CEQ: Credibility/Expectancy Questionnaire.

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Table 3. Assessment schedule for participants in the waitlist control group, followed by a waiting period.

Process/assessment	Intervention period (followed by a waiting period)				Follow-up period (followed by a waiting period)					
	Week 1	Week 2	Week 3	Week 4	1 month	2 months	3 months	4 months	5 months	6 months
Screening	N/A[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Informed consent	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
bMBCT[b]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Waitlist	I[c]	I	I	I	N/A	N/A	N/A	N/A	N/A	N/A
WHO-HPQ[d]	N/A	N/A	N/A	A[e]	N/A	N/A	A	N/A	N/A	A
FFMQ[f]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
UWES-9[g]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
SWLS[h]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
FS[i]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
SPANE[j]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
EQ[k]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
PSS[l]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
ICECAP-A[m]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
TPS[n]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
CEQ[o]	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
Health service use	N/A	N/A	N/A	A	N/A	N/A	A	N/A	N/A	A
Homework engagement	A	A	A	A	A	A	A	A	A	A

[a]N/A: not applicable.

[b]bMBCT: brief mindfulness-based cognitive therapy.

[c]I: intervention.

[d]WHO-HPQ: World Health Organization Health and Work Performance Questionnaire.

[e]A: assessment.

[f]FFMQ: Five Facet Mindfulness Questionnaire.

[g]UWES-9: 9-item Utrecht Work Engagement Scale.

[h]SWLS: Satisfaction With Life Scale.

[i]FS: Flourishing Scale.

[j]SPANE: Scale of Positive and Negative Experience.

[k]EQ: Experiences Questionnaire.

[l]PSS: Perceived Stress Scale.

[m]ICECAP-A: Investigating Choice Experiments Capability Measure for Adults.

[n]TPS: Team Psychological Safety.

[o]CEQ: Credibility/Expectancy Questionnaire.

Sample Size

The primary outcome will be analyzed using the mixed model repeated measurement (MMRM) method to compare the amount of change between groups before and after the intervention (α .05, β .10). To the best of our knowledge, no previous studies have indicated the effect size of MBPs on presenteeism among employees. The sample size was calculated based on the results of a study that showed the effect of MBPs on the quality of life (effect size=0.44) [37]. We estimated that a total of 166 participants are required; however, the sample size was set at a maximum of 220 participants, considering the dropout rate (assumed to be 25%). The dropout rate was referred to the study of an online MBP in the workplace by Aikens et al [44], which reported the dropout rate was 23%.

Statistical Analysis

Statistical analyses and reporting of this trial will be based on the intention-to-treat approach. Analyses with complete samples will be also performed to verify the robustness of the results.

The full analysis data set will include all randomized subjects who underwent at least 1 procedure of the intervention.

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For baseline variables, we will generate summary statistics with proportions and frequencies for categorical variables and means and SDs for continuous data. For primary and secondary outcome analyses, we will analyze the mean changes from baseline using the MMRM method. Analyses conducted using the MMRM method will include the fixed and categorical effects of intervention, time, and the intervention × time interaction. Imputation will not be performed for missing values, because mixed models can deal with missing data through the maximum likelihood. All comparisons are planned, and all *P* values will be 2-sided. The significance level will be set at 5% for all statistical analyses. All analyses will be conducted using Stata version 16 (StataCorp).

We will also conduct a multivariate analysis to verify the predictors and mediators of the primary and secondary outcomes. A detailed analytical plan will be presented separately.

Adverse Events

The research team will immediately contact the Ethics Review Committee at the Keio University School of Medicine if the participants report any serious adverse events. Serious adverse events are defined as follows: (1) death by suicide, (2) death by nonsuicide, (3) a suicide attempt (self-injurious behavior that admits a suicide attempt), (4) an event that may lead to death, (5) psychiatric hospitalization, (6) general hospitalization due to an adverse event, (7) disability leading to inactivity due to an adverse event, or (8) any events judged to be medically serious based on the Japanese version of Common Terminology Criteria for Adverse Events v3.0 by the Japan Clinical Oncology Group/the Japan Society of Clinical Oncology [66]. Participants are asked to report any adverse events at the end of each session.

Ethics Approval

The authors confirmed that all procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the tenets of the 1975 Declaration of Helsinki, revised in 2008. All procedures involving human participants and patients were approved by the Ethics Review Committee of the Keio University School of Medicine (Reference 2021-0101). All included participants provided informed consent after all procedures were explained in detail. They were allowed to withdraw their consent at any time without any negative consequences.

Dissemination

We expect the results of our research to be presented at conferences and published as papers in academic journals. The results of this research will adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement.

Results

We started recruiting participants in August 2021, and the intervention began in October 2021. A total of 104 participants have been enrolled in the study as of October 2021. The intervention is scheduled to be completed in December 2023. Data collection will be completed by the end of January 2024.

Discussion

Summary

The aim of this study is to evaluate the effectiveness and cost-effectiveness of bMBCT in the workplace, especially for productivity. This study is valuable because it will fill certain gaps in the existing MBCT research. First, previous studies have revealed that the effectiveness of MBPs for physical and psychological indicators (eg, stress, burnout, and sleep well-being,) is promising; however, its effects on productivity are still unclear. This study is expected to clarify this important aspect of the use of MBPs in the workplace. Second, as the participants of this study are being recruited from 3 companies in different industries (security, education, and processed foods), the generalizability of the study findings will be enhanced because the cohorts of previous studies were recruited from a single company. Third, this study will focus on the evaluation of the effectiveness of online bMBCT in the workplace. Since the accumulated evidence on the effect of online bMBCT is still insufficient, the results of this study will advance the understanding of the use and effect of online bMBCT in the workplace. This is particularly important in the current scenario where many employees are forced to work from home. Furthermore, we will compare the effectiveness of bMBCT with follow-up and bMBCT without follow-up. The participants in the waitlist control group will receive bMBCT without follow-up once the waiting period is completed. Although this is not a direct RCT-based comparison, we can preliminarily evaluate the differences between the effect of bMBCT with and bMBCT without follow-up. Finally, we included a scale for the assessment of an organization's culture. Although previous studies have revealed that an individual's productivity is affected by individual factors and their organization's culture, such as team psychological safety, the interaction between individual and organizational factors has not been assessed to date. In the multivariate analysis, we plan to investigate the effect of differences in an organization's culture on the study outcomes. We are aware that focusing on productivity may possibly induce the increase of the "craving mind" of the participants, which is contrary to the purpose of MBPs. Such misuse of MBPs could have a negative impact on employees' health and well-being. Therefore, we will also assess these outcomes as well as productivity in order to evaluate the suitability of our MBP.

Limitations

This study has the following limitations. First, as all measures assessed are in self-report format, uncertainty regarding objectivity remains. Second, since we do not have an active control group (we set the waitlist as the control group), we cannot detect the effects that are specifically attributable to bMBCT. However, considering that the main objective of this study is to investigate the effectiveness of augmenting typical daily life with bMBCT rather than to assess the efficacy of bMBCT, we considered the research design to be acceptable for that purpose. Third, although we encourage the participants to report any serious adverse events at the end of each session, we will not assess mild-to-moderate adverse events. Therefore, the adverse events caused by this intervention might be underestimated. Despite the aforementioned limitations, we

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believe that this study will provide valuable information for future clinical trials in this field.

Conclusion

This study has the potential to provide new data on the relationship between MBPs and occupational health and productivity.

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Data Availability

The data sets are available from the corresponding author on reasonable request.

Authors' Contributions

MS drafted the grant proposal and is responsible for the study implementation, study management, data collection, and supervision. MS, MY, and A Ninomiya designed the study. MS, MY, A Ninomiya, and NG developed the contents of the brief mindfulness-based cognitive therapy (bMBCT). MS, MY, A Ninomiya, and MN administered the intervention. MS drafted the manuscript. MY, A Ninomiya, NG, MN, A Nakagawa, ZS, and MM refined the study protocol. All authors critically reviewed the manuscript for content and approved the final version.

Conflicts of Interest

The author ZS works as a co-developer at the Mindfulness-Based Cognitive Therapy (MBCT) and receives royalties from the Guildford Press for three books related to MBCT.

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Abbreviations

bMBCT: brief mindfulness-based cognitive therapy
CEQ: Credibility/Expectancy Questionnaire
EQ: Experiences Questionnaire
FFMQ: Five Facet Mindfulness Questionnaire
FS: Flourishing Scale
ICECAP-A: Investigating Choice Experiments Capability Measure for Adults
MBP: mindfulness-based program
MMRM: mixed model repeated measurement
PSS: Perceived Stress Scale
RCT: randomized controlled trial
SPANE: Scale of Positive and Negative Experience
SWLS: Satisfaction With Life Scale
TPS: Team Psychological Safety
UWEC-9: 9-item Utrecht Work Engagement Scale
WHO-HPQ: World Health Organization Heath and Work Performance Questionnaire

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Protocol

Continuous Versus Intermittent Nutrition in Pediatric Intensive Care Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: *Intermittent fasting* is a time-restricted feeding strategy with proven health benefits, which is based on multiple metabolic and endocrine changes, in several patient populations and healthy participants. In the pediatric intensive care unit (PICU), artificial feeding is usually administered 24 hours a day, although solid evidence supporting this practice is lacking. This discards the potential benefits of fasting in this population. We hypothesize that intermittent nutrition with a focus on an overnight feeding interruption (*intermittent fasting*), as compared with 24-hour continuous nutrition, is a feasible and safe strategy, with potential benefits, for critically ill children.

Objective: The aim of the Continuous versus Intermittent Nutrition in Pediatric Intensive Care randomized controlled trial (RCT) is to investigate a strategy of intermittent nutrition with a focus on an overnight feeding interruption period versus 24-hour nutrition during the first 14 days in the PICU.

Methods: The *Continuous versus Intermittent Nutrition in Pediatric Intensive Care* study is an investigator-initiated RCT in a tertiary referral PICU. Critically ill children (term newborn to 18 years), expected to stay in the PICU for ≥48 hours, and dependent on artificial nutrition, are eligible for inclusion. This study will randomize critically ill children (n=140) to a *continuous* versus *intermittent* nutrition strategy. In both groups, similar daily caloric targets will be prescribed. In the *continuous* group (control), nutrition will be administered 24 hours a day, with a maximum interruption period of 2 hours. In the *intermittent* group (intervention), nutrition will be interrupted during an age-dependent overnight fasting period. The study intervention will last until admission day 14, initiation of oral intake, or discharge from the PICU, whichever comes first. The primary outcome is the difference in ketosis between the groups under the condition of noninferiority regarding caloric intake. Secondary outcomes are feeding intolerance; the proportion of severe and resistant hypoglycemic events and severe gastrointestinal complications; and additional observed effects on nutritional intake, circadian rhythm, and clinically relevant outcome measures of the intermittent feeding strategy compared with continuous nutrition.

Results: The study was approved by the Dutch national ethical review board in February 2020. The first patient was enrolled on May 19, 2020. By May 2022, a total of 132 patients had been included in the study. Recruitment of the last patient is expected in Q3 2022.

Conclusions: Although *intermittent fasting* has been proven to have many health benefits in both animal and human studies, the feasibility and safety of this strategy in a PICU setting must be investigated. This RCT will help physicians gain more insight into the feasibility, safety, and potential clinical effects of intermittent feeding with overnight fasting in critically ill children.

Trial Registration: Netherlands Trial Register NL7877; https://trialsearch.who.int/Trial2.aspx?TrialID=NL7877

International Registered Report Identifier (IRRID): DERR1-10.2196/36229

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KEYWORDS

pediatric intensive care unit; PICU; pediatric critical illness; time-restricted feeding; intermittent fasting; feeding intolerance; ketones; circadian rhythm

Introduction

Nutritional Support for Children in Intensive Care

For a long time, observational studies have suggested that a substantial proportion of critically ill children, most notably infants, develop a pronounced caloric deficit, which has been associated with adverse outcomes [1-4]. This led to recommendations to provide early artificial nutrition via the enteral or parenteral route, targeting to cover at least the calculated or measured resting energy expenditure (REE), compensate for negative protein balance in critical illness, attenuate catabolism, and avoid, possible lethal, complications [5]. To be able to reach caloric targets early in this patient category that is frequently perceived as intolerant to enteral feeding, continuous 24-hour feeding has become a preferable strategy [6].

However, recently, the focus on high macronutrient intake in the acute phase of critical illness has been reconsidered. *The Pediatric Early versus Late Parenteral Nutrition in the Intensive Care Unit (PEPaNIC) randomized controlled trial (RCT)* revealed the beneficial effects of withholding parenteral nutrition (PN) and accepting a macronutrient deficit during the first week of critical illness, such as a decrease in the incidence of new infections, a shortening of the length of stay in the pediatric intensive care unit (PICU) and in the hospital, and a reduction in health care costs [7-9]. This strategy of accepting relative underfeeding of macronutrients in the first week of critical illness has even been shown to be beneficial in patients who are most vulnerable to low nutritional intakes, such as patients who are undernourished and term neonates [10,11]. Withholding PN had no negative effect on participants' anthropometric measurements during their PICU stay. Moreover, it did not negatively affect their long-term health but actually improved certain parts of their neurocognitive outcome 2 and 4 years later [12,13]. These counterintuitive findings of the beneficial impact of low macronutrient intake during the first week of critical illness were at least partially explained by a fasting response, as observed with increased ketogenesis [14].

Intermittent Fasting During Pediatric Critical Illness

Owing to the *Pediatric Early versus Late Parenteral Nutrition in the Intensive Care Unit* trial, the potential benefit of macronutrient restriction, or a fasting response, during the first week of critical illness is more recognized. However, knowledge on when safe fasting ends and potentially detrimental effects of starvation start, is lacking. An alternative *fasting mimicking* strategy could be an intermittent feeding pattern, in which a daily fasting response is induced while still providing sufficient amounts of nutrients. *Intermittent fasting* has been widely studied, and the observed health effects of these intermittent feeding strategies are based on changes in metabolic, endocrine, and epigenetic pathways that are also crucial in critical illness [15].

Aims

Although evenly distributing the daily caloric intake over 24 hours has long been perceived to be more feasible than intermittent feeding in critically ill children, hard evidence for the superiority of continuous feeding over intermittent fasting is lacking [5]. All of the available studies on intermittent feeding in critically ill children examined bolus feeding, and none of those examined the potential of overnight fasting [15]. Currently, no data are available on when the fasting response in critically ill children commences. Furthermore, the severity of illness and nutritional status of the child probably affect the dynamics of a fasting response [15]. Therefore, a study examining the fasting response and potential impact of overnight fasting in critically ill children is warranted. Therefore, the aim of the *Continuous versus Intermittent Nutrition in Pediatric Intensive Care* (ContInNuPIC) RCT is to investigate a strategy of intermittent nutrition with a focus on an overnight feeding interruption period versus 24-hour nutrition during the first 14 days in the PICU.

Methods

Ethics Approval and Informed Consent Procedure

The protocol and informed consent forms were approved by the Dutch national ethical review board *Centrale Commissie Mensgebonden Onderzoek* (CCMO; NL72302.000.19). The monitor verifies that the trial will be performed in accordance with the protocol described in the European Medicine Agency's *Note for guidance on good clinical practice CPMP/ICH/135/95* and the *Declaration of Helsinki*. Eligible patients and, if applicable, their parents or legal guardians, will be informed by one of the members of the research team orally in plain language and in writing. This member of the research team will not be involved in the treatment of the patient. Informed consent will be provided in writing by the parents or legal guardians and confirmed by the child if they are aged ≥12 years. Patients aged ≥16 years will be asked for consent if possible; otherwise, parents or legal guardians will act as legal representatives. For planned admissions, informed consent will be obtained before surgery if possible. For unplanned admissions (or patients with planned admissions whose consent could not be obtained before surgery), informed consent will be obtained within 24 hours after becoming eligible for the study.

Patients' Eligibility

Inclusion Criteria

Upon admission to the PICU, all the children will be screened for eligibility for inclusion in the ContInNuPIC clinical study. All patients identified by the research team will be logged.

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Critically ill children, term newborn to aged 18 years, who are likely to stay in the PICU for >48 hours and to be dependent on artificial nutrition, are eligible for inclusion.

Patients will be considered critically ill if they meet at least one of the following criteria:

- Respiratory support (excluding low flow nasal cannula)
- Hemodynamic support (pharmacological or mechanical)
- Continuous renal replacement therapy on account of acute renal failure

Patients already on home respiratory support will be considered critically ill only if they have significantly deteriorated compared with normal functioning; that is, need for an increase in the level of support (eg, higher pressure rates, higher fraction of inspired oxygen, or need for hemodynamic support).

Exclusion Criteria

Patients fulfilling ≥1 of the following criteria will be excluded:

- Preterm neonates (<37 weeks postmenstrual age [PMA] upon admission to the PICU)
- *Do not resuscitate* code at the time of PICU admission
- Expected death within 24 hours
- Readmission to the PICU >48 hours after already having been included in the ContInNuPIC trial
- Transfer from another PICU or neonatal intensive care unit (ICU) after a stay of ≥3 days or having received artificial nutrition (any PN or enteral nutrition [EN] with a caloric intake >10% of predicted REE per day)
- Ketoacidotic or hyperosmolar coma
- Metabolic diseases requiring a specific diet or with a contraindication to (intermittent) feeding
- Short bowel syndrome or other conditions requiring PN before admission
- Participation in another RCT in the PICU with an intervention that might influence the clinical outcome

Data Collection at Study Entry

At baseline, data on demographic (age, sex, race, ethnicity, and preadmission body weight, and height) and clinical characteristics of the patients will be obtained. For all patients, risk of mortality scores (*Pediatric Index of Mortality score*) [16], disease severity scores (*Pediatric Logistic Organ Dysfunction score*) [17], and the nutritional risk score (*Screening Tool for Risk on Nutritional status and Growth score*) [18] will be calculated, and the *Risk-Adjustment in Congenital Heart Surgery* classification [19] for patients of cardiac surgery will be recorded. In addition, comorbidities, such as the presence of a congenital disease or syndrome, gestational age at birth, presence or history of cancer, diabetes mellitus, kidney disease, liver disease, chronic heart disease, home ventilatory support, and sepsis upon admission, will be noted. In addition, for all patients, baseline results of routine clinical chemistry will be recorded.

Randomization Procedure

Randomization of participants to *continuous* or *intermittent* nutrition groups will be performed using the ALEA randomization tool (ALEA Clinical, FormsVision), a dedicated computerized system accessible 24 hours a day and 7 days a week. The computer algorithm allocates every consecutive eligible patient to 1 of the 2 treatment arms in a one-to-one allocation ratio using permuted blocks of 10. Patients will be stratified into 3 age groups: neonates (≤44 weeks PMA), infants (<1 year), and children (≥1 year).

Blinding

It was considered not feasible to blind treating physicians and patients for the allocated treatment during the time window of the randomized intervention. All outcome assessors and investigators not directly involved in patient care, such as statisticians and laboratory personnel, will be fully blinded to the treatment allocation.

Protocol Adherence

The medical and nursing staff of the PICU were informed and trained extensively during regular meetings before the start of the trial and were familiarized with the protocol. To optimize protocol compliance, reminders for study interventions and measurements will be incorporated into the electronic patient data management system. Moreover, the research team will provide a daily follow-up of all included patients.

Nutritional Support

Caloric Intake

During the study, nutritional intake will be provided to both allocation groups according to the current pediatric critical care nutrition guidelines [5,20,21]. In all patients from both study arms, EN will be started as soon as possible (<24 hours), provided that they are hemodynamically stable and without formal contraindications. EN will be administered through a gastric or postpyloric tube and gradually increased using a stepwise protocol (Figure 1), guided by the clinical judgment of the responsible clinician. Caloric goals will be calculated upon admission according to the body weight–based or body weight and length–based Schofield equation for the estimation of REE [22]. In line with the international nutritional guidelines for critically ill children, caloric intake is targeted to reach 1×REE at the end of the first week [5]. After 1 week, caloric target intake increases further to a maximum caloric intake of 1.3×REE for older children and adolescents and up to 2×REE for neonates and infants [20]. The research team will provide nutritional advice based on the standard protocol on a daily basis. The responsible clinician will decide the actual amount of nutrition prescribed based on the protocol, the nutritional intake the day before, and the tolerance of the administered nutrition. If EN cannot be started or increased according to the protocol, the reasons will be recorded in the database.

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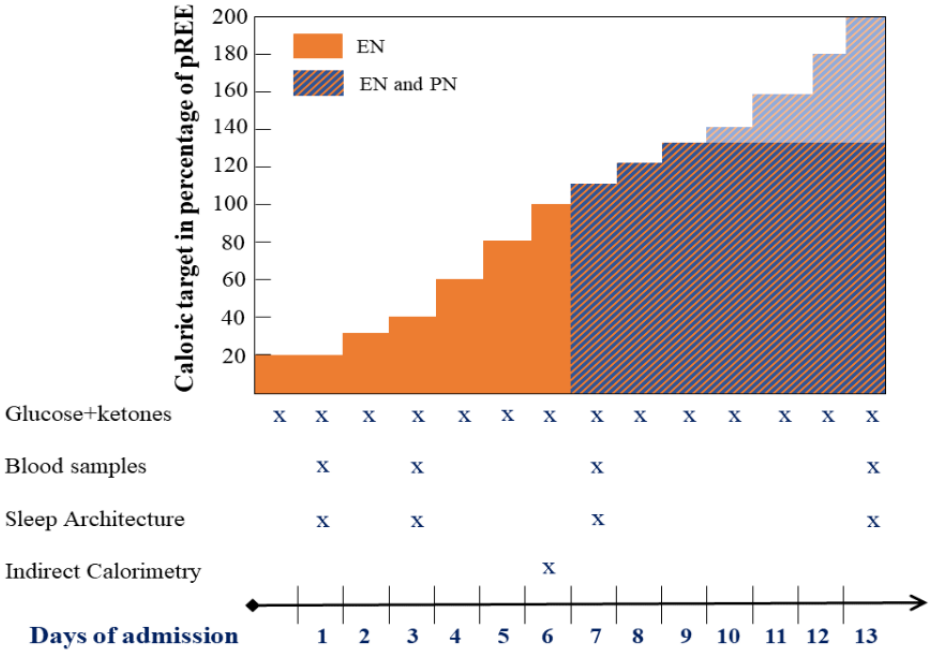
Figure 1. Daily caloric target and timeline of primary study measurements. For details, see text. EN: enteral nutrition; PN: parenteral nutrition; REE: resting energy expenditure.



EN Support

In neonates and infants, breast milk, the patient's standard milk formula, or a protein energy–dense formula will be used. For patients aged >1 week, breast milk will be enriched with breast milk fortifiers, and if a protein energy–dense formula is indicated, other fortifiers such as triglycerides can be added as well. Older children usually receive a standard enteral feeding formula or a protein energy–dense formula. A protein energy–dense formula will be used in case the patient is subjected to strict fluid restrictions or is unable to reach caloric targets. Hydrolyzed or semielemental formulas will be used when patients are allergic to or do not tolerate regular formulas (Table 1) [23].

Table 1. Stepwise approach for nutritional therapy in the pediatric intensive care unit[a].

Step	Nutritional therapy	Consideration
Step 1	• Infants: standard polymeric formula or breast milk • Children: standard polymeric formula	May result in nutritional deficits because of the lower energy and protein content of these formulas and breast milk
Step 2	• Polymeric protein: energy-enriched formula	Higher energy and protein content may overcome nutritional deficits, especially in patients with fluid restriction
Step 3	• Semielemental protein: energy-enriched formula	Absorption, tolerance, and use of proteins and fats may be altered, and semielemental feeds are considered as an alternative
Step 4	• If insufficient EN[b] (<80%) or no EN is possible >1 week after admission: start PN[c]	Especially in children with intestinal failure; appropriate growth and normal body composition difficult to achieve and risk of associated liver disease

[a]Source: Joosten et al [23].

[b]EN: enteral nutrition.

[c]PN: parenteral nutrition.

PN Support

During the first week, only EN without supplemental PN will be provided to conform with current guidelines [5,20]. Beyond day 7, if EN is insufficient (<80% of the target intake), parenteral macronutrients will be additionally provided through PN until EN reaches >80% of the target intake. If standard PN formulas are not suitable or are contraindicated for the patient, a tailor-made PN formula can be ordered by the dietician. To reduce the risk of refeeding syndrome on the first day of PN, half the target amount of PN will be provided [24].

Intervention Group: Intermittent Nutrition

For patients randomized to the *intermittent* nutrition group (intervention group), all nutritional support will be provided during the day and withheld during the overnight feeding interruption period. The overnight feeding interruption period will be designed in an age-dependent manner. The feeding interruption period will be from 2 AM to 10 AM in neonates (≤44 weeks PMA), from 12 AM until 10 AM in infants (<1 year), and from 10 PM to 10 AM in children (≥1 year), as shown in Figure 2. The daily planned nutritional intake will be provided during the condensed feeding period over the day. The starting

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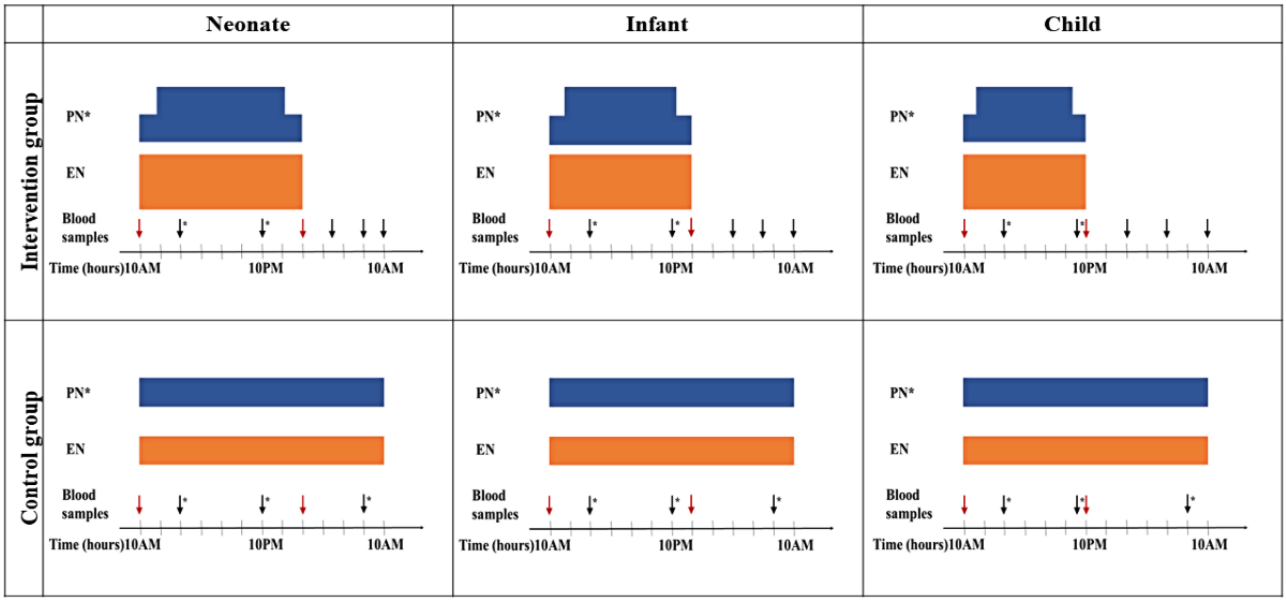
time of nutritional intake is set to 10 AM to facilitate procedures that require fasting to be performed in the morning. PN (beyond day 7, if necessary) will be provided during the daily age-dependent feeding periods and tapered over 1 hour during the starting and stopping of PN to reduce the risk of swift metabolic shifts (Figure 2) [25,26].

Figure 2. Randomization and age group–specific feeding schedules and measurements. Glucose and ketone level measurements are indicated with black arrows; during the fasting interval these measurements are performed at set time points (black arrows without asterisk); during feeding these measurements are performed regularly, but not at specific time points (black arrows with asterisk). Blood samples for metabolism analyses are at set time points in both fasted and fed state and are indicated with red arrows. *Parenteral nutrition is only supplied in the second week of pediatric intensive care unit (PICU) admission, when enteral nutrition is insufficient. For details, see text. EN: enteral nutrition; PN: parenteral nutrition.



Control Group: Continuous Nutrition

Patients randomized to the *continuous* nutrition strategy (control group) will receive nutrition according to current management for 24 hours a day, with a maximum planned interruption period of 2 hours (Figure 2). Planned feeding interruptions exclude interruptions because of clinical ICU care (eg, interventions such as intubation and surgical procedures). Feeding interruptions, timing, and reason will be recorded in the database. PN (beyond day 7, if necessary) will be provided continuously for 24 hours a day without interruption (Figure 2).

Medication and Supplementation

In all patients, medication will be provided in sodium chloride–based intravenous fluids instead of glucose-based intravenous fluids unless contraindicated. Medication and fluids can also be administered during the overnight feeding interruption period. If EN is insufficient (<80% target intake) during the first week, parenteral trace elements, minerals, and vitamins will be administered daily to all patients in both treatment groups similarly [27]. Intravenous micronutrient substitution will be stopped when patients receive at least 80% of their caloric needs via the enteral route.

Blood Glucose Management

Upon request of the national ethical review board (CCMO) on account of safety concerns, for patients in the intervention group, a glucose intake infusion will be provided during the overnight feeding interruption period (1.0 mg/kg/minute in neonates and 0.5 mg/kg/minute in infants) to reduce the risk of hypoglycemia. In children aged >1 year, no baseline glucose infusion during the overnight feeding interruption period will be provided unless clinically indicated. Glucose level measurements will be performed at least once daily during the feeding period, regularly during fasting intervals and when clinically indicated. Blood glucose management will be performed according to the local protocol. In short, blood glucose levels will be targeted from 4.0 to 7.8 mmol/L in all age groups. In patients with hyperglycemia (glucose >10 mmol/L) in 2 measurements (with 1 hour between measurements), the glucose intake will be first reduced, and if this is not sufficient, a continuous insulin infusion will be started using a stepwise nurse-driven glucose control protocol. If the blood glucose levels are <2.6 mmol/L, a bolus of 1 mL/kg glucose 10% will be provided and the baseline glucose infusion will be increased until the blood glucose level is >4.0 mmol/L. The glucose levels will be measured again within 30 minutes and 1 hour of treatment. In patients randomized in the *intermittent* group, if insulin is provided, this will be stopped 1 hour before the start of the overnight feeding interruption period.

Other Procedures and Guidelines

No other medical treatments were prescribed in the study protocol. The patients will be weaned from the ventilator and from hemodynamic support according to standardized guidelines. As the timing of PICU discharge to a regular ward may be affected by the availability of beds in regular wards, which could induce bias, we will analyze the *time to discharge from PICU* as the *time to being ready for discharge from PICU*. A patient is considered *ready for discharge* as soon as all clinical conditions for PICU discharge have been fulfilled (no longer in need of, or at risk of, vital organ support).

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Per-Protocol Stop of Study

A switch to oral intake will be made as soon as it is deemed safe by the clinician responsible for the patient.

The study intervention will last until admission day 14, until the child could be fed by mouth (oral feeding), or until discharge from the PICU, whichever comes first. After day 14, the intervention will stop, and nutritional support will be provided according to standing orders when oral intake remains insufficient.

Discontinuation of the Study Intervention

We defined a stopping rule (no-go) for individual patients to be withdrawn from the study who develop the following:

- Hypoglycemia (<2.6 mmol/L) with clinical symptoms (eg, pallor, transpiration, irritability, lethargy, loss of consciousness, and convulsions) or severe hypoglycemia (<2.2 mmol/L) *and* who are resistant to parenteral glucose administration; *resistance* is defined as no elevation of glucose within 1 hour after parenteral glucose bolus (1 mL/kg glucose 10%) administration and elevation (double) of standard glucose infusion via the standard local protocol
- Acute, nonocclusive mesenteric ischemia (ie, intestinal perforation and necrotizing enterocolitis) not attributed to an anatomical substrate (eg, volvulus)

Handling of Readmissions to the PICU

Patients participating in the study who are readmitted to the PICU within 48 hours of discharge and who are still within the 14-day time window of the initial randomization will continue to receive the nutrition strategy they were randomly assigned to during their initial PICU admission. Patients readmitted >48 hours after PICU discharge after participation in the ContInNuPIC study will not be eligible for reinclusion and will be fed at the discretion of the attending physician.

Study Blood Samples

For all patients, daily plasma glucose levels will be measured and analyzed at the bedside using a blood gas analyzer (ABL90 FLEX PLUS, Radiometer) or point of care meter (Accu-Chek Inform II, Roche Diabetes Care), and daily ketone levels (3-β-hydroxybutyrate) will be measured using the StatStrip Glucose/Ketone meter (Nova Biomedical). In the *intermittent* feeding group, glucose and ketone levels will be measured more frequently during the feeding interruption period (Figure 2).

Additional blood samples for other analyses of metabolism (eg, glucagon, insulin, and free fatty acids) and circadian rhythm (eg, gene expression and cortisol and melatonin) will be taken upon ICU admission and on days 3, 7, and 14 (Figure 2). The blood samples for metabolism will be collected using serum-separating tubes in both fasted (before 10 AM) and fed states (before 10 PM, 12 AM, or 2 AM, depending on the age group) for the intervention group or at similar time points for the continuous group. The blood samples for circadian rhythm will be collected in EDTA tubes every 4 hours during a 24-hour period (a total of 7 samples per 24 hours). The blood samples for gene expression will be collected in *PAXgene* RNA tubes (PreAnalytiX) once daily on the selected days at 10 AM. These additional blood samples will be taken from lines placed for clinical purposes or in combination with draws requested for clinical purposes. Owing to ethical considerations, the number of blood samples will be calculated using the body weight of the individual patient to ensure a maximum of 5% of blood volume for the entire study.

After collection, the blood samples will be immediately stored in a refrigerator. Within 24 hours after collection, the blood samples from serum-separating tubes and EDTA tubes will be centrifuged at 20 °C, and serum or plasma will then be separated and stored at −80 °C for future measurements. The *PAXgene* tubes will not be centrifuged and will be first stored at −20 °C for 1 day before storage at −80 °C to prevent breakage of the tubes. In addition, plasma phosphate, magnesium, and potassium levels will be determined in residuals of clinical plasma samples by the clinical chemical laboratory on days 0 to 4, 7 to 10, and 14.

Circadian Rhythm Measurements

The circadian rhythm is expected to be affected by the feeding strategy. Electroencephalography, electrooculography, and electromyography will be recorded for 24 hours on admission, day 3, day 7, and day 14 (with a margin of 1 day) or before discharge if the discharge is before day 14. Multichannel registration will be performed using a standard device (Brain RT, OSG or Morpheus, Micromed SpA). Melatonin and cortisol will be measured in the study blood samples, as melatonin and cortisol both have a clear relationship with circadian rhythms [28,29]. The blood samples used for gene expression analysis may be used to determine the internal time of peripheral blood mononuclear cells [30]. The difference between this internal time and the time of blood draw is a measure of circadian disturbances. In addition to the blood samples, salivary melatonin and cortisol levels will be measured to evaluate the possibility of measuring the circadian rhythm in saliva [31]. As ambient light and sound may affect and thus confound circadian rhythm [32,33], quantitative light and sound measurements will be taken at the bedside during ICU stay. All routinely monitored vital signs (including heart rate, respiratory rate, oxygen saturation, perfusion index, body temperature, central venous pressure, end-tidal carbon dioxide, arterial blood pressure, oxygen saturation, and electrocardiogram waveforms) will be stored at 1 Hz to 200 Hz intervals for further analysis.

Data Handling and Record-Keeping

Data will be collected electronically in a pseudonymized electronic case record form (eCRF) with an audit trail unambiguously linked to the source file using the *OpenClinica* clinical data management system (OpenClinica Community; version 3.12.2; OpenClinica LLC). Every day, the types and amounts of EN and PN delivered will be registered in the eCRF. Interruptions in EN delivery and gastrointestinal intolerance will be registered daily. The duration (in minutes) and the cause of interruption of EN delivery will be recorded. The data will be manually transferred into and checked for accuracy in the eCRF by the research team. Extensive range and consistency checks will be performed by the monitor of the study. All systemically administered medications, analyses of routine clinical chemistry, and whole blood glucose levels during the stay in PICU will be registered in the electronic patient file to

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be retrieved after completion of the study. The vital status at 30 days (and at later follow-up times) will be recorded for all patients in consultation with the National Personal Records Database. When this information is not available, the vital status will be checked through the hospital information system or regional network of pediatricians and general practitioners. All original records, such as consent forms, case report forms, and relevant correspondence, will be archived according to national regulations.

Outcome Measures

Primary End Points

The primary outcome of this study will be the feasibility of a daily feeding and fasting cycle (*intermittent feeding* strategy) compared with a continuous 24 hours per day feeding strategy in critically ill children. The primary outcome is defined as the difference in ketosis (3-β-hydroxybutyrate levels) between the groups under the condition of noninferiority regarding caloric intake. The amount of nutritional intake is defined as the daily caloric intake as a percentage of the estimated REE based on the body weight–based or body weight and length–based Schofield equation.

Secondary End Points

Secondary end points will comprise outcomes regarding the safety, feasibility, and efficacy of the intervention. The primary safety outcome is defined as the difference in the incidence of severe and resistant hypoglycemic events and severe gastrointestinal complications between the groups. For definitions of severe and resistant hypoglycemia and severe gastrointestinal complications, see the *Discontinuation of the Study Intervention* section.

The secondary safety outcomes comprise the following:

- Overall blood glucose control (hypoglycemic incidents and hyperglycemic incidents)
- Complications of nutritional support
- Hyperlactatemia during the feeding interval

As patients with a feeding and fasting cycle in the *intermittent* group may be considered at increased risk for hypoglycemia during the fasting interval, we will also report hypoglycemic incidents (glucose <2.2 mmol/L) during the time window of the randomized intervention for both groups as the number of nights with at least one episode of hypoglycemia divided by the total number of days of the intervention. As patients in the *intermittent* group may be considered at increased risk for hyperglycemia during the condensed feeding period, we will report the hyperglycemic incidents (glucose >10 mmol/L) during the time window of the randomized intervention for both groups as the number of days with at least one episode of hyperglycemia divided by the total days of the intervention.

Possible complications of nutritional support are shown in Textbox 1.

Hyperlactatemia is defined as an increase in arterial lactate levels above 2 mmol/L during the feeding interval.

Other secondary outcomes will be feeding intolerance and metabolic (eg, course of ketones, lactate, and free fatty acids) and endocrine responses (eg, insulin and glucagon). Enteral feeding intolerance is defined according to the definition by Eveleens et al [34] (Multimedia Appendix 1). Furthermore, we will evaluate any observed effects of the intermittent feeding strategy compared with continuous nutrition on nutritional intake, circadian rhythm, and clinically relevant outcome measures.

The effects on nutritional intake and circadian rhythm that will be investigated are presented in Textbox 2.

Clinically relevant outcome measures will be collected until 30 days after admission and are presented in Textbox 3.

Textbox 1. Possible complications of nutritional support.

Complications possibly related to feeding tubes:

- Complicated insertion (eg, nasal bleeding)
- Mechanical complications (feeding tube displacement and obstruction)

Complications possibly related to parenteral feeding:

- Mechanical complications (occlusion and dislodging of central venous catheters)
- Clinical complications (pneumothorax, hemothorax, arterial puncture, and central line replacement because of the suspicion of catheter-related bloodstream infections)

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Textbox 2. Possible effects on nutritional intake and circadian rhythm.

Nutritional intake

- The proportion of patients receiving at least a caloric intake of 67% of predicted resting energy expenditure (pREE) before or at the end of the first week and the proportion of patients receiving at least a caloric intake of 100% of pREE before or at the end of the first week
- The proportion of days caloric targets are reached divided by the total days in the study per patient
- Median caloric intake as a percentage of pREE
- The proportion of patients requiring supplemental parental nutrition beyond day 7
- The time to oral intake

Circadian rhythm

- Cortisol and melatonin patterns in blood and in saliva
- Circadian rhythm in gene expression
- Sleep architecture (quantity and quality)
- Circadian rhythm in vital signs

Textbox 3. Clinically relevant outcome measures.

Clinically relevant outcome measures

- Time to final (live) weaning from mechanical respiratory support and duration of mechanical ventilation
- Time to final (live) weaning from pharmacological or mechanical hemodynamic support and duration of such support
- Time to (live) discharge from the pediatric intensive care unit (PICU) and duration of PICU stay
- Time to (live) discharge from the hospital and duration of hospital stay for both the index hospitalization and total hospitalization, including stay in the referred hospital
- Newly acquired infections, which are defined as a microbiologically or laboratory-confirmed infection in combination with the start of treatment or clinical suspicion of infection, as assessed by the clinician responsible for the patient
- Mortality during the time window of the randomized intervention during PICU stay, during hospital stay, and after 30 days
- Acute kidney failure: Patients in need of renal replacement therapy (RRT) during PICU stay and the duration of RRT (for patients requiring RRT); Patients with acute kidney injury according to the *Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease* criteria [35]
- Patients with newly acquired liver failure according to the *Pediatric Acute Liver Failure* criteria or with a clinical diagnosis of acute liver failure [36]

Other Outcomes

Further metabolomic, endocrine, and inflammatory measurements on stored samples in the context of mechanistic analyses are planned. Moreover, these samples may be used for pharmacokinetics, pharmacodynamics, and autophagy analyses. In addition, we will evaluate parental stress (*Parental Stress Score*–PICU) [37] and the overall workload among (PICU) nurses (National Aeronautics and Space Administration Task Load Index) [38]. The detailed protocols and methods for the statistical analyses for these outcomes will be reported separately. Finally, a follow-up study after enrollment in the ContInNuPIC (concerning, eg, neurocognitive and physical function) will be planned as well; however, the details are beyond the scope of this study protocol.

Trial Organization

The sponsor (Erasmus MC, Rotterdam, The Netherlands) provides direct access to the eCRF, the source data, and the trial master file for monitoring and regulatory inspection. The sponsor has appointed 1 monitor. Monitoring will be performed and reported according to the sponsor's standard operating procedures. The clinical research team guarantees a daily follow-up of patient screening and inclusion, availability of requested clinical data in the clinical patient files, and protocol compliance. Noncompliance to the protocol and other questions or problems will be discussed with the principal investigator and reported to the study monitor. Regular meetings will be organized between the principal investigator and clinical research team to discuss the daily progression of the ContInNuPIC trial. Serious adverse events occurring during the intervention will be directly reported to the sponsor and the accredited ethical commission (CCMO) and registered in the database.

Statistical Analysis

General Rules

A CONSORT (Consolidated Standards of Reporting Trials) flow diagram will be reported [39]. All analyses will be primarily performed according to an intention-to-treat analysis. To perform additional per-protocol analysis, we anticipated that up to 30% of the patients will not be able to receive artificial nutrition during their admission to the PICU.

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Categorical variables will be summarized as counts and frequencies and analyzed using the chi-square test or Fisher exact test. Continuous variables will be summarized using either mean and SD or median and IQR, depending on the distribution of the variables.

All analyses will be performed primarily for the complete group. In secondary analyses, analyses can be stratified according to different age groups (neonates, infants, and children). Adjustment for baseline risk factors, including the diagnostic group, age group, severity of illness, and severity of nutritional risk, will only be used for secondary analyses. Multiple imputation will only be used in secondary analyses to deal with missing data for confounders. For all end points, differences will be considered statistically significant when the 2-sided *P* value is <.05 or when the 1-sided *P* value is <.025 in the case of noninferiority tests, without correcting for multiple testing.

Primary Outcomes

To assess a significant difference in ketosis between the 2 arms, a 2-tailed *t* test will be performed on the patient means of the highest ketone levels in each fasting period (or similar time point in the control group). A linear mixed model will be used to assess the noninferiority of caloric intake (repeatedly measured over time) in the intervention group, with a noninferiority margin of 33%.

Secondary Outcomes

The statistical analysis plan for secondary outcomes will be published separately. In short, the safety of the intervention will be assessed by comparing the incidence of both severe and resistant hypoglycemic events and severe gastrointestinal complications using the Cox proportional hazard analysis. Feeding intolerance will be analyzed using a mixed effects logistic model. Moreover, mixed models will be used for the assessment of other longitudinal data such as analyses of the course of ketones and other metabolic markers. Kaplan-Meier plots will be used to document time-to-event effects, and the time-to-event effect size will be estimated using the Cox proportional hazard analysis. All time-to-event analyses will be performed on data censored at 30 days. As death is a competing risk for the duration of care outcomes, nonsurvivors will be censored beyond the longest duration of such care required for survivors.

Sample Size Calculation

To provide a careful estimate of the number of patients required to answer whether the intervention is feasible, we based the sample size on a (1) a fasting response with ketogenesis and (2) sufficient nutritional intake.

We calculated the sample size to detect a fasting response with ketogenesis. In adults who are critically ill (n=70), 12 hours of fasting increased ketones compared with full feeding periods (ketones +0.47, SD 0.07 mmol/L; *P*<.001) [40]. In a study of healthy children, ketones increased from 0.08 mmol/L in the fed state to 0.34 mmol/L (90% CI 0.02-1.78 mmol/L) after 15 hours of fasting [41]. Using these data, we assumed baseline ketones of 0.10 mmol/L (fed state) and 0.20 mmol/L in the fasted state, with an SD of 0.16 mmol/L. To perform additional per-protocol analysis, we increased the sample size by 30%. Ultimately, the sample size of 140 should be able to detect, with at least 90% power (2-tailed power) and 95% certainty, the assumed increase in mean ketone levels of 0.10 mmol/L. Regarding nutritional intake, we considered a reduction in cumulative (caloric) intake, corrected for PICU length of stay, of >33% in the intervention group as clinically relevant based on the currently available literature [2]. The sample size (N=140, 70 per arm) is expected to be able to detect, with at least 80% power (1-tailed power) and 80% certainty, a reduction of 33% in cumulative caloric intake.

Results

This study was approved by the Dutch national ethical review board (CCMO) in February 2020. The study was initiated on May 11, 2020, and the first patient was enrolled on May 19, 2020. As of May 12, 2022, 132 patients have been included in the ContInNuPIC trial. Recruitment of the last patient is expected in Q3 2022.

Discussion

Hypothesis

Although solid evidence for the superiority of continuous feeding over intermittent feeding is lacking, almost all critically ill children worldwide are fed 24 hours a day. This is assumed to result in an improved nutritional intake with fewer gastrointestinal and metabolic complications. However, this approach conceals the fact that a fasting response might be beneficial for the convalescence of critical illness.

We hypothesize that in critically ill children, intermittent feeding with an overnight fasting period will lead to increased ketogenesis without lowering the daily total nutritional intake. Moreover, we hypothesize that this overnight fasting strategy will not affect feeding intolerance, glycemic control, or safety. This hypothesis is currently being tested in this study in a large tertiary referral PICU (Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands).

The Potential of an Intermittent Feeding Strategy in Pediatric Critical Illness

An important feature of the intermittent feeding strategy that is hypothesized to contribute to the beneficial effects is the transition to ketone body metabolism [42]. This ketone body metabolism contributes to the conservation of brain function and stimulation of several cellular pathways involved in stress resistance, neuroplasticity, and mitochondrial biogenesis [15]. The activation of autophagy, stimulated by the fasting state [43,44], is hypothesized to exert beneficial effects as well, as this is a process that is crucial for cellular function and integrity and recycling of macronutrients and metabolites [45-47]. Moreover, if the fasting period is implemented during the night, it might help preserve the circadian rhythm, as nutrient intake, or the fasting response, is the most important entrainment signal for the peripheral clock system [48,49]. This preservation of the circadian rhythm might be crucial in the treatment of critically ill patients, as the circadian rhythm is believed to be often disrupted in patients who are critically ill, and this is

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associated with impaired outcomes [50-54]. The preservation of circadian rhythm is hypothesized to improve sleep and metabolism, and it might even exert beneficial effects on tissue repair, immune response, and delirium risk [15]. A possible problem with implementing an overnight fast is the higher nutritional load during the daytime that is needed to reach the same caloric goals. However, only feeding during the daytime and thus delivering nutrition at a time when the body is attuned to food processing and nutrient uptake, might actually improve the feeding tolerance and glycemic control of patients who are critically ill [15].

In addition to the hypothesized beneficial effects because of the transition to a fasting response and preservation of the circadian rhythm, *intermittent fasting* might also have other beneficial effects. Reperfusion injury, muscle weakness, and immune response are believed to benefit from *intermittent fasting* as well [15]. Thus, *intermittent fasting* might be a favorable treatment option for critically ill children.

Strengths and Limitations

An important strength of this study is that the data collection is extensive, which will allow us to carefully correct for possible confounders in the analysis and further investigate the possible underlying beneficial mechanisms of intermittent feeding. Moreover, the studied patient population is very heterogeneous, which makes the findings generalizable to the general PICU population.

However, this study has some limitations that should be addressed. One of the limitations is the relatively small sample size, which does not allow for the drawing of conclusions regarding the effect on clinical outcomes. If this study shows that an intermittent feeding strategy with overnight fasting is safe and feasible, a larger RCT will be necessary to investigate its impact on clinical outcomes. Another limitation of this study is that some of the secondary outcome measures will not be performed in all patients, as some measurements (such as circadian rhythm measurements) are not suitable for patients who are very critically ill.

Conclusions

An intermittent feeding strategy with an overnight fasting period would potentially be capable of providing a fasting response while still providing sufficient nutritional intake, thereby improving clinical outcomes. To our knowledge, this is the first study to investigate such an intermittent feeding strategy in critically ill children. This RCT will help PICU physicians gain more insight into the possibility of omitting nutritional support during the night for critically ill children.

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Authors' Contributions

KV participated in the design of the study and the analysis plan and wrote the manuscript along with SCATV. ABGC participated in the design of the study and analysis plan and helped to draft the manuscript. RCJdJ designed the analysis plan and revised the manuscript for important intellectual content. RDE participated in the design of the study and revised the manuscript for important intellectual content. KFMJ conceived the study, study design, and analysis plan and helped to draft the manuscript. SCATV conceived the study, the study design, and the analysis plan and wrote the manuscript together with KV. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Definition for enteral feeding intolerance in critically ill children in whom enteral nutrition is indicated and attempted; registered over a 24-hour period.
[DOCX File , 17 KB - resprot_v11i6e36229_app1.docx]

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Abbreviations

CCMO: Centrale Commissie Mensgebonden Onderzoek
CONSORT: Consolidated Standards of Reporting Trials
ContInNuPIC: Continuous versus Intermittent Nutrition in Pediatric Intensive Care
eCRF: electronic case record form
EN: enteral nutrition
ICU: intensive care unit
PICU: pediatric intensive care unit
PMA: postmenstrual age
PN: parenteral nutrition
RCT: randomized controlled trial
REE: resting energy expenditure

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Protocol

A Comparison of the Effects of Stochastic Resonance Therapy, Whole-Body Vibration, and Balance Training on Pain Perception and Sensorimotor Function in Patients With Chronic Nonspecific Neck Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Neck pain is a prevalent pathological condition, and together with low back pain, it presents as the leading cause of years lived with disability worldwide in 2015 and continues to contribute substantially to the global burden of disease.

Objective: This study will investigate and compare the effects of stochastic resonance therapy (SRT), whole-body vibration (WBV), and balance training (BLT) in the management of chronic nonspecific neck pain.

Methods: In total, 45 participants with chronic neck pain will be randomly allocated into SRT, WBV, and BLT groups. Pain intensity, pressure pain threshold, neck disability, and cervical joint position sense will be measured before, immediately after, and 15 minutes after the first intervention session and after 4 weeks of intervention. A follow-up postintervention measurement would be taken after 4 weeks. The SRT group will train on an SRT device (SRT Zeptor Medical plus noise, Zeptoring). The WBV group will train on a Galileo vibration device (Novotec Medical), while the BLT group will perform balance exercises. All participants shall train 3 times a week for a period of 4 weeks. Mixed ANOVA will be used to determine the main and effects of interactions within (before intervention, post intervention 1, post intervention 2, post intervention 3, and follow-up) and between (SRT, WBV, and BLT) factors on the study outcome variables.

Results: Recruitment of participants started in May 2021, and as of May 2022, a total of 20 patients have been enrolled in the study. All participants are expected to have completed the trial by the end of 2022, and data analysis will commence thereafter.

Conclusions: The outcome of this study will shed closer light on the effects of SRT, WBV, and BLT on pain and function in patients with chronic neck pain.

Trial Registration: German Clinical Trials Register DRKS00023881; https://tinyurl.com/ycxuhj37

International Registered Report Identifier (IRRID): DERR1-10.2196/34430

(JMIR Res Protoc 2022;11(6):e34430) doi:10.2196/34430

KEYWORDS

neck pain; stochastic resonance therapy; whole-body vibration; cervical joint position sense; pressure pain threshold; balance training; chronic neck pain; sensorimotor function; rehabilitation; pain; therapy; chronic pain; rehabilitative technology; chronic nonspecific neck pain

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Introduction

Neck pain is a prevalent pathological condition, and together with low back pain, it presents as the leading cause of years lived with disability worldwide in 2015 [1] and continues to contribute substantially to the global burden of disease. The point prevalence of neck pain from the systematic analysis of the Global Burden of Diseases, Injuries, and Risk Factors Study in 2017 is estimated at 3% to 4% per 100,000 population [2]. The recurrence and chronicity of neck pain are further estimated to be 14% to 37%, respectively [3]. In most cases of neck pain, except for cases of diagnosed myelopathy and fracture, the pathomechanism of neck pain, similar to that of low back pain, is not fully understood [3-5]. Nevertheless, a variety of sensorimotor impairments have been observed in patients with neck pain, such as increased postural instability [6] and decreased cervical joint position sense (CJPS) acuity [7,8]. These sensorimotor impairments have in common that they (1) rely largely on proprioceptive information and (2) assess egocentric body orientation in space [9].

Several interventions were proposed to counteract pain and sensorimotor dysfunction in patients with chronic neck pain. Based on a recent systematic review, motor control exercises primarily targeting the deep cervical flexor muscles, yoga, and strength training may be regarded as equally effective in reducing pain and disability in patients with chronic neck pain [10]. Apart from these rather common countermeasures, there are further promising interventions for patients with neck pain, such as balance training (BLT) or vibration. The concept of BLT as a modulator or countermeasure for neck pain has been explored for the first time by Beinert and Taube [11]; their results suggest that BLT can reduce pain intensity and ameliorate cervical joint repositioning errors [11]. In contrast to repositioning or strength tasks, the neck muscles are presumed to be unconsciously activated while the individual tries to maintain body equilibrium during BLT [11]. Furthermore, BLT was shown to improve γ-aminobutyric acid–mediated (GABAergic) intracortical inhibition [12,13]. Appropriate inhibitory control is needed to suppress the perception of pain [14], and, so far, unpublished results from our laboratory demonstrate increased intracortical inhibition co-occurring with reduced pain perception in a patient experiencing pain after the administration of BLT.

Another intervention that reduces pain and improves CJPS in patients with neck pain is locally applied vibration [15,16]. Vibration can be applied locally on specific muscles or tendons or as whole-body vibration (WBV) [17]. Both types of vibration stimulate proprioceptors; for example, muscle spindles [18,19]. This is of interest because the deep layers of cervical flexor and extensor muscles display a large number of muscle spindles and might contribute with their connections to the vestibular system [20,21] to the egocentric body orientation in space [20]. The mechanism by which vibration activates muscles is described as the “tonic vibration reflex” [19,22]. It is believed that the vibration stimuli excite the muscle spindles, which, in turn send signals to the spinal cord where the polysynaptic reflex system is activated, consequently causing muscle contractions [17,22,23].

Clinically, applying local muscle vibration in patients with neck pain reduced neck pain and improved CJPS [15,16]. Thus far, the application of WBV in patients with chronic neck pain has not been studied, but research shows that neck muscles are stimulated during WBV training [24]. Thus, WBV may be a potential treatment candidate that can reduce pain and improve sensorimotor functions in patients with neck pain. In other studies that did not include patients with neck pain, potential therapeutic benefits of WBV have been reported to include positive effects in patients with cerebral palsy [25], potential improvement of CJPS in people with forward head posture [17], and reduction of pain in patients with chronic low back pain [25,26].

Stochastic resonance therapy (SRT) is a form of whole-body vibration therapy that uses randomized stimuli that are amplified with the help of noise [27]. The vibration output from SRT is different from that of a regular WBV in that it is random and unpredictable. Thus, the patient is constantly challenged to adapt to the multidimensional perturbations from the device’s standing platform [28,29]. Previous studies have suggested potential therapeutic benefits of the SRT [28,30-32]. For example, Kaut et al [31] reported increased postural stability in patients with Parkinson disease after administration of SRT. SRT is also known to reduce musculoskeletal pains [32,33]. Furthermore, a recent systematic review and meta-analysis indicated improvements in postural control and balance performance in healthy young adults, older adults, and people with lower extremity injuries after stochastic stimulation [34].

Until now, the effects of SRT and WBV in cervical pain are not known. Thus, this study aims to answer the research question which treatment among BLT, WBV, and SRT has the greatest effect in reducing pain intensity, the pressure pain threshold (PPT), and neck disability and in improving CJPS acuity in patients with chronic neck pain.

Methods

Trial Design

The trial uses a single-blind randomized controlled design and conforms to the Standard Protocol Items: Recommendations for Interventional Trials guidelines [35].

Study Setting and Participants

The study will be conducted at the Reha Center Michaeliskarree GmbH (an outpatient rehabilitation center) in Hof, Bavaria, Germany. Participants will be recruited through advertisement posters placed at the rehabilitation center and other health facilities in the neighborhood. We will recruit a total of 45 participants for the study, who are allocated to 3 arms of 15 participants per group: SRT, WBV, and BLT. We plan to recruit 2 additional patients per group to be sure that our design will not be underpowered in case of an approximately 15% dropout.

The progression of the trial is summarized in Figure 1. Participants will be included in the study if they have grade 1 neck pain without daily interference and grade 2 neck pain, which interferes with daily activities [36] for 3 months or longer, are between the ages of 18 and 65 years, and sign a written informed consent form. The following exclusion criteria are

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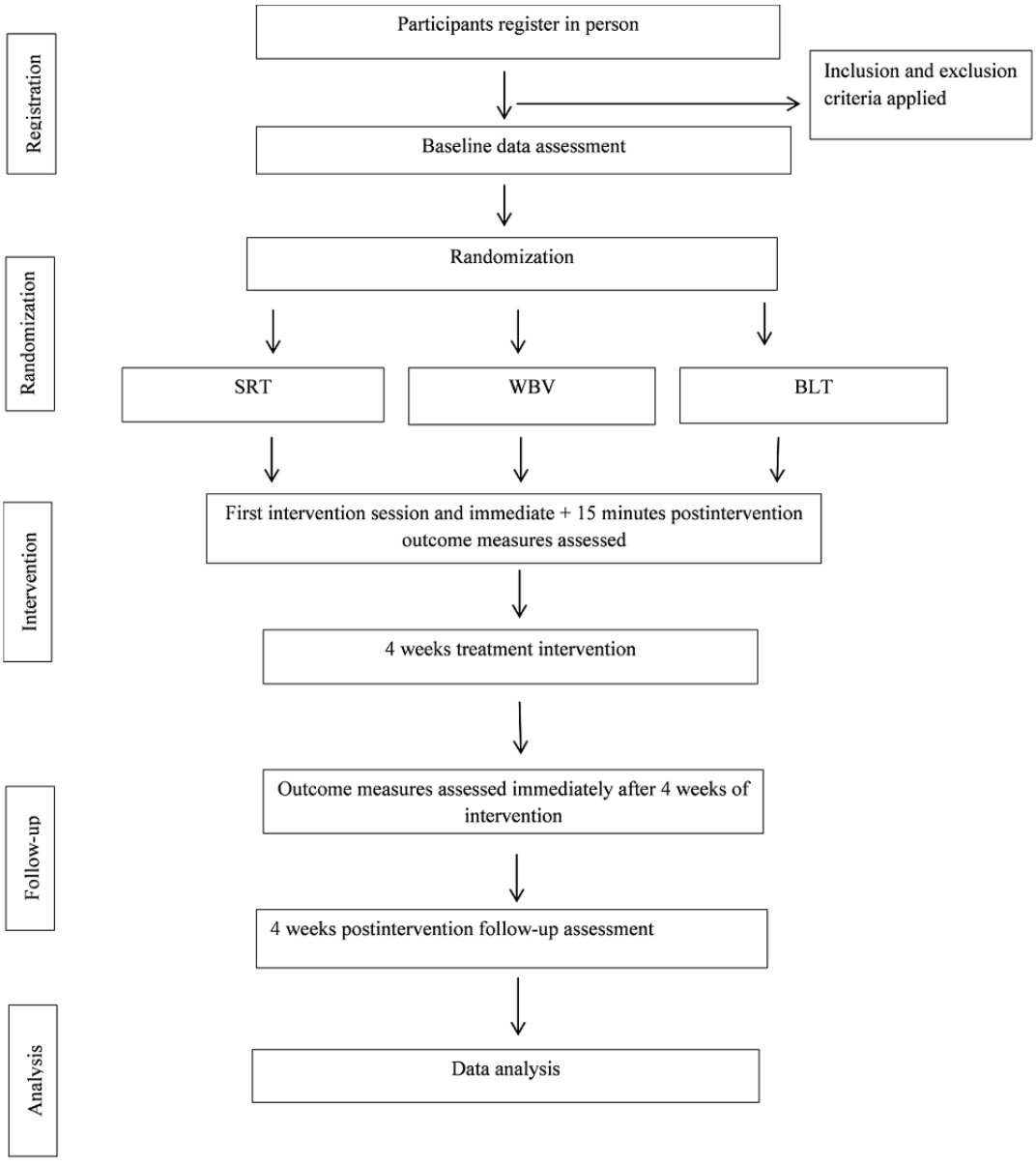
applied: the presence of potential contraindications to vibrations (eg, pregnancy and fresh medical procedures), uncontrolled high blood pressure or low blood pressure, kidney stones, glaucoma, acute thrombosis, advanced osteoporosis, presence of neurological conditions, epilepsy, rheumatoid arthritis, acute hernia, schizophrenia, pacemaker, aneurysm, heart arrhythmias and tumors or metastases, and uncontrolled diabetes. Furthermore, patients with the following pre-existing conditions shall be excluded: vertigo, dizziness, diabetic disorders, vertebrobasilar insufficiency, limiting pain, difficulties understanding instructions, difficulties adopting the required posture on the devices, whiplash-associated disorder, and traumatic injury to the neck.

Figure 1. Flowchart of the study protocol. BLT: balance training, SRT: stochastic resonance therapy, WBV: whole-body vibration.



Interventions

All 3 groups will train 3 times per week for 4 weeks. The SRT group will train on an SRT device (SRT Zeptor Medical-plus noise, Zeptoring), while the WBV group will train on Galileo Sport (Novotec Medical). The BLT group will perform balance exercises on different unstable devices. All participants will be instructed not to seek any other neck-specific therapy except in case of an emergency, and such events should be documented and reported to the researchers.

Training Protocol for SRT and WBV Groups

The participants are instructed on how to use the devices. In the first 3 visits (first week), the participants will train while standing on both legs on the device surface with slightly bent knees at approximately 30°. As from the second week of intervention, the training will progress to include more challenging activities on the device (see Table 1).

The participants are instructed to place one leg at the front and the other one behind, similar to a semitandem stance. Following

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this, participants are invited to alternately raise one leg and stand on the other leg for 30 seconds first and later transfer a ball from one hand to the other. Furthermore, the trainer throws a ball to the participants, which they catch and throw back to the trainer. Finally, they are asked to try to close their eyes while standing on one leg. The progression of the challenges is implemented for each participant on an individual basis.

Table 1. Description of the intervention's progression.

Exercise levels and details	Targeted repetitions
Balance training [37]	
Level 1 (static balance)	
Static stance (wobbly and spinning surfaces with eyes opened or closed)	30 s hold × 4 repetitions
Single leg stance (firm, soft, wobbly, or spinning surfaces with eyes opened or closed)	30 s hold × 6 repetitions
Tandem stance (firm, soft, wobbly, or spinning surfaces with eyes opened or closed)	30 s hold × 6 repetitions
Level 2 (dynamic balance with mental tasks)	
Throwing or catching a ball while tandem stance (on firm, soft, wobbly, or spinning surfaces, counting backward in multiples of 7, or reciting the alphabet backward from Z to A)	30 s hold × 6 repetitions
Throwing or catching a ball while single leg standing (on firm, soft, wobbly, or spinning surfaces, counting backward in multiples of 7, or reciting the alphabet backward from Z to A)	30 s hold × 6 repetitions
Tandem walking (forward or backward, on a soft surface, with eyes opened or closed, counting backward in multiples of 7, or reciting the alphabet backward from Z to A)	10 repetitions
Stochastic resonance therapy (2-6 Hz, 3 mm)	
Level 1 (static balance)	
Two-legged stance	60 s × 8 repetitions
Tandem stance	60 s × 8 repetitions
Single leg stance (eyes opened or closed)	30 s × 16 repetitions
Level 2 (dynamic balance)	
Throwing or catching a ball while standing on a single leg	30 s × 16 repetitions
Transferring a ball from one hand to the other while standing on a single leg	30 s × 16 repetitions
Level 3 (dynamic balance with mental tasks)	
Throwing or catching a ball while standing on a single leg (counting backward in multiples of 7 or reciting the alphabet backward from Z to A)	30 s × 16 repetitions
Whole-body vibration (5 Hz, 4 mm)	
Level 1 (static balance)	
Two-legged stance	8 min × 1 repetition
Tandem stance	8 min × 1 repetition
Single leg stance (eyes opened or closed)	30 s × 16 repetitions
Level 2 (dynamic balance)	
Throwing or catching a ball while standing on a single leg	30 s × 16 repetitions
Transferring a ball from one hand to the other while standing on a single leg	30 s × 16 repetitions
Level 3 (dynamic balance with mental tasks)	
Throwing or catching a ball while standing on a single leg (counting backward in multiples of 7 or reciting the alphabet backward from Z to A)	30 s × 16 repetitions

Training Parameters for SRT and Galileo Vibration Devices

Stochastic Resonance Therapy (SRT)

The "medium trim" of the program "chronic head, neck and back pain by muscle imbalance" will be selected on the SRT device. The vibration frequency of this program ranges between 2 Hz and 6 Hz at an amplitude of 3 mm. The program comprises 8 series of vibration bouts, each lasting 60 seconds with a 60-second break between bouts. The last bout is for cooling down.

Galileo Vibration

The Galileo device elicits a side alternating vibration at a 4-mm amplitude. Its frequency will be adjusted to 5 Hz to ensure that

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the settings of both the Galileo and SRT devices are similar. The participants train on the device for a total duration of 15 minutes (including 8 minutes of active training and a 7-minute break).

Training Protocol for the BLT Group

The BLT group will perform 15 minutes of balance exercise training (8 minutes active training and a 7-minute break) 3 times per week for 4 weeks. Each training session shall comprise different balance exercises, and the difficulty of the exercises will be progressively adjusted throughout the training (see Table 1). Participants will have to stand on wobbling boards, spinning tops, soft mats, and other devices with a reduced base of support. For exercises performed on one leg, one leg is trained first for 30 seconds and the other leg afterward for the same duration. Furthermore, task difficulty will be progressively increased (smaller base of support, standing with eyes closed, catching a ball, counting backward in steps of 7, etc) for each participant in an individual and adapted manner. There will be a 30-second rest period after every set of exercises.

Outcome Measures

Overview

Pre- and postintervention measurements and outcome data shall be assessed by EOI. EOI is a sport scientist with a cumulative work experience of 6 years as a physical education teacher and sports therapist. EOI is trained in using the underlisted assessment instruments and procedures.

Pain intensity, PPT, neck disability, and CJPS are measured before, immediately after, and 15 minutes after the first intervention session and after 4 weeks of the intervention. A follow-up postintervention measurement will be taken after 4 weeks.

Pain Intensity

Pain intensity will be assessed using the numeric rating scale (NRS) for pain. The NRS is a reliable (0.67) and valid (0.67) instrument for measuring pain in patients with neck pain without upper extremity symptoms [38]. The NRS has also been shown to be sensitive to intervention-induced changes [38].

Cervical Joint Position Sense (CJPS)

The participants will wear on their head a cervical goniometer (CROM, Performance Attainment Associates) attached with a laser pointer (P2, NOBO) and will be required to sit straight and comfortably without resting their back on a chair placed 90 cm away from the target. The target is a board that can be adjusted so that the center of the board is at eye level for each participant when seated and looking straight ahead. This initial head position is defined as the neutral head position (NHP) and will be marked on the target screen. From this NHP, the blindfolded patients are instructed to rotate their head to the side and then to turn their head back to the NHP and provide a verbal signal by saying “now” when they think they have returned to the NHP with the laser pointer. The point at which they made the stop signal is marked, and the distance between this point and the NHP is measured in centimeters. This procedure will be repeated 8 times for right as well as left head rotations. A systematic review of the literature by de Vries et al [8] and colleagues demonstrated that CJPS tests are efficient in identifying CJPS acuity errors in patients with neck pain when at least 6 repetitions are performed. The CJPS test has fair to high test-retest reliability (intraclass correlation coefficient=0.39-0.78) [39] and good discriminative, convergent, and divergent validity scores [40].

Neck Disability

The German version of the Neck Pain and Disability Scale (NPAD-d) will be used to assess the functional capacity of the patients. The NPAD-d has an excellent reliability and validity score (Cronbach α=.94) [41].

Pressure Pain Threshold (PPT)

The PPT will be measured using a pressure algometer (Wagner Instruments). Standing behind the seated participant, the assessor will incrementally apply pressure on the trigger point of the levator scapulae muscle at the angulus superior of the scapula until the participant calls out “now” to indicate the onset of painful pressure. The assessor stops immediately and records the reading on the algometer at which point the participant started to feel pressure pain. To enhance the reliability of the test, 3 repetitions are carried out on the left and right sides. The PPT test has high interrater and test-retest reliability (intraclass correlation coefficient=0.75-0.95) as reported in a previous study [42].

Randomization and Allocation of Concealment

The participants will be randomly allocated to the SRT, WBV, or BLT group. Randomization will be performed electronically using the QuickCalc software (GraphPad Software) and sealed in a brown nontransparent envelope. A physiotherapist who is not involved in the study will allocate the patients into groups. The sequencing and allocation will be concealed from the participants and other members of the research team. Furthermore, the analyst is blinded to the actual treatment of participants. All the actors involved will be unblinded after the final measurement from the last patient.

Sample Size

The total sample and subgroup size were determined by conducting an a priori power analysis using the G-Power software (version 3.1.9.7; G-Power) by applying repeated measures ANOVA and selecting within- and between-group interactions with an effect size *f* set at 0.4 (large effect size), α of .05, and β of .90. Estimation of large effect sizes is based on previous results obtained from among patients with neck pain and on the therapy duration and frequency.

Statistical Analysis

Statistical analyses will be performed using SPSS (version 24; SPSS Inc). Descriptive statistics will be used to report the study population’s demography and characteristics. The Gaussian distribution of data will be assessed using the Shapiro-Wilk test. Thereafter, mixed ANOVA will be used to determine the main and interaction effects of within (before intervention, after intervention 1, after intervention 2, after intervention 3, and follow-up) and between (SRT, WBV, and BLT) factors on the study outcome variables. Mean (SD) values, effect sizes, and 95% CIs are reported.

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Ethics Approval, Study Registration, and Consent to Participate

The study will be conducted in accordance with the tenets of the Declaration of Helsinki. Ethical approval was obtained from the ethics committee of the Deutsche Hochschule für Gesundheit und Sport (DHGS-EK-2021-001), and the study was registered with the German Clinical Trials Register (DRKS00023881) and in the World Health Organization's International Clinical Trials Registry Platform (U1111-1262-6569). Participants will be required to sign the informed consent form and return it during recruitment to the same physiotherapist who informs them of their study group allocation.

Protocol Amendments

Any major amendment to the study protocol will be communicated to the responsible ethics committee and the trial registration body.

Confidentiality and Access to Data

Data are anonymized by asking the participants during recruitment to generate their research code by combining the last 2 letters of their mothers' first name, the last 2 letters of their fathers' first name, and their birth date. For example, if the first name of a participant's mother is Helga, the first name of the father is Herbert, and patient's date of birth is December 5, 1992, the participant's code is GART12. Data will be safely stored in a lockable cupboard and can only be accessed by the researchers.

Safety and Data Monitoring

Participants are insured by the existing insurance policy at Reha Center Michaeliskarree. During the trial, participants will be continuously monitored for possible occurrence of any side effects of the treatments. Most side effects as reported from previous studies, and as observed by the investigators, are minor and disappear shortly afterward. In the event of an established more serious side effect, the patient will be immediately referred to the hospital. All documented side effects will be reported in a separate publication. The lead investigator and research team will monitor the safety and scientific integrity of the trial.

Results

Recruitment of participants started in May 2021. In total, 20 patients have been enrolled as of May 2022. All participants are expected to have completed the trial by the end of 2022, and analysis of data will commence thereafter.

Discussion

Expected Findings

We hypothesize that all 3 interventions will reduce neck pain and improve the sensorimotor function of the cervical spine. Furthermore, we hypothesize that SRT elicits larger effects than WBV owing to the random and multidimensional nature of the former, thus being a more challenging application of the vibration stimuli. Finally, we hypothesize that BLT elicits the most beneficial effects as it incorporates the coordinatively most challenging tasks and is known to upregulate the inhibitory GABAergic system in the brain, which is also needed to suppress the perception of pain.

Manufacturers of vibration devices have touted their benefits for muscle activation, bone strengthening, and treatment of several health conditions. Indeed, some of these claims are supported by research, as suggested by the latest up-to-date reviews of the literature and meta-analysis [43,44]. However, to the best of our knowledge, this would be the first study to investigate the treatment effects of SRT and WBV in patients with chronic nonspecific neck pain and to compare these effects with BLT. The results from this study will contribute to our understanding of the role of WBV (stochastic and nonstochastic) and BLT in the management of chronic neck pain. It is hoped that this study spurs further research in the application of SRT, WBV, and BLT as treatment options for neck pain. Future studies should further explore how the human neck region responds to WBV stimuli and if this response is correlated with pain reduction and sensorimotor function improvement.

Limitations

A potential limitation of the study is the strict exclusion criteria, which were set to eliminate the possible risk exposure of patients with pre-existing contraindications for WBV. As a result, some patients with neck pain who could have benefited from the treatments were excluded.

To minimize bias, analysts were blinded, but owing to the work setting at the trial center, the data assessor could not be blinded. To reduce potential assessor bias, very strict measurement criteria were applied.

Dissemination Policy

The results will be communicated to the participants and shared publicly through publication in peer-reviewed journals and at international scientific conferences.

Conclusions

The outcome of this study will particularly elucidate the effects of SRT, WBV, and BLT on pain and function in patients with chronic neck pain.

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Data Availability

Data sets are not included in this protocol but may be released upon a reasonable request to the corresponding author.

Authors' Contributions

EOI conceived the project. EOI, WT, and KB designed the study. EOI, WT, and KB developed the intervention protocols. EOI drafted the first copy of the manuscript, which was edited by KB and WT. Data will be collected by EOI. WT, KB, and EOI will perform the statistical analyses and conceptualize, read, and approve the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BLT: balance training
CJPS: cervical joint position sense
GABAergic: γ-aminobutyric acid–mediated
NHP: neutral head position
NPAD-d: German version of the Neck Pain and Disability Scale
NRS: numeric rating scale
PPT: pressure pain threshold
SRT: stochastic resonance therapy
WBV: whole-body vibration

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Protocol

Using Digital Media to Improve Dementia Care in India: Protocol for a Randomized Controlled Trial

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Abstract

Background: India is undergoing a demographic transition characterized by population aging and is witnessing a high dementia rate. Although nearly 7 million people live with dementia in India, dementia awareness is poor, and current resources addressing dementia care are basic and often incomplete, duplicated, or conflicting. To address this gap, this study aims to use digital media, which has had a massive technological uptake in India, to improve dementia care in India.

Objective: The objective of this paper is to describe an intervention study design that examines the feasibility and acceptability of Moving Pictures India, a digital media resource to improve dementia care in India.

Methods: This study employs a mixed methods design and is divided into 4 phases: (1) video interviews with Indian caregivers and health professionals; (2) coproduction of resources; (3) pilot randomized controlled trial (RCT); and (4) dissemination and analytics. The pilot RCT will follow an experimental parallel group design with 2 arms aiming to assess the impact, feasibility, and acceptability of the developed resources. The primary outcome measures for the pilot RCT will be feasibility and acceptability, while the secondary outcome measures will be caregiver burden, mood, and quality of life.

Results: This study received funding from the Alzheimer's Association in the United States in July 2021. In 2023, we will enroll 60 dementia caregivers (40 caregivers in the intervention arm and 20 in the control) for the pilot RCT. The study has been approved by the National Institute of Mental Health and Neuro Sciences Ethics Committee (26th IEC (BEH.SC.DIV.)/2020-21 dated November 11, 2020); the Health Ministry's Screening Committee, India (proposal ID 2020-10137); the Curtin University Human Research Ethics Committee (approval number HRE2020-0735); and the NARI Research Governance Office (site-specific approval dated March 17, 2021).

Conclusions: This protocol is designed to deliver unique, coproduced, and evidence-based media resources to support caregivers of persons with dementia in India and other countries aiming to utilize digital media for dementia care. If the intervention is found feasible and acceptable, postpiloting analytics and qualitative feedback will be used to develop an implementation trial to evaluate the effectiveness of the potential low-risk high-benefit intervention in practice.

Trial Registration: Clinical Trials Registry-India CTRI/2021/01/030403; http://ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=50794

International Registered Report Identifier (IRRID): DERR1-10.2196/38456

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KEYWORDS

dementia; care; India; digital health; film

Introduction

India, like the rest of the world, is experiencing population aging, and this demographic transition will have a significant impact on age-related conditions such as dementia [1]. With nearly 7 million people affected [2], India has the fastest growing dementia rate worldwide and will soon host one of the largest populations of people with dementia. A large proportion of people with dementia are cared for by their immediate and extended families [3]. The role of family is paramount in dementia care in India and is rooted in the traditional concept of "seva," which emphasizes service, honor, and respect for older people and a social expectation that they will be cared for by their children [4].

Despite affecting millions in India, the symptoms of dementia are often viewed as a normal part of aging, and there is a lack of awareness about the symptoms, treatment, and challenges associated with caring for a person with dementia [5]. Some family caregivers have no basic knowledge of dementia; many, despite receiving a dementia diagnosis, do not understand the implications of the diagnosis for themselves or their relatives with dementia [1,6]. Limited understanding can result in the person with dementia not receiving the necessary support and treatment to address their needs and improve their well-being, and it can also lead caregivers to feel publicly stigmatized, ashamed, or distressed [5]. Concomitant with a lack of care infrastructure and scarcity of resources, such as respite- and long-term care facilities, is the fact that family caregivers are often very isolated and without support [7]. In these circumstances, caregivers often experience increased burden, a decline in their mental and physical health, and a loss of income and productivity because of caregiving [8-11].

To ameliorate these burdens, greater focus on imparting knowledge and skills to empower caregivers for persons with dementia is crucial [5]. As many family caregivers enter their new role unprepared, they need information about what dementia care involves, care pathways, social and clinical care, sources of help, and other services available [12]. Provision of culturally salient dementia care resources, during diagnosis and postdiagnosis, may help caregivers gain perspective about their family member's behaviors. Such resources would also help families understand dementia as a medical condition rather than attributing symptoms to moral deficits in the person themselves or in the care provided by their caregivers.

Technological innovations, especially digital media, can help improve dementia care. Digital media, particularly smartphones, can help caregivers access information online, monitor their own physiological and biometric data along with that of the person with dementia, and set reminders for medications and other therapies [13,14]. According to a report by the India Cellular & Electronics Association, nearly 830 million people in India are smartphone users, thus making smartphones and digital media crucial dissemination platforms for content creators and service providers [15].

In Australia, an innovative multimedia project called Moving Pictures is producing short films on dementia care, which are coproduced with people from culturally and linguistically diverse backgrounds [16]. The project is a collaboration between the National Ageing Research Institute (NARI) and Curtin University, and the films produced are based on the stories and lived experiences of family caregivers of people living with dementia as well as the expert views of key service providers. Taking into context the need for dementia care resources and the current technological uptake in India, authors from India, Australia, and UK have collaborated to develop Moving Pictures India to improve dementia care in India using digital media. The aim of Moving Pictures India is to coproduce 9 short films on common issues in dementia care with caregivers and stakeholders and to pilot the resources developed to determine whether the findings would support a large implementation trial. There are 4 main objectives of the study: (1) to video interview Indian caregivers and health professionals about cultural understandings of dementia, social and clinical care, sources of help, and care pathways; (2) coproduce 9 short films on dementia care with caregivers and stakeholders; (3) pilot the resources with caregivers to assess feasibility and acceptability using a randomized controlled trial (RCT) design; and (4) disseminate the films online for free and use analytics and qualitative feedback to develop an implementation trial. This paper describes the protocol of the study.

Methods

Methodological Approach

The methodological approach for the study follows the United Kingdom Medical Research Council guidelines for the development and evaluation of complex interventions [17]. The process of designing and evaluating complex health interventions includes development, feasibility and piloting, evaluation, reporting, and implementation. Mobilizing this methodology, this study uses robust mixed methods including video interviews, stakeholder consultation, community forums, a quasi-experimental trial, and big data analytics. Owing to its mixed methods design, this study is divided into 4 different phases based on the main objectives. The methods of each phase including the research design are described as follows.

Phase 1. Video Interviews: Intervention Development

In the first year of the study, video interviews with family caregivers and health professionals will be recorded to create the films for mobile devices targeting family caregivers and the Indian public. Family caregiver interviews will focus on initial perceptions of dementia symptoms, at what point medical intervention was sought and why, examples of successful collaboration between caregivers and services, and how the dementia care pathway unfolds for families. Health professional

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interviews will focus on working with doctors; going to the hospital; pain; eating, nutrition, and dental care; hygiene and incontinence; and later stages and palliative care. The topics for discussion in the interviews are based on patient and public involvement and clinician consultation.

Inclusion Criteria

We will recruit family caregivers who are currently caring for a family member with dementia for at least 6 months. Health professionals include medical specialists (eg, geriatricians, old age psychiatrists), nurses, allied health care workers (eg, physiotherapists, social workers), or related professionals (eg, care coordinators, direct care workers) involved in providing health and community services to people living with dementia. We will include participants who speak either English, Hindi, or Kannada, have the capacity to consent, and are willing to participate in a video interview, snippets of which will be included in the final Moving Pictures India films and resources.

Recruitment and Sampling

The aim is to purposively recruit 25 family caregivers speaking either of the 3 aforementioned languages and representing different genders and socioeconomic classes, along with 25 health professionals who satisfy the inclusion criteria. The sample size was determined based on the research team's extensive experience of sampling to ensure sufficient diversity. Participants will be invited to participate in a 30- to 60-minute video interview conducted in English, Hindi, or Kannada. Purposive and snowball sampling will be employed for recruitment. Data will be collected in Bengaluru, India.

Upon confirmation of interest, the researcher will forward a copy of the participant information and consent form (PICF) either by email or regular mail with a prepaid envelope. Contact will be made a few days later to gauge interest, answer any relevant questions, and arrange the interview. If the consent form is not received by the research team prior to the interview, it will be completed before starting the interview. All participants will be provided with a verbal overview of the study, time to read the PICF (if not done earlier), and an opportunity to seek clarification about any study-related matter from the researcher prior to the interview.

Data Analysis

Data will be translated, transcribed into English, and thematically analyzed [18-20] by the research team using NVivo version 12 or the latest version of the software. Deductive analysis will be used, informed by the cross-cultural care literature, and will focus specifically on how concepts such as aging (eg, "budhapan"), dementia (eg, "yadarsht khona" or losing memory), dementia symptoms (eg, "bak bak" or useless, repetitive talk), and care (eg, "seva") are understood cross-culturally and in light of India's rapid modernization and reduced availability of adult children to provide familial care. Digital resources will be cut from the recordings.

Phase 2. Coproduction of Films and Resources: Intervention Development

In the second year, the data from the first phase will be storyboarded to form the basis of 9 films and animations. The themes for the storyboards are based on common issues in dementia care arrived at through the researchers' prior work [4,16] and will focus on the following themes: (1) signs of dementia; (2) care pathways; (3) self-help for caregivers; (4) recognizing and responding to unmet needs; (5) working with doctors and going to hospital; (6) pain; (7) eating, nutrition, and dental care; (8) hygiene and incontinence; and (9) later stages and palliative care. Storyboards will be internally reviewed for cultural appropriateness followed by realist and critical evaluation at a stakeholder workshop in Bengaluru using the nominal group technique. The nominal group technique is designed to democratically elicit ideas and is widely used in health and education research. It involves group members first working alone, then sharing ideas and undertaking group discussions, and finally, voting and ranking [21]. Stakeholders at the workshop will include the investigator team, film editor, dementia services, clinicians, researchers, and artists. Following stakeholder approval, the storyboards will be converted to Hindi/Kannada films (by the film editor) and animations (by the designer).

To evaluate the appropriateness of the films and animations, they will be member-checked with the original interview participants as well as with community members to ensure believability and trustworthiness [22]. Interview participants and community members will complete a survey (eg, whether expectations were met, level of enjoyment and interaction, key learnings, etc) in English, Hindi, and/or Kannada via telephone or online. Film and animation screenings with community members will be completed using a workshop format, and feedback will be used to improve the resources. A flowchart of this phase is illustrated in Figure 1.

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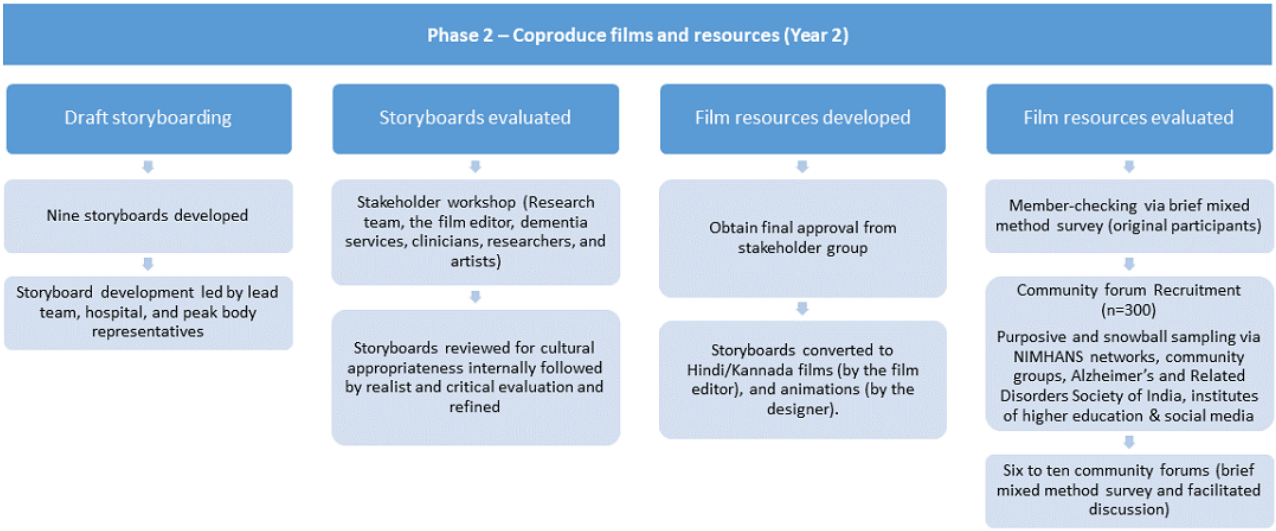
Figure 1. Study protocol flowchart of phase 2: Coproduction of films and resources. NIMHANS: National Institute of Mental Health and Neuro Sciences.



Inclusion Criteria

Members of stakeholder groups and the community members must be 18 years of age or over, have a smartphone, have the capacity to provide consent, and be literate in either English, Hindi, or Kannada.

Recruitment and Sampling

Family caregivers and health professionals who participated in phase 1 of the study will be asked to provide feedback on resources once they are completed. Community members (n=~300) speaking either of the 3 aforementioned languages, representing different genders and socioeconomic classes, and satisfying the inclusion criteria will be recruited in Bengaluru to test the films and resources. Bengaluru is one of the most multicultural and ethnically diverse cities in India and has a large migrant population due to its status as the information technology hub of the country [23,24]. Recruitment will be facilitated via invitations/advertisement (through email, hard copies, social media posts, newsletters, and public notices) to local senior citizens' groups, social groups, Alzheimer's and Related Disorders Society of India Bengaluru Chapter, community and health services, and institutes of higher education. Upon request, a member of the research team will give a talk about the study to groups of interested individuals. Participants will be invited to participate in one of 6-10 workshops (1-2 hours) in which films and resources will be screened and evaluated.

Phase 3. Pilot RCT: Intervention Assessment

To evaluate the impact of the resources produced, a pilot RCT will be conducted in the second and third year of the study (Figure 2). The pilot RCT will follow an experimental parallel group design with two arms aiming to assess the impact, feasibility, and acceptability of the resources of Moving Pictures India. The aims of the pilot RCT will be: (1) to test the feasibility of a full RCT with feasibility prespecified as >70% of participants expressing interest, consenting to participate, and >80% participation in follow up; (2) to test acceptability, prespecified as >70% of participants rating the intervention "very acceptable."

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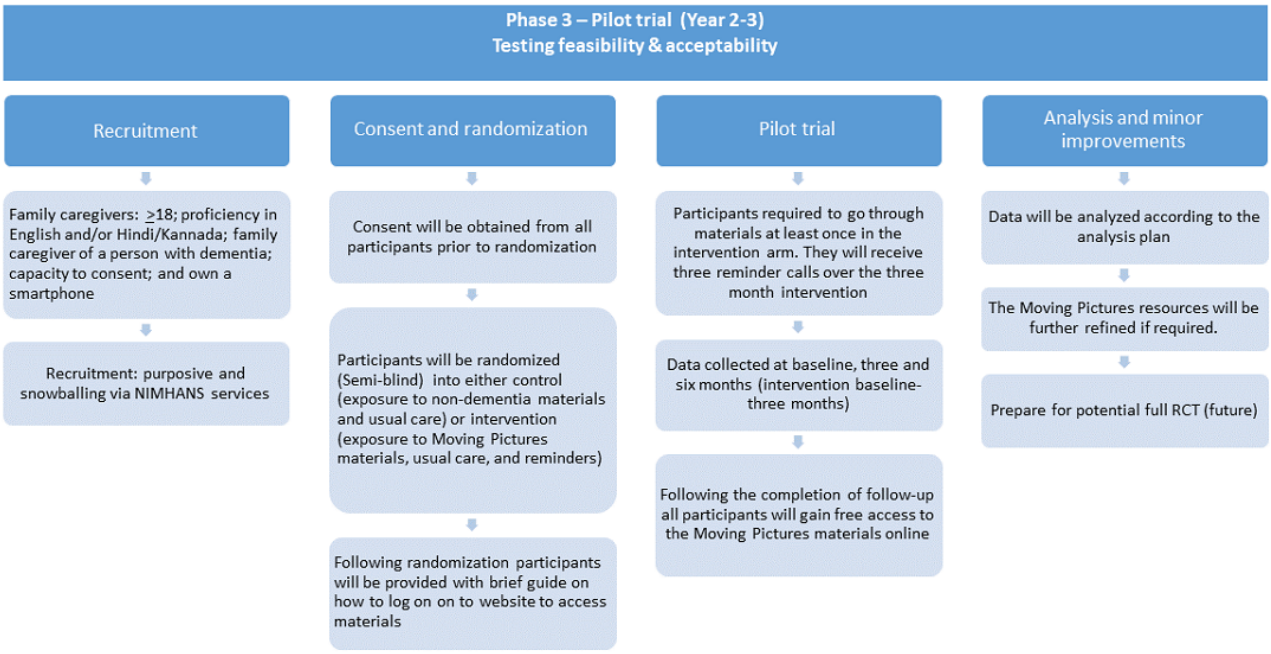
Figure 2. Study protocol flowchart of phase 3: pilot randomized controlled trial. NIMHANS: National Institute of Mental Health and Neuro Sciences; RCT: randomized controlled trial.



Inclusion and Exclusion Criteria

Participant inclusion criteria are aged 18 years and up, proficient in English and/or Hindi/Kannada, self-reported family caregiver of a person with dementia who has been involved in the caregiving process for at least 6 months, capacity to consent, and own a smartphone. Participants involved in the development phase will be excluded.

Recruitment and Sampling

Participants will be recruited in Bengaluru, India. Purposive and snowball sampling will be employed for recruitment. Family caregivers who accompany people with dementia to the Geriatric Clinic and Services Unit at the National Institute of Mental Health and Neuro Sciences (NIMHANS) will be recruited. Furthermore, advertisements will be posted in public spaces in the NIMHANS facility and distributed in hard or soft copy by the research team to relevant clients, through relevant NIMHANS services and other support and social groups. The materials will contain contact details for the NIMHANS-based research team (email/phone). Potential participants will be able to contact the research team to express their interest in the study. The researcher will describe the study procedures, and if the participant agrees to the study, the researcher will confirm the participant's eligibility. Alternatively, if potential participants learn about the study from a NIMHANS service provider, the latter will provide the contact details of the research team or, with verbal consent from the interested individual, forward their details to the research team, who will make the initial contact to provide the necessary study information. Upon confirmation of interest, the researcher will forward a copy of the PICF either by email or regular mail with a prepaid envelope, or it can be obtained from the research team located at NIMHANS upon request. Contact through phone or email will be made a few days later to confirm interest, answer any questions, and arrange for a brief meeting to sign the consent form. Signed consent can also be provided by mail or electronically.

Randomization and Blinding

Following consent, participants will be randomized into either an intervention arm that comprises usual clinical care plus access and use of the digital resources or a control arm comprising usual clinical care and access to nondementia resources (eg, a pamphlet on healthy living). Randomization will be done using computer-generated random number sequences, and the process will be overseen by a researcher not involved in the study. After allocation to groups, participants will be able to choose to receive specific instructions on how to access materials relevant to the condition (a brief instructional booklet) they have been allocated to either electronically, by regular mail, or in person. As a booster, participants in the intervention arm will also receive a monthly phone call from the research associate to help sustain intervention engagement over the long term, which is a risk to any digital trial [25]. Caregivers will not be told whether they are in the intervention or the control group to reduce potential bias. However, this blinding is not expected to be of any disadvantage, as all participants will have free and unlimited access to the Moving Pictures India materials after the pilot RCT.

Outcome Measures

The primary outcome measures for the pilot RCT will be feasibility and acceptability, while the secondary outcome measures for the pilot RCT will be (1) caregiver burden, as measured by the Zarit Burden Interview [26]; (2) caregiver mood, as measured by the Center for Epidemiological Studies Depression 10-item scale [27]; and (3) caregiver quality of life, as measured by the World Health Organization Quality of Life Scale [28].

Validated, translated versions of the Zarit Burden Interview and World Health Organization Quality of Life Scale measures are

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already available in English, Hindi, and several other Indian languages. All the secondary outcome measures will be self-rated and measured at baseline, 3 months, and 6 months via regular mail, telephone, or online. Sociodemographic data (eg, age, gender, socioeconomic status, relation to the person with dementia, years as a caregiver) will also be collected. The schedule of enrolment, interventions, and assessments for the pilot RCT is presented in Figure 3.

Figure 3. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flowchart of the schedule of enrollment, interventions, and assessments for the phase 3 pilot randomized controlled trial.

	Study period			
	Enrolment	Allocation	Postmeasurement	Postmeasurement
Time point	$-t_1$	t_0	t_1 (3 months)	t_2 (6 months)
Enrolment				
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Exposure to Moving Pictures India materials, usual care, and reminders		←	—	→
Exposure to nondementia materials and usual care		←	—	→
Assessments				
Primary outcomes				
Feasibility and acceptability			✓	✓
Secondary outcomes				
Zarit Burden Interview (ZBI)		✓	✓	✓
Center for Epidemiological Studies Depression-10 item scale (CES-D10)		✓	✓	✓
World Health Organization Quality of Life Scale (WHOQOL-BREF)		✓	✓	✓
Sociodemographic data (eg, age, gender, socioeconomic status, relation to the person with dementia, years as a caregiver)	✓			

Statistical Analysis

To estimate parameters of feasibility and acceptability with sufficient precision, which will help inform the future implementation trial, 40 participants from the intervention arm and 20 from the control arm are expected. The expected values for the proportion of family caregivers rating the intervention as “very acceptable” are 70% (95% CI 59%-87%) or 70% (95% CI 62%-85%) for participants for whom outcomes are completed at the 6-month follow-up. Achieving these expected values will be a priori criteria for progression to an implementation trial without modification of the intervention.

Repeat measures ANOVA will examine changes over time. The proportions of eligible family caregivers approached who agreed to take part in the study will be reported with a 95% CI, and any reasons for refusal will be summarized. Characteristics of people with dementia and their family caregivers that are included in the study will be summarized using means (with SD), medians (with interquartile ranges), counts, and proportions, as appropriate. Scores measured pre- and postintervention will be summarized at each time point (eg, using means and SD) and as differences between the randomization groups with 95% CI. Completeness of these scores will also be described. We will estimate parameters to help inform development of the implementation trial, particularly, the proportion of family caregivers using the intervention and for whom outcomes were completed at the 6-month follow-up.

Postpilot Revision

If required, specific changes based on the research team’s postpilot experience and participant feedback will be incorporated into the intervention before dissemination of the resources.

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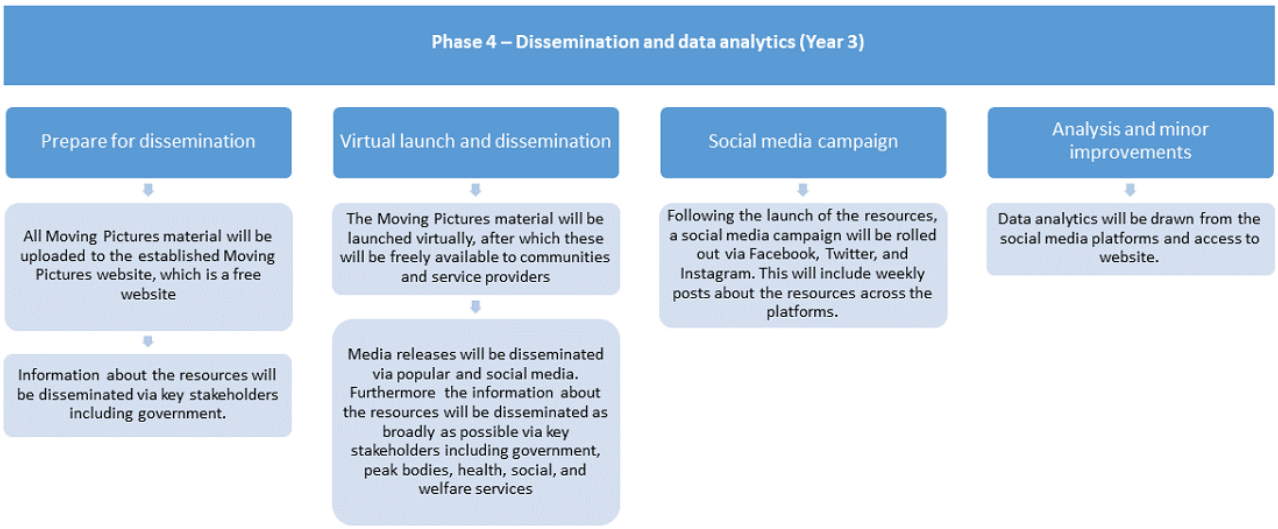
Phase 4. Dissemination and Analytics: Intervention Dissemination

Following postpilot minor revisions (if any), all the resources developed in the study will be disseminated via the mobile-optimized Moving Pictures website. Key stakeholders (eg, the Indian Ministries of Health and Social Justice, state and local government health and welfare offices, Alzheimer's and Related Disorders Society of India, Alzheimer's International; Alzheimer's Association in the United States, community groups, health services, and media) and consumers (caregivers, people with dementia, and the general public) will receive a media release with links to the website. Social media campaigns will also be run at regular intervals on Facebook, YouTube, WhatsApp, and Twitter. To evaluate the reach and uptake of these digital resources, analytics data will examine website traffic and viewing trends over 6 months. The feedback in the comment sections will be reviewed and visits to the website will be counted. A flowchart of this phase is illustrated in Figure 4.

Figure 4. Study protocol flowchart of phase 4: dissemination and analytics.



Ethics Approval

The procedures outlined in this study are in accordance with the Declaration of Helsinki, and this study has been approved by the NIMHANS Ethics Committee (26th IEC (BEH.SC.DIV.)/2020-21 dated November 11, 2020); the Health Ministry's Screening Committee, India (proposal ID 2020-10137); the Curtin University Human Research Ethics Committee (approval number HRE2020-0735); and the NARI Research Governance Office (site-specific approval dated March 17, 2021).

Data Storage and Transfer

As the data are being collected in India, data will be stored securely onsite; specifically, hard copy data will be stored in a locked filing cabinet in the office of the investigators. Signed documents will be converted to electronic files, which will then be password protected and stored on the secured NIMHANS network. When in the field, data will be stored on the research staff member's laptop, which is password protected and backed up to an external hard drive that will also be password protected if required. All data (hard and soft copies) will be stored securely stored and destroyed 7 years after publication. Electronic copies of all data will be securely shared with the Australian research team. During data analysis and write-up, the data will be stored on a secured server in the password-protected folder only accessible by the Moving Pictures research team. Upon completion, all data will be securely transferred and stored under secure conditions at Curtin University and NARI, Australia, for 7 years after the research is published and then securely destroyed.

Project Dissemination

Data will be published in deidentified form in academic and other publications (book chapters, conference presentations, media releases, social media posts, etc) under pseudonyms or participant IDs. For example, the participant might be described in the following manner: Asha Chand (pseudonym), female, age, caregiver for mother. Data used in films and resources may be identifiable, as we will be using the video data from the interviews in the resources. Caregivers will be assigned pseudonyms, and health providers will be using their own names and affiliations as specified in the PICFs. The films will be accessible via the Moving Pictures website to anyone in the community, and efforts will be made to disseminate the resources as broadly as possible. There are no plans to make the dataset publicly available after deidentification.

Results

This study was funded by the Alzheimer's Association. It brings together complementary expertise across multiple disciplines such as anthropology, psychology, psychiatry, geriatrics, film and media studies, disability studies, and social work.

Postdissemination analytics and qualitative feedback will be used to develop an implementation trial; explore how different strategies for dissemination and integrating the resources in local service provisions impact relevant caregiver variables like

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caregiver burden, mood, and quality of life; and evaluate the effects of the approaches to improve the uptake and utilization of the intervention. From July to December 2023, we will enroll 60 dementia caregivers (40 caregivers in the intervention group and 20 in the control) for the pilot RCT and follow them up for 6 months. This study is expected to conclude in June 2024.

Discussion

Overview

Although dementia has been recognized as a global public health priority, a huge gap between dementia care needs and resources still exists, especially in low- and middle-income countries. There is a clear need for the development of dementia literacy and care resources that emphasize identifying dementia through awareness, offer interventions to manage the symptoms of dementia, and promote well-being of both the caregiver and the person with dementia. In this paper, we have outlined the design of an intervention study that involves the development of a digital media resource to improve dementia care in India and determine the feasibility and acceptability of the developed resource using an RCT design. This study will be one of the first to deliver coproduced, evidence-based media resources to support caregivers of people with dementia in the Indian context.

Comparison With Prior Work

The flexible, nonlinear approach of the UK Medical Research Council framework that guides the methodology of this study has previously been used in the design processes for the development of new technology-based interventions across disciplines [29-31]. This protocol emphasizes the importance of all the stages involved in developing and evaluating complex interventions, such as Moving Pictures India, and provides equal focus on development and piloting work as it does to the evaluation and proper consideration of the practical issues of implementation.

Through the process of coproducing films, we will gain an understanding of how dementia is perceived cross-culturally. This is an important aspect for dementia literacy and care, as dementia in India is typically viewed as a natural part of aging with cultural explanations used to describe dementia such as “chinnan” (childishness) [32]. The outcomes defined for the study, as well as the instruments to measure the outcomes, have been used in earlier studies with caregivers of people with dementia [29,33-36].

Limitations

Although there are no foreseeable risks associated with participation in this study, there are some factors that may hinder recruitment and participant retention. Digital media is not a common support intervention for caregivers of persons with dementia in India, and acceptance of the program, especially by older caregivers such as spouses, could hamper recruitment. Lack of time to take part in the study due to care responsibilities could also be a factor in retention and recruitment. Nonadherence in eHealth interventions has been reported to be high in earlier studies [37,38]. Another limitation could be that only motivated and active caregivers who are internet or media savvy will take part in the study, which could possibly limit the generalizability of the results and acceptance of the program for the anticipated larger trial. Notwithstanding the limitations, the protocol includes potentially useful approaches for implementation, the most significant of which is the involvement of stakeholders and the utilization of a multifaceted approach involving a mixture of interactive workshops, feedback, reminders, and local consensus processes in the design of the research to ensure relevance [39,40].

Conclusions

This research protocol directly addresses a looming public health crisis in India by promoting dementia awareness and developing resources to support caregivers in delivering high-quality care at home. It offers solutions that are culturally specific, scalable, and based on knowledge of local resources and burden of disease [41]. Thus, it has the potential to improve the lives of millions of people in India. The design selected leverages India’s significant online presence, and resources will be available to those who have difficulty accessing face-to-face information and support on account of being too busy, having difficulty traveling, and/or living in rural areas. Importantly, the lessons learned from this study are highly transferable. India also has a diaspora of 30 million people, the largest in the world [42]. Concerns regarding suboptimal dementia care in Indian communities have been expressed by caregivers and key service providers in the Moving Pictures Australia study [16]. Similar concerns have also been echoed from studies in the United Kingdom and Canada [43,44]. With the integrated insights from Moving Pictures Australia and Moving Pictures India, this protocol will yield an intervention that will be transferrable to multiple diaspora communities in low-, middle-, and high-income countries and will explore how different strategies for dissemination and integrating resources in local service provisions could impact caregiver burden, mood, and quality of life.

Acknowledgments

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Data Availability

Raw footage of the video interviews cannot be entirely deidentified and will not be publicly available. Other data set generated during this study, such as deidentified transcripts and anonymized survey data, RCT data, and data analytics, will be available from the corresponding author upon reasonable request.

Conflicts of Interest

BB is the lead principal investigator and JA is the principal investigator of the Moving Pictures Australia study.

Multimedia Appendix 1
Blinded peer-review assessment scores and comments from the Alzheimer's Association Research Grant Review Committee - Alzheimer's Association Research Grant (AARG).
[PDF File (Adobe PDF File), 108 KB - resprot_v11i6e38456_app1.pdf]

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Abbreviations

NARI: National Ageing Research Institute
NIMHANS: National Institute of Mental Health and Neuro Sciences
PICF: participant information and consent form
RCT: randomized controlled trial

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Protocol

Impact of Web-Based Cognitive Behavioral Therapy for Insomnia on Stress, Health, Mood, Cognitive, Inflammatory, and Neurodegenerative Outcomes in Rural Dementia Caregivers: Protocol for the NiteCAPP CARES and NiteCAPP SHARES Randomized Controlled Trial

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Abstract

Background: Chronic insomnia affects up to 63% of family dementia caregivers. Research suggests that chronic insomnia prompts changes in central stress processing that have downstream negative effects on health and mood, as well as on cognitive, inflammatory, and neurodegenerative functioning. We hypothesize that cognitive behavioral therapy for insomnia (CBT-I) will reverse those downstream effects by improving insomnia and restoring healthy central stress processing. Rural caregivers are particularly vulnerable, but they have limited access to CBT-I; therefore, we developed an accessible digital version using community input (NiteCAPP CARES).

Objective: This trial will evaluate the acceptability, feasibility, and short-term and long-term effects of NiteCAPP CARES on the sleep and stress mechanisms underlying poor caregiver health and functioning.

Methods: Dyads (n=100) consisting of caregivers with chronic insomnia and their coresiding persons with dementia will be recruited from Columbia and surrounding areas in Missouri, United States. Participant dyads will be randomized to 4 weeks (plus 4 bimonthly booster sessions) of NiteCAPP CARES or a web-based sleep hygiene control (NiteCAPP SHARES). Participants will be assessed at baseline, after treatment, and 6- and 12-month follow-ups. The following assessments will be completed by caregivers: 1 week of actigraphy and daily diaries measuring sleep, Insomnia Severity Index, arousal (heart rate variability), inflammation (blood-derived biomarkers: interleukin-6 and C-reactive protein), neurodegeneration (blood-derived biomarkers: plasma amyloid beta [Aβ40 and Aβ42], total tau, and phosphorylated tau [p-tau181 and p-tau217]), cognition (Joggle battery, NIH Toolbox for Assessment of Neurological and Behavioral Function, and Cognitive Failures Questionnaire), stress and burden, health, and mood (depression and anxiety). Persons with dementia will complete 1 week of actigraphy at each time point.

Results: Recruitment procedures started in February 2022. All data are expected to be collected by 2026. Full trial results are planned to be published by 2027. Secondary analyses of baseline data will be subsequently published.

Conclusions: This randomized controlled trial tests NiteCAPP CARES, a web-based CBT-I for rural caregivers. The knowledge obtained will address not only what outcomes improve but also how and why they improve and for how long, which will help us to modify NiteCAPP CARES to optimize treatment potency and support future pragmatic testing and dissemination.

Trial Registration: ClinicalTrials.gov NCT04896775; https://clinicaltrials.gov/ct2/show/NCT04896775

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KEYWORDS

caregiver; CBT-I; cognition; dementia; inflammation; insomnia; neurodegeneration

Introduction

Background

Approximately 16 million Americans serve as unpaid informal caregivers (CGs), providing 18.6 billion hours of care, which translates into US $244 billion in health care savings [1]. The number of persons with dementia in the United States is projected to rise from 5.7 million to >14 million in the next 30 years, and most persons with dementia (70%) are cared for at home by a family member [1]. This rise in the number of persons with dementia is likely to increase the number of CGs, especially in rural areas, where populations are aging faster than those in urban areas [2]. Chronic insomnia (≥3 months difficulty initiating and maintaining sleep, early morning awakening, or nonrestorative sleep) affects up to 63% of CGs [3,4] and tends to endure (18 years on average in our CG studies) [4,5]. Factors associated with CG insomnia include changes in central stress processing (increased sympathetic nervous system arousal) [3,6] as well as worse health and daytime functioning (increased depression, stress, and cognitive dysfunction). Research [3-5] shows that cognitive behavioral therapy for insomnia (CBT-I) is an efficacious treatment for the chronic and particularly long-lasting insomnia experienced by CGs and suggests that it may restore healthy central stress processing [7]. However, rural CGs have less access to care, including CBT-I, because of significant shortages of both primary and specialty care providers in rural areas [8]. Web-based CBT-I will allow for greater dissemination, particularly for rural CGs and persons with dementia who may have challenges receiving treatment because of trained provider scarcity [9] and the burden associated with traditional in-office delivery.

It has been shown by our team as well as another group of researchers that in-person brief CBT-I (bCBT-I) improves CG sleep and mood (small to large effects) [10-12]. Early research by McCurry et al [12] found that in-person bCBT-I improved CG sleep (efficiency and quality) and depression immediately and 3 months after treatment compared with a waitlist. Our team also found that in-person bCBT-I improved sleep, depression, and anxiety in older adult CGs of persons with dementia [10]. McCrae et al [11] also found that bCBT-I (2 in-person sessions and 2 telehealth sessions) improved sleep in rural older adults for at least 3 months compared with the sleep hygiene control. Our new pilot data also suggest that CBT-I translates well to telehealth [7,13]. However, telehealth delivery still requires considerable time commitment from trained therapists (already in short supply). Thus, web delivery represents an important, logical next step that would maximize therapist time (ie, web-based moderation and feedback vs 1 hour per week one-on-one sessions), reduce CG travel burden, and give both therapist and CG scheduling flexibility. Web delivery would also enhance disseminability because the majority of Americans (including rural and older Americans) use the internet and have access to it [14]. Moreover, several meta-analyses of web-based CBT-I have indicated moderate to large effect sizes for sleep improvement that are comparable to in-person CBT-I effects [15,16]. Although web-based CBT-I has not been tested in CGs, web interventions have successfully improved noninsomnia health outcomes in stroke and CGs [7,17]. These findings provide support for the development and evaluation of web-based CBT-I for CGs (NiteCAPP CARES) in the proposed study.

Several considerations were taken into account in the development of NiteCAPP CARES. For instance, given prior work showing that providing CGs with behavioral sleep instructions for their persons with dementia led to improved sleep in persons with dementia (measured using actigraphy) [7], NiteCAPP CARES uses a dyadic approach that targets sleep for both the CG and care recipient. In addition, following recommendations from other CBT-I studies [16], NiteCAPP CARES uses a guided therapy approach with trained therapy moderators monitoring the progress of CGs and persons with dementia, providing feedback, and answering questions. Taking a dyadic, guided therapy approach may optimize the impact of CBT-I on CG mechanisms and outcomes.

Research suggests that CG chronic insomnia results in changes in central stress processing that have downstream negative effects on health and daytime functioning. CGs experience increased subjective stress and arousal because they witness the distress experienced by persons with dementia and because of the physical and time demands of caregiving [4,5]. Research shows that persons with chronic insomnia have alterations in heart rate (HR) and HR variability (HRV) while awake before sleep and during stage 2 non–rapid eye movement sleep [18], as well as lower wake-to-sleep HR reduction and SD of normal-to-normal heartbeat intervals compared with controls [19], consistent with disrupted autonomic nervous system (ANS) functioning (increased sympathetic activity). In CGs, increased self-reported stress is associated with altered HRV during the first half of sleep (lower high-frequency power values), indicative of impaired ANS functioning [19]. Our preliminary results have shown that HRV can be altered because bCBT-I increased resting HRV in adults with comorbid insomnia [10]. Collectively, the findings in comorbid insomnia and our preliminary data suggest that physiological arousal serves as a mechanism underlying other CG symptoms.

CGs also face mental and physical health–related challenges regarding mood and cognition, as well as neurodegenerative and inflammatory biomarkers. Sleep may play a role in CGs' high levels of anxiety and depression [20] because our research shows that nights of poor sleep (ie, higher total wake time and poorer sleep quality) were associated with greater next-day negative affect in CGs [10]. Research, including ours, shows

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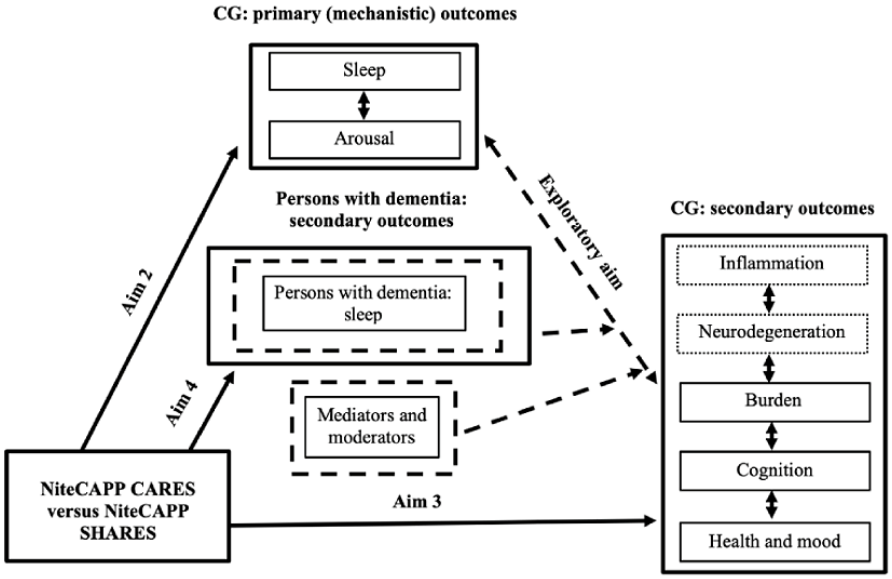
that CBT-I can improve depression in CGs [12,21,22]. In addition, CGs perform worse on tests of processing speed [23,24], attention [23,25,26], executive function [26], and memory [26,27] than same age non-CGs. Our recent trial shows that telehealth CBT-I can improve CG executive functioning and processing speed [10]. Moreover, preclinical studies link poor sleep to increased Alzheimer disease–related biomarkers (plasma amyloid beta [Aβ] and tau), suggesting that sleep is essential for protein clearance and reduction of neuronal aggregations contributing to plaques and tangles (hallmark pathology of Alzheimer disease) [27]. Risk of developing Alzheimer disease is elevated in CGs versus non-CGs (up to 6 times greater) [28], and CGs have increased peripheral inflammatory biomarker levels (eg, C-reactive protein) [29]. Sleep quality improvements are associated with reductions in inflammatory markers associated with Alzheimer disease, that is, C-reactive protein (small effects) and interleukin-6 concentrations (large effects) [29], as well as expression of inflammatory-related genes [30]. These studies suggest that targeting poor sleep may lower Alzheimer disease–related biomarker levels, thereby mitigating risk and delaying disease progression. The proposed trial will examine whether treating CGs' sleep disturbances through NiteCAPP CARES may help mitigate their neurodegenerative risks.

The Cognitive Activation Theory of Stress [31] underlies the basic premise guiding the proposed trial, namely that CGs experience chronic insomnia, arousal, and inflammation that are associated with central nervous system changes that negatively affect other CG health outcomes (Figure 1). Specifically, arousal, poor sleep, and inflammation lead to critical changes in the hypothalamic-pituitary-adrenal axis and ANS, primarily sympathetic activation functioning, that contribute to lower health-related quality of life, increased depression and burden, and decreased cognitive functioning. We propose that NiteCAPP CARES holds promise for improving multiple CG health outcomes by improving common underlying mechanisms (sleep and arousal), thereby restoring healthy hypothalamic-pituitary-adrenal axis and ANS functioning. NiteCAPP CARES will engage these mechanisms using established sleep techniques (sleep education, sleep hygiene, and stimulus control), modified techniques (for older adults and CGs; sleep compression and brief relaxation), techniques for other CG issues (problem solving and stress management), and by targeting sleep change in persons with dementia (direct participation of persons with dementia or CG administration of behavioral techniques).

Figure 1. Conceptual model. Aim 1 (not shown) examines feasibility and acceptability of NiteCAPP CARES and NiteCAPP SHARES. Sleep change in person with dementia will be examined as an outcome (aim 4) and a potential moderator (exploratory aim: dashed lines) of the relationship between changes in caregiver (CG) primary and secondary outcomes. Refer to the Outcomes section for a list of potential mediators (eg, adherence) and moderators (eg, sleep change in person with dementia, interpersonal processes, and shared lifestyle factors). Biomarkers of neurodegeneration and inflammation will be examined as exploratory CG secondary outcomes (dotted box outline). NiteCAPP CARES: cognitive behavioral therapy for insomnia; NiteCAPP SHARES: active web-based sleep hygiene and related education control.



The base NiteCAPP platform was developed in 2019 by the study team and was based on a 4-session CBT-I treatment protocol developed by the first author (CSM) and used for research [10,32] and clinical service delivery for >20 years. Initial adaptations for CGs to create NiteCAPP CARES were made following the Medical Research Council recommendations for evaluating complex medical interventions, including community participation, usability testing, and validation. The details of the preliminary work are available elsewhere [7]. Although the findings from these usability studies were promising and demonstrated the preliminary feasibility and acceptability of NiteCAPP CARES as well as its efficacy for improving sleep and other variables for CGs, they warrant further investigation in a larger sample and comparison with an active control condition across a wider range of outcomes. The proposed trial offers the following methodological improvements: inclusion of an active control group (web-based sleep hygiene and related education [NiteCAPP SHARES]),

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increased number and length of follow-ups, and a dyadic approach (because persons with dementia experience poor sleep and nighttime behavior that negatively affects CGs). In sum, the proposed trial addresses significant gaps in the literature and the need for effective insomnia treatment for CGs and persons with dementia.

Objectives

The overarching goal of this randomized controlled trial (RCT) is to evaluate the acceptability, feasibility, and short-term and long-term effects of NiteCAPP CARES on the sleep and stress mechanisms underlying poor CG health and functioning. Our first specific aim is to examine the feasibility and acceptability of NiteCAPP CARES and an active web control (sleep hygiene and related education [NiteCAPP SHARES]). We hypothesize that NiteCAPP CARES and NiteCAPP SHARES will have high rates of completion (≥75% of sessions), adherence (≥75% of the techniques implemented), satisfaction (≥7.5 out of 10 on the Satisfaction Survey), and utility (≥3.5 out of 5 on the Internet Intervention Utility Questionnaire).

Our second specific aim is to examine the effects of NiteCAPP CARES on the primary (mechanistic) CG outcomes in our theory-driven conceptual model; that is, to examine the effects of 4 weeks of CBT-I compared with 4 weeks of NiteCAPP SHARES on CG sleep (insomnia severity and self-reported sleep onset latency, wake time after sleep onset, and sleep efficiency) and arousal immediately after treatment and at 6- and 12-month follow-ups. We hypothesize that compared with NiteCAPP SHARES, NiteCAPP CARES will improve CG sleep and decrease arousal.

Our third specific aim is to examine the effects of NiteCAPP CARES on the secondary CG outcomes in our theory-driven conceptual model; that is, to examine the effects of 4 weeks of CBT-I compared with weeks of NiteCAPP SHARES on CG health, mood, burden, cognition, inflammation, and neurodegeneration immediately after treatment and at 6- and 12-month follow-ups. We hypothesize that compared with NiteCAPP SHARES, NiteCAPP CARES will improve these CG outcomes.

Our fourth specific aim is to test the effect of NiteCAPP CARES on persons with dementia, the secondary outcome in our theory-driven conceptual model; that is, to examine the effects of 4 weeks of CBT-I compared with 4 weeks of NiteCAPP SHARES on sleep change in persons with dementia (objective measurement through actigraphy and total sleep time) immediately after treatment and at 6- and 12-month follow-ups. We hypothesize that compared with NiteCAPP SHARES, NiteCAPP CARES will improve sleep in persons with dementia.

Our exploratory aim is to examine the relationships between CG primary and secondary outcome changes and their potential mediators (eg, adherence) and moderators (eg, sleep change in persons with dementia, interpersonal processes, and shared lifestyle factors).

Methods

Trial Design and Study Setting

Dyads (n=100) consisting of CGs with chronic insomnia and their coresiding persons with dementia will be recruited from Columbia and surrounding areas in Missouri, United States, and randomized to 4 sessions of NiteCAPP CARES or NiteCAPP SHARES. The groups will receive bimonthly boosters. Baseline and posttreatment assessments as well as 6-month and 12-month follow-ups will measure sleep, arousal, biomarkers of inflammation and neurodegeneration, health, mood, burden, and cognition.

Graduate therapists and assessors will obtain written informed consent from CGs and persons with dementia, if possible. If the person with dementia is unable to consent (determined by consultation with the first author [CSM]), a legally authorized representative must sign a consent form on their behalf. If the person with dementia becomes unable to provide consent during the course of the study, the legally authorized representative will be asked to reconsent on behalf of the care recipient. Dyads in both groups will receive US $125 at baseline, US $150 after treatment, US $175 at 6-month follow-up, and US $200 at 12-month follow-up, as well as treatment at no cost. NiteCAPP SHARES participants will be offered NiteCAPP CARES at no cost after the study.

Eligibility Criteria

The CG inclusion criteria are as follows: (1) aged ≥18 years, (2) CG living with persons with dementia, (3) willing to be randomized, (4) able to read and understand English, (5) diagnosed with insomnia [33-35], and (6) no newly prescribed or over-the-counter sleep medications for ≥1 month or stabilized for ≥6 months. Insomnia diagnosis requires (1) sleep complaints for ≥6 months, (2) adequate opportunity and circumstances for sleep, (3) at least one of the following: difficulty falling asleep or staying asleep or waking too early, (4) daytime dysfunction (mood, cognitive, social, or occupational) because of insomnia, and (5) baseline diaries indicate >30 minutes of sleep onset latency or wake after sleep onset on ≥3 nights.

The CG exclusion criteria are as follows: (1) unable to consent, (2) cognitive impairment (based on score of ≤25 on the Montreal Cognitive Assessment), (3) sleep disorder other than insomnia (ie, apnea (Apnea-Hypopnea Index score>15), (4) bipolar or seizure disorder, (5) other major psychopathology except depression or anxiety (eg, suicidal or psychotic), (6) severe untreated psychiatric comorbidity, (7) psychotropic or other medications (eg, clonidine) that alter sleep, and (8) nonpharmacological treatment for sleep or mood outside of current trial.

The inclusion criteria for persons with dementia are as follows: (1) probable or possible Alzheimer disease (self-report or primary care physician's written confirmation), (2) at least one problem on the Nighttime Behavior Inventory ≥3 nights per week, (3) able to tolerate actigraphy, (4) not taking any new sleep medications for ≥1 month or stabilized ≥6 months, (5) untreated sleep disorder for which CBT-I is not recommended

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(ie, sleep apnea), and (6) scoring <32 on the sleep apnea scale on the Sleep Disorders Questionnaire.

Randomization and Blinding

Computer randomization will be performed by the team's biostatistician, using a permuted block randomization technique stratified by baseline sleep medication use (yes or no) [36]. Other personnel (except for therapists, supervisor, and project coordinator) will be blinded to randomization.

Procedures

Screening

A sleep psychologist (principal investigator CSM) will diagnose insomnia and make referrals for other suspected sleep disorders (eg, apnea). Screening will be carried out in four stages:

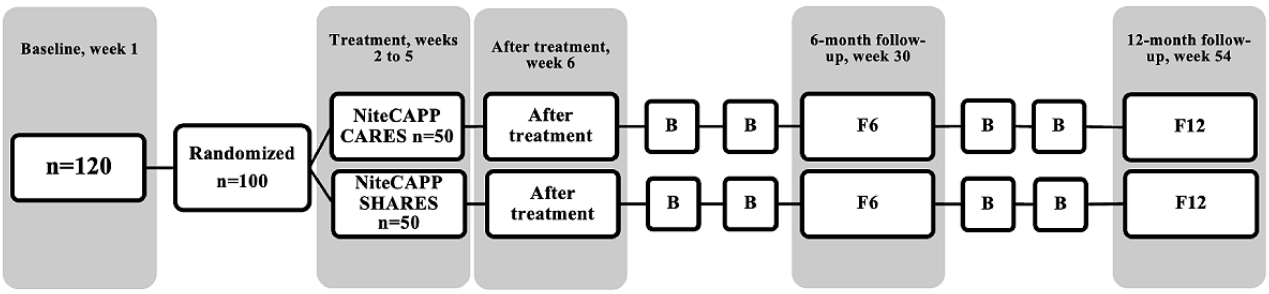
- Stage 1: brief screener (15 minutes). The project coordinator will (1) conduct a brief structured interview to address the inclusion and exclusion criteria and establish a probable insomnia diagnosis and (2) administer the Montreal Cognitive Assessment (CG must score >25, a cutoff chosen to maintain consistency with our prior clinical trial).
- Stage 2: clinical interview (50 minutes). The assessor will (1) conduct a semistructured sleep and psychiatric interview and (2) facilitate and assist with web-based baseline questionnaire completion.
- Stage 3: apnea testing (1 overnight session). This consists of 1 night of at-home sleep testing using disposable WatchPAT One devices (Itamar Medical Ltd) to rule out sleep disorders other than insomnia (ie, apnea). The assessor will instruct CGs on how to use WatchPAT One devices in their own homes so that the CGs can sleep in their own beds. Referrals will be made for those disqualified. The WatchPAT One (a wrist-worn device with 2 finger sensors) measures peripheral arterial tone, oximetry, actigraphy, HR, body position, and snoring.
- Stage 4: sleep diary confirmation of insomnia (5 minutes per day). Electronic baseline diaries will confirm insomnia diagnosis and must show >30 minutes of sleep onset latency or wake after sleep onset on ≥3 nights over 7 days. Diaries will be collected electronically through Qualtrics software with personal web-enabled devices or (if needed) study-provided devices and internet service.

Interventions

Both arms (NiteCAPP CARES and NiteCAPP SHARES) include 4 web-based sessions and 4 bimonthly, 20-minute boosters (Figure 2) with a therapist moderator (predoctoral graduate students in an American Psychological Association–accredited psychology program at the University of Missouri). Details of the development of NiteCAPP have been published and are available [7]. Each session is completed individually by CGs (with persons with dementia to the extent able) in a single sitting (<45 minutes). Each session should be completed in 7 days, with the next session released only after the previous one is completed. All procedures will be conducted at participants' homes. Session content details for NiteCAPP CARES and NiteCAPP SHARES are provided in Textboxes 1 and 2, respectively.

Both interventions will be dyadic, and CGs will work with persons with dementia to implement behavioral strategies similar to those used by McCrae et al [10] and McCurry et al [12]. Active participation of persons with dementia is a goal but may be limited because of dementia symptoms. Behavioral strategies for persons with dementia will be tailored based on baseline assessment (use of actigraphy in persons with dementia, nighttime behaviors, and dementia severity and other questionnaires). To provide a guided therapy approach, trained moderators (psychology doctoral students) will (1) monitor adherence and progress (log-in details and log completion), (2) provide weekly email feedback on sleep patterns and progress, (3) answer questions within 24 hours through a web-embedded message forum, and (4) provide bimonthly boosters (discuss maintenance and troubleshoot problems).

Figure 2. Session and booster timeline. The randomization numbers refer to dyads (ie, caregivers and their coresiding persons with dementia). B: booster session; F6: 6-month follow-up; F12: 12-month follow-up; NiteCAPP CARES: cognitive behavioral therapy for insomnia; NiteCAPP SHARES: active web-based sleep hygiene and related education control.



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Textbox 1. Session content for NiteCAPP CARES.

1. Sleep hygiene, sleep education, and stimulus control

- Sleep hygiene will be taught, and participants are instructed to adhere to the following rules (the goal of sleep hygiene is to eliminate sleep-interfering behaviors):
  - avoid caffeine after noon
  - within 2 hours of going to bed, avoid exercise and heavy meals
  - within 1 hour of bedtime, avoid screen time
  - use the bed for sleeping only

2. Sleep compression, relaxation, and problem solving

- The therapist moderator and caregiver and person with dementia will work together to create a sleep prescription and set regular bed and wake times consistent with the prescription. Caregiver and person with dementia will be instructed to practice relaxation techniques. Caregiver will be provided suggestions on how to solve the challenges associated with caregiving for a person with dementia.

3. Coping and stress management and cognitive therapy

- Sleep prescription for caregiver and person with dementia will be updated as appropriate. Coping and stress management techniques will be taught. Caregiver and person with dementia will be taught how to identify maladaptive thoughts and replace them with balanced thoughts.

4. Review and education and plan for maintenance of behavior change

- Sleep prescription for caregiver and person with dementia will be updated as appropriate. Caregiver and person with dementia will be provided information on how to maintain sleep changes.

5. Booster sessions

- In this brief (approximately 20 minutes) telephone session, techniques from sessions 1 to 4 will be reviewed. The therapist moderator will encourage continued practice of techniques and assist in troubleshooting of problems.

Textbox 2. Session content for NiteCAPP SHARES.

1. Expanded sleep education and sleep hygiene

- Participants are provided sleep education regarding sleep and the brain, mood, behavior, health, and weight. Sleep hygiene will be taught and participants are instructed to adhere to the following rules (the goal of sleep hygiene is to eliminate sleep-interfering behaviors):
  - avoid caffeine after noon
  - within 2 hours of going to bed, avoid exercise and heavy meals
  - within 1 hour of bedtime, avoid screen time
  - use the bed for sleeping only

2. Insomnia education and sleep hygiene support

- Participants are provided education on sleep stages and cycles, sleep disorders, and safety precautions regarding sleep.

3. Targeted sleep education and sleep in dementia

- Participants are provided targeted sleep education and education about sleep in dementia.

4. Review and education and plan for maintenance of behavior change

- Sleep prescription for caregiver and person with dementia will be updated as appropriate. Caregiver and person with dementia will be provided information on how to maintain sleep changes.

5. Booster sessions

- In this brief (approximately 20 minutes) telephone session, techniques from sessions 1 to 4 will be reviewed. The therapist moderator will encourage continued practice of techniques and assist in troubleshooting of problems.

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Treatment Integrity

The 3-step method formulated by Lichstein [37] will be used to measure treatment integrity.

Step 1: Treatment Delivery and Training

Moderators use web-based manuals. Practice begins with mock web-based sessions (ie, moderator and patient interactions), followed by web-based sessions with volunteers. The principal investigator (CSM), a licensed psychologist who is board certified in behavioral sleep medicine, will score all training sessions. Training lasts approximately 8 weeks until the moderators obtain mastery (scoring 100 on each session's *Moderation Score Sheet*). All moderator-provided feedback will be delivered through email. Transcripts of moderator and participant interactions will be stored, and 25% will be scored by the consultant (a licensed psychologist). A senior consultant (a licensed psychologist) will double score the initial 10 sessions and 10 boosters and then 10% of the remaining sessions for reliability. Consultants will inform the principal investigator (CSM) of scores <95% for supervisory and training purposes. The principal investigator (CSM) will review 25% and the moderators will review 25% of each other's sessions for ongoing training and supervision. Only consultant reviews will be used to assess fidelity.

Step 2: Treatment Receipt

Each week, participants will be emailed a link to their assigned session. Automatic prompts and moderator emails will be used to encourage session completion. To ensure treatment comprehension, participants will be encouraged to ask questions using the embedded communication portal. Moderators will monitor and respond within 24 hours to messages sent through the system. Web-based materials will describe and reinforce treatment content. Time spent viewing web-based sessions will be monitored and recorded. Participants will complete a brief web-based quiz at the end of session 2.

Step 3: Treatment Enactment

To ensure that assignments are completed (eg, relaxation session completed and instructions followed), web-based materials contain simple written instructions. Participants will maintain daily electronic diaries and logs. Participants will complete a patient satisfaction and experience survey at the posttreatment and follow-up assessments. Reasons for withdrawal will be assessed using a withdrawal questionnaire.

Treatment Credibility and Expectancy

At the end of session 2, participants will complete a treatment credibility questionnaire. The treatment credibility questionnaire is a 4-item scale that assesses the participant's reaction to therapist and treatment efficacy, and participants provide ratings of 1 (strongly disagree) to 10 (strongly agree). Higher scores represent better treatment credibility.

Outcomes

A summary of study outcome measures is provided in Table 1 and schedules of outcome and process measures are provided in Tables 2 and 3.

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Table 1. Outcome measures.

Outcome category and measure	Details
Aim 1: feasibility and acceptability	
Completion and adherence	
Percentage of sessions completed	Percentage of sessions completed
Five instructions followed on logs	Percentage of instructions followed as indicated on treatment adherence logs
Utility and treatment satisfaction	
Internet Intervention Utility Questionnaire [38]	This is a 16-item measure designed to assess usability, likeability, usefulness, understandability, and convenience of an internet intervention using a 5-point Likert scale, ranging from 0 (not at all) to 4 (very); 2 additional open-ended questions ask about the most and least helpful aspects of the program.
Satisfaction Survey	This is a 9-item measure designed to provide feedback on the study, including its structure, assessments, scheduling, working with study staff, and the usability of the intervention platforms using a 10-point Likert scale, ranging from 1 (strongly disagree) to 10 (strongly agree), and open-ended questions.
Aim 2: primary and mechanistic caregiver outcomes	
Sleep	
Daily sleep diaries	Daily electronic diaries assess caregiver sleep onset latency (lights out until sleep onset), wake after sleep onset, and sleep efficiency (total sleep time/time in bed × 100%).
Insomnia Severity Index [39]	This is a 7-item measure designed to assess the nature, severity, and impact of insomnia using a 5-point Likert scale, ranging from 0 (no problem) to 4 (very severe problem).
Arousal	
Peripheral arousal: HRV[a]	HRV will be assessed using a Holter monitor during an established stress reactivity protocol. Participants will be seated at rest and undergo Holter monitoring procedures: (1) 5 minutes, baseline; (2) 30 seconds, vibrotactile stimuli (Conair WM200X) at 80 Hz oscillations applied to left hand; (3) 3 minutes, recovery; (4) 30 seconds, vibrotactile stimuli applied to right hand; (5) 3 minutes, recovery; (6) cold pressor stimulation to right hand (place hand at bottom of bowl of ice water calibrated to 4 °C); (7) 3 minutes, recovery; and (8) cold pressor stimulation to left hand. Time and spectral analysis of short-term HRV during baseline, vibration, and cold pressor stimuli will be conducted using Pathfinder software (Spacelabs Healthcare). Time (reflects beat-to-beat variability: RMSSD,[b] pNN50[c]) and frequency (reflects underlying HR[d] rhythms: high, 0.15-0.4 Hz; low, 0.04-0.15 Hz; very low, <0.04 Hz, and LF[e]:HF[f] ratio] domains will be examined. Vibration and cold pressor hand placement order will be counterbalanced every 10 participants to account for order effects.
Chronic stress: hair cortisol	With permission, research staff will cut hair strands as close as possible to scalp (forearm if needed [40]; minimum 50 mg of hair per sample).
Perceived Stress Scale [41]	This is a 10-item measure designed to assess past-month stress levels in response to everyday situations using a 4-point Likert scale ranging from 0 (never) to 4 (very often).
Kingston Caregiver Stress Scale [42]	This is a 10-item measure designed to assess three categories—caregiving, family, and financial issues—using a 5-point Likert scale ranging from 1 (feeling fine or no stress) to 5 (extreme stress).
Dysfunctional Beliefs and Attitudes about Sleep [43]	This is a 30-item measure designed to assess dysfunctional beliefs and attitudes about sleep using a 10-point Likert scale ranging from 0 (strongly disagree) to 10 (strongly agree).
Aim 3: secondary health-related caregiver outcomes	
Health and mood	
SF-36[g] [44]	This is a 36-item measure designed to assess quality of life using a 5-point Likert scale ranging from 1 (poor) to 5 (excellent).
Beck Depression Inventory [45]	This is a 21-item measure designed to assess depressive symptomatology using a 4-point Likert scale ranging from 0 (absence of symptoms) to 3 (severe).
State-Trait Anxiety Inventory [46]	This is a 20-item measure designed to assess anxiety using a 4-point Likert scale ranging from 1 (not at all) to 4 (very much so).
Burden	

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Outcome category and measure	Details
Zarit Burden Scale [47]	This is a 22-item measure designed to assess burden using a 5-point Likert scale ranging from 0 (never) to 4 (nearly always).
Quality of life of caregiver of patient with dementia [48]	This is a 20-item measure designed to assess how caregiver quality of life changes after beginning caregiving using yes or no questions and a 10-point sliding scale ranging from 0 (easy) to 10 (hard).
Cognition	
Daily Joggle battery [49]	Web-based battery designed to assess daily cognitive performance in multiple domains, including processing speed and attention (psychomotor vigilance and digit symbol substitution tasks), visuospatial ability and memory (visual object learning and line orientation tasks), verbal learning and memory (auditory verbal learning task), and executive functioning and working memory (abstract matching and n-back tasks).
NIH Toolbox for Assessment of Neurological and Behavioral Function [50]	Computerized measure designed to assess cognitive performance in multiple domains, including processing speed and attention (pattern comparison task), visuospatial ability and memory (picture sequence learning task), verbal learning and memory (auditory verbal learning task), and executive functioning and working memory (dimensional card sort and a flanker inhibition tasks).
Cognitive Failures Questionnaire [51]	This is a 25-item measure designed to assess an individual's perception of their own daily cognitive failures (eg, absentmindedness and memory errors) using a 5-point Likert scale ranging from 0 (never) to 4 (very often).
Inflammation	
Blood-based biomarkers	High-sensitivity CRP[h] and IL-6[i]. Plasma proteins are digested with trypsin, and peptides specific for CRP and IL6 are quantified using multiple reaction monitoring mass spectrometry.
Neurodegeneration	
Blood-based biomarkers	Aβ[j]40/42, tau, p-tau[k]-181, and p-tau-217. Plasma is extracted (Aβ40/42), or plasma proteins are digested with trypsin, and peptides are quantified using multiple reaction monitoring mass spectrometry.
Aim 4: persons with dementia: secondary outcome (sleep change in persons with dementia)	
Actigraphy	Actiwatch 2 (Philips Respironics) is a watch-like device that will be worn 24/7 during each 1-week assessment to monitor light and gross motor activity. Data will be analyzed using 30-second epochs and a validated algorithm (Actiware-Sleep version 3.3; Mini Mitter Co, Inc) to estimate total wake time.
Exploratory aim: moderators	
Demographics	
Demographics	Socioeconomic status, race and ethnicity, education level, marital status, financial strain, residence, menopause symptoms, medications, comorbidities, distance (miles) to the nearest provider, and rurality (Rurality Index [52]).
Interpersonal	
Patient-Caregiver Functional Unit Scale [53]	This is a 43-item measure designed to assess how much assistance the person with dementia needs and caregiver feelings about helping using yes or no questions and 2 types of Likert scales: a 3-point scale ranging from 0 (without help) to 2 (completely unable) and a 4-point scale ranging from 0 (no) to 3 (both physically and emotionally difficult).
Shared lifestyle	
Godin-Shephard Leisure-Time Physical Activity Questionnaire [54]	This is a 3-item measure designed to assess how many times per week an individual engages in mild, moderate, or strenuous activity and asks the number of times per week the items were accomplished.
Fruit and vegetable servings	Amount of fruit and vegetable servings per day
Respite and assistance	
Respite	Amount and type of respite
Assistance	Assistance provided by secondary informal caregivers (number, relationship, hours: face-to-face vs other).
Dementia severity of persons with dementia	

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Outcome category and measure	Details
Dementia Severity Rating Scale [55]	This is an 11-item measure designed to assess severity of functional and cognitive decline in patients with Alzheimer disease using various Likert scales.
Nighttime behaviors of persons with dementia	
Neuropsychology Inventory Nighttime Behavior Scale [56]	This is an 8-item measure designed to assess frequency and severity of detrimental sleep behaviors, such as wandering, in the dementia patient using yes or no questions.

[a]HRV: heart rate variability.

[b]RMSSD: root mean square of successive RR interval differences. RR interval is the time between 2 detected heartbeats, calculated for every QRS event.

[c]pNN50: The proportion of NN50 divided by the total number of NN (R-R) intervals. NN50 is the number of times successive heartbeat intervals exceed 50 ms. RR interval is the time between 2 detected heartbeats, calculated for every QRS event. NN interval is the time (normalized) between 2 detected heartbeats, calculated for every QRS event.

[d]HR: heart rate.

[e]LF: low frequency.

[f]HF: high frequency.

[g]SF-36: Short Form-36 Health Survey Questionnaire.

[h]CRP: C-reactive protein.

[i]IL-6: interleukin-6.

[j]Aβ: plasma amyloid beta.

[k]p-tau: phosphorylated tau.

Table 2. Schedule of outcome measures.

	Baseline	Treatment	After treatment	Boosters	6-month follow-up	12-month follow-up
Assessment period, weeks	1	4	1	1	1	1
Screening, apnea testing, consent and assent, and demographics	✓					
HRV,[a] ISI,[b] PSS,[c] KCGSS,[d] inflammation and neurodegeneration biomarkers, cortisol, actigraphy, SF-36,[e] BDI,[f] STAI,[g] DBS,[h] ZBS,[i] QoL,[j] daily Joggle battery, NIH Toolbox for Assessment of Neurological and Behavioral Function, CFQ,[k] P-CG FUS,[l] G-S L-T PAQ,[m] fruit and vegetable servings per day, respite, secondary CG[n] outcomes, DSRS,[o] NPI,[p] and NBS[q]	✓		✓		✓	✓
Electronic daily diaries	✓	✓	✓	✓	✓	✓

[a]HRV: heart rate variability.

[b]ISI: Insomnia Severity Index.

[c]PSS: Perceived Stress Scale.

[d]KCGSS: Kingston Caregiver Stress Scale.

[e]SF-36: Short Form-36 Health Survey Questionnaire.

[f]BDI: Beck Depression Inventory.

[g]STAI: State-Trait Anxiety Inventory.

[h]DBS: Dysfunctional Beliefs about Sleep.

[i]ZBS: Zarit Burden Scale.

[j]QoL: Quality of life of caregiver of patient with dementia.

[k]CFQ: Cognitive Failures Questionnaire.

[l]P-CG FUS: Patient-Caregiver Functional Unit Scale.

[m]G-S L-T PAQ: Godin-Shephard Leisure-Time Physical Activity Questionnaire.

[n]CG: caregiver.

[o]DSRS: Dementia Severity Rating Scale.

[p]NPI: Neuropsychological Inventory.

[q]NBS: Nighttime Behavior Scale.

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Table 3. Schedule of process measures.

	Baseline	Treatment	After treatment	Boosters	6-month follow-up	12-month follow-up
Assessment period (weeks)	1	4	1	1	1	1
Treatment integrity: delivery and receipt and enactment		✓		✓		
Treatment credibility: quiz and improvement expectancy		✓	✓		✓	✓
Sleep knowledge and working alliance		✓	✓	✓	✓	✓

Study Timeline

The study timeline is provided in Table 4.

Table 4. Study timeline.

	Project year									
	1		2		3		4		5	
	First half	Second half	First half	Second half	First half	Second half	First half	Second half	First half	Second half
Develop manual of operating procedures, register with ClinicalTrials.gov, publish trial protocol, and train moderators and assessors	✓									
Recruit, collect baseline measurements, and deliver treatment		✓	✓	✓	✓	✓	✓			
Collect assessment after treatment		✓	✓	✓	✓	✓	✓	✓		
Collect 6- and 12-month follow-up assessments			✓	✓	✓	✓	✓	✓	✓	
Offer and provide NiteCAPP CARES[a] to NiteCAPP SHARES[b] participants				✓	✓	✓	✓	✓	✓	✓
Final data analysis and dissemination (continues after grant ends) and final report									✓	✓

[a]NiteCAPP CARES: cognitive behavioral therapy for insomnia.

[b]NiteCAPP SHARES: active web-based sleep hygiene and related education control.

Analytical Approach

Power Analysis

Power will be simulated using SAS 9.4 statistical software (SAS Institute Inc) using a generalized estimating equations (GEE) design (clusters are individuals measured over 4 time points) with an autoregressive working correlation structure (correlation decreases as time point distance increases, ρ=0.5, 1 million Monte Carlo integrations simulated) [57]. The approach described by Schluchter [58] will fit GEE models with and without mediator to estimate mediated effect (exploratory aim). Sample size of 80 is powered (>.80) to detect small to large Cohen *d* mediation effects. Given an anticipated dropout rate of 15% to 20%, we will recruit a total sample of 120.

Evaluations of Aims

Tests of Hypotheses

All analyses will use intent-to-treat using all randomized participants. All assumptions will be tested. If the normality assumption is violated, the nonparametric Mann-Whitney *U* test will be used.

Testing of Aim 1: Feasibility and Acceptability of NiteCAPP CARES and NiteCAPP SHARES

The feasibility and acceptability of NiteCAPP CARES and NiteCAPP SHARES will be evaluated using average completion rates (number of sessions completed), adherence (measured through sleep diaries and logs), and satisfaction and utility ratings. These variables will be compared for NiteCAPP CARES and NiteCAPP SHARES using independent samples 2-tailed *t* tests.

Testing of Aims 2 to 4: Primary and Mechanistic and Secondary Outcomes

A mediated GEE model [58] (clusters are individuals measured over 4 time points) will test causal paths between intervention effects on the primary and secondary outcomes (Figure 3). On the basis of a priori hypotheses, separate GEE models, including group (NiteCAPP CARES and NiteCAPP SHARES), time (baseline, after treatment, and 6-month and 12-month follow-ups), and their interaction as predictors, will be conducted for each primary CG outcome (aim 2: insomnia severity, sleep onset latency, wake after sleep onset, sleep efficiency, arousal, and inflammation), secondary CG outcome (aim 3: health, mood, burden, and cognitive performance), and secondary outcome for persons with dementia (aim 4: actigraphy

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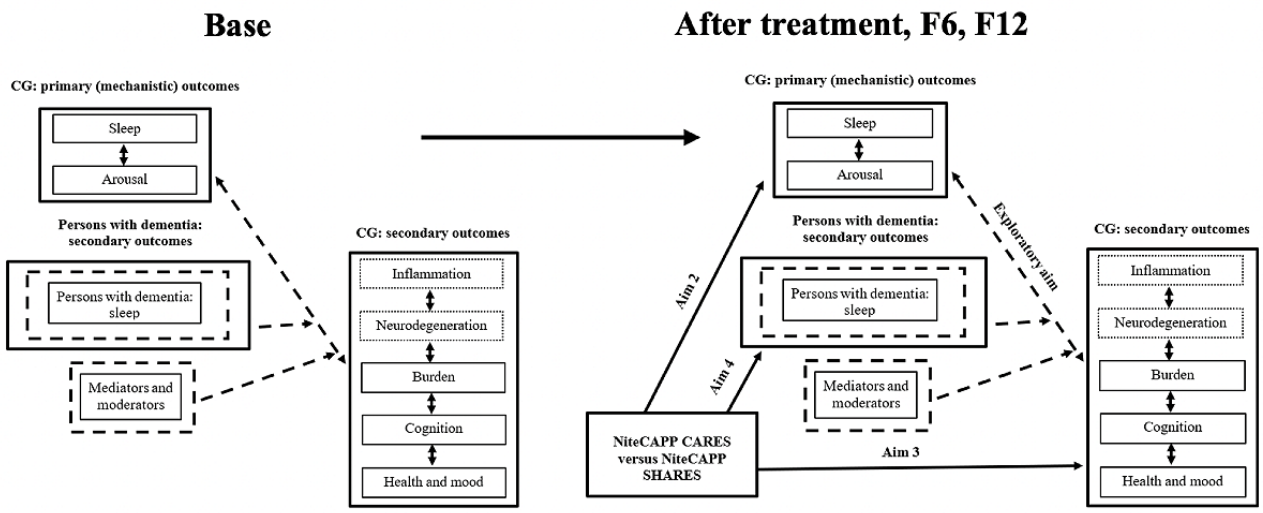
total wake time for persons with dementia). Potential covariates affecting the mechanistic outcomes (Table 2) or technology use by CGs and persons with dementia (eg, Internet Intervention Utility Questionnaire [38]) will be assessed and used as covariates if significant.

Figure 3. Mediated generalized estimating equations model. Analyses will also be conducted examining the paths from after treatment to 6-month follow-up and from 6-month follow-up to 12-month follow-up. Base: baseline; CG: caregiver; F6: 6-month follow-up; F12: 12-month follow-up; NiteCAPP CARES: cognitive behavioral therapy for insomnia; NiteCAPP SHARES: active web-based sleep hygiene and related education control; Post: after treatment.



Testing of Exploratory Aim

We will evaluate primary and secondary outcome change relationships and their potential mediators and moderators (Table 2). Mediated GEE will be used to compare NiteCAPP CARES versus NiteCAPP SHARES. Moderating effects will be tested using interactions (Table 2).

Missing Values

The SAS PROC GEE weighted model handles missing data completely at random or at random. When measures are collected over time, some participants may not complete the study. Unlike repeated measures ANOVA, which excludes them from analysis, weighted GEE retains them (increasing power and producing unbiased estimates).

Patient and Public Involvement

Patients and the public are not involved in any of the following study procedures: development of research questions and outcome measures or plan for results dissemination. The Community Advisory Board (CAB) will assess the burden of the intervention and may help with recruitment. Every participant will fill out a patient satisfaction and experience survey after treatment and at 6-month and 12-month follow-ups. This questionnaire asks CGs and persons with dementia which modules were most and least useful for them, how they felt about the length of the program, suitability for CGs and persons with dementia, and so on. Trial results will be communicated to participants and the public through peer-reviewed manuscripts.

Ethics Approval

All procedures were approved by the University of Missouri Institutional Review Board on May 6, 2021 (2053682); safety officer Dr Susan McCurry on November 24, 2021; the National Institute of Aging (NIA) on January 26, 2022; and the University of South Florida Institutional Review Board on March 10, 2022 (003936). The NIA and the safety officer reviewed and approved the study protocol, manual of operating procedures, informed consent form, and monitoring plan with emphasis on data integrity and patient safety issues in November 2021. The safety officer will review these biannually. Any changes to these procedures that are recommended by the safety officer will be adopted with institutional review board and NIA approval. The safety officer will review adverse events and monitor study results, focusing on efficacy, recruitment progress, randomization, compliance, retention, protocol adherence, operating procedures, forms completion, intervention effects, participant safety, and minority inclusion. The principal investigator (CSM) registered the study with ClinicalTrials.gov (NCT04896775) on May 21, 2021, and will submit annual reports to the funding agency.

Our team includes a CAB comprising 8 CGs, 4 persons with dementia, and 4 local experts. The CAB structure and procedures are based on the CAB Toolkit described by Kubicek and Robles [59]. The CAB will meet twice each year, with each meeting lasting 2 hours (respite care costs for persons with dementia will be paid by the grant). The team includes a consultant CG advocate who is a trained facilitator, and she will facilitate the CAB meetings.

Results

This work is supported by the National Institutes of Health's NIA (R01AG066081). Recruitment procedures started in February 2022. All data are expected to be collected by 2026.

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Full trial results are planned to be published by 2027. Secondary analyses of baseline data will be subsequently published.

We will present the findings at national conferences, including the Associated Professional Sleep Societies (APSS or SLEEP) and the Gerontological Society of America, in the final year of the project. An abstract reporting the findings of the preproposal focus group was presented at the August 2020 internet-based SLEEP meeting, and a brief report based on these findings is currently under review. The web-based treatment materials will be shared electronically and will be widely available to clinicians. The findings will also be disseminated to the dementia and dementia caregiving communities through websites and other resources. The team's community CG advocate and CAB will be involved in planning for broad dissemination to the dementia and CG communities. They will also help to ensure that materials used to disseminate findings are written for, and easily understood by, lay audiences in rural areas.

Discussion

The overarching goal of this RCT is to evaluate the acceptability, feasibility, and short-term and long-term effects of NiteCAPP CARES on the sleep and stress mechanisms underlying poor CG health and functioning. To the best of our knowledge, there is no current web-based CBT-I treatment that is tailored for CGs of persons with dementia and none that involve the person with dementia in treatment.

Strengths and Limitations

This study includes several strengths. It is a novel 4-week web-based CBT-I (NiteCAPP CARES) in CGs and persons with dementia (using a dyadic approach) that integrates sleep education, sleep hygiene, stimulus control, sleep compression, relaxation, problem solving, coping and stress management, and cognitive restructuring techniques. This study uses a rigorous methodology and NiteCAPP CARES will be examined in comparison with an active web control (NiteCAPP SHARES). Long-term follow-ups at 6 and 12 months will enable examination of the persistence of the behavioral outcomes of NiteCAPP CARES. The potential limitations include participant attrition at follow-up, which may contribute to selection bias associated with systematic differences between participants completing NiteCAPP CARES and those completing NiteCAPP SHARES.

Future Directions

Future directions for this RCT include a multisite effectiveness trial to determine generalizability across different areas. In addition, once NiteCAPP CARES is enhanced based on the results of this RCT, it needs to be tested within other populations (nonrural CGs and other underserved populations) for broader dissemination. Finally, dismantling studies could examine the most effective components of NiteCAPP CARES treatment to further streamline the treatment.

Conclusions

This RCT tests NiteCAPP CARES, a web-based CBT-I for rural CGs. The Cognitive Activation Theory of Stress and our research as well as research conducted by others [7,31] support our novel hypothesis that NiteCAPP CARES will improve CG health, mood, burden, and cognition by targeting sleep, arousal, and inflammation. This trial addresses what improves as well as how, why, and for how long (up to 1 year). This trial is a necessary first step, and the results from this study will help us to modify NiteCAPP CARES to optimize treatment potency and support future pragmatic testing and dissemination.

Acknowledgments

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Disclaimer

The study sponsor was not actively responsible or involved in the study design and will have no involvement in collection, management, analysis, or interpretation of data. The sponsor will have no involvement in future manuscript preparation and decision to submit for publication. This research was conducted using previous patient involvement in the pilot study. Patients were invited to comment on the feasibility and acceptability design of NiteCAPP CARES, and they indicated that more simple language would be preferable. In response, for this randomized controlled trial, we edited NiteCAPP CARES to simplify the language. Patients were invited to contribute to the writing and editing of this document for readability or accuracy.

Authors' Contributions

All authors made substantial contributions to the concept and design of the study. CSM and AFC drafted the initial protocol, with input from all authors. MG and AFC drafted the statistical analysis plan. CSM and BM drafted the biomarker data collection plan. MP assisted in web development. CSM and DQB drafted the screening procedures. DQB, JS, and MR drafted the recruitment and referral procedures. MG, NN, and AFC conducted the initial data processing. CSM, AFC, MAS, and AS drafted the manuscript. CSM, AFC, MAS, and AS revised the manuscript. All authors reviewed and approved the revised manuscript.

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Conflicts of Interest

DBB has consulted for Yamo Pharmaceuticals LLC, Impel Pharmaceuticals Inc, Quadrant Biosciences, Stalicla Biosciences, and Scioto Biosciences Inc, and has spoken for Biogen Inc not related to their product. None of these are related to the work herein.

Multimedia Appendix 1
Peer-reviewer report from the Center for Scientific Review Special Emphasis Panel Member Conflict: Stress, Sleep, Disparities, and Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 176 KB - resprot_v11i6e37874_app1.pdf]

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Abbreviations

ANS: autonomic nervous system
Aβ: plasma amyloid beta
bCBT-I: brief cognitive behavioral therapy for insomnia
CAB: Community Advisory Board
CBT-I: cognitive behavioral therapy for insomnia
CG: caregiver
GEE: generalized estimating equations
HR: heart rate
HRV: heart rate variability
NiteCAPP CARES: cognitive behavioral therapy for insomnia
NiteCAPP SHARES: active web-based sleep hygiene and related education control

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RCT: randomized controlled trial

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Protocol

Study of the Kinetics of the Determinants of Performance During a Mountain Ultramarathon: Multidisciplinary Protocol of the First Trail Scientifique de Clécy 2021

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Abstract

Background: The growing interest of the scientific community in trail running has highlighted the acute effects of practice at the time of these races on isolated aspects of physiological and structural systems; biological, physiological, cognitive, and muscular functions; and the psychological state of athletes. However, no integrative study has been conducted under these

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conditions with so many participants and monitoring of pre-, per-, and postrace variables for up to 10 days over a distance close to 100 miles.

Objective: The aim of this study was to evaluate the kinetics of the performance parameters during a 156 km trail run and 6000 m of elevation gain in pre-, per-, and postrace conditions. The general hypothesis is based on significant alterations in the psychological, physiological, mechanical, biological, and cognitive parameters.

Methods: The Trail Scientifique de Clécy took place on November 11, 2021. This prospective experimental study provides a comprehensive exploration of the constraints and adaptations of psychophysiological and sociological variables assessed in real race conditions during a trail running of 156 km on hilly ground and 6000 m of elevation gain (D+). The study protocol allowed for repeatability of study measurements under the same experimental conditions during the race, with the race being divided into 6 identical loops of 26 km and 1000 m D+. Measurements were conducted the day before and the morning of the race, at the end of each lap, after a pit stop, and up to 10 days after the race. A total of 55 participants were included, 43 (78%) men and 12 (22%) women, who were experienced in ultra–trail-running events and with no contraindications to the practice of this sport.

Results: The launch of the study was authorized on October 26, 2021, under the trial number 21-0166 after a favorable opinion from the Comité de Protection des Personnes Ouest III (21.09.61/SIRIPH 2G 21.01586.000009). Of the 55 runners enrolled, 41 (75%) completed the race and 14 (25%) dropped out for various reasons, including gastric problems, hypothermia, fatigue, and musculoskeletal injuries. All the measurements for each team were completed in full. The race times (ie, excluding the measurements) ranged from 17.8206 hours for the first runner to 35.9225 hours for the last runner. The average time to complete all measurements for each lap was 64 (SD 3) minutes.

Conclusions: The Trail Scientifique de Clécy, by its protocol, allowed for a multidisciplinary approach to the discipline. This approach will allow for the explanation of the studied parameters in relation to each other and observation of the systems of dependence and independence. The initial results are expected in June 2022.

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KEYWORDS

ultramarathon; trail-running; sports physiology; sleep deprivation; fatigue; blood biology; muscular function; biomechanics; motivation; cognition; self-esteem

Introduction

Background

Trail running is a sport discipline defined by the International Trail Running Association as a pedestrian competition taking place in a natural environment in a semi–self-sufficient or self-sufficient manner and with respect for sports ethics, fairness, solidarity, and the environment [1].

The practice of the ultratrail, the leader of ultraendurance events, shows an exponentially popular craze. In France, for example, since the first edition of the Ultra Trail du Mont Blanc, the number of finishers has risen from 67 in 2003 to 1685 in 2017, to 1556 in 2019, and to 1521 in 2021, and the number of registration requests has risen from 722 to 5575 [2]. In 2001, 150 trails were organized in France, and there were >2500 in 2015 [3]. A study conducted by the French Federation of Sports and Leisure Industries reported a niche of approximately 3.5 million trail runners out of the 17 million *runners* identified in France in 2017 [4].

A Craze for Research Around the Disciplines of Ultraendurance

In parallel with this popular craze, ultraendurance and ultratrail in particular are areas of increasing interest to the scientific community. When looking at the number of publications that include the terms *ultratrail* or *ultraendurance* or *ultramarathon* indexed on PubMed, 650 references are found, with a significant increase in recent years (a total of 3 in 2000, a total of 20 in 2010, a total of 65 in 2015, and a total of 70 in 2020). However, the volume of publications remains low compared with other disciplines; for example, the terms *soccer* or *tennis* lead to 9974 and 8127 indexed articles, respectively.

This contrast is linked to not only the relative youth of the ultraendurance disciplines but also the lack of funding available for research in sports medicine and sports science in general [2]. Furthermore, most of the publications were observational studies. Less than 5% of the articles listed were randomized controlled trials, and <1% were systematic reviews or meta-analyses [2].

Ultraendurance disciplines and the mountain ultramarathon, in particular, offer a vast field of research in public health, basic sciences, and human sciences. The relative youth of the discipline and the material and logistical constraints of setting up in situ biomedical research during mountain ultramarathon races explain the low number of studies [3].

For example, when analyzing the studies published on PubMed from 2019 to 2021 with the words *ultramarathon* or *ultratrail*, out of the 171 articles published, only 23 (13.5%) studies were able to conduct a pre-, per-, and postrace protocol. Unfortunately, these studies often focus on one variable or field of study [5-26], particularly cardiac, renal, or psychomotivational functions. Moreover, of these 23 studies, 12 (52%) protocols were conducted on a treadmill [5,13,19,27], on roads or nontechnical trails [6,10,12,18,23,28], on short distances [16], or in an extreme environment [7].

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In 2019, the study by Belinchón-deMiguel et al [24] took an integrative approach to performance by integrating physiological measurements such as anthropometry, heart rate (HR), blood pressure, oxygen saturation, muscle strength, and hydration; participants' training parameters; nutritional parameters; and psychological parameters such as perceived stress and general mental health status. However, these measurements were only performed in the pre-postrace period, as they could not shed light on their kinetics. Other parameters were not studied, such as psychomotivational factors, thermoregulation, cardiac function, myotendinous activity, and inflammation. The health risks associated with the practice of this discipline have not been studied.

The lack of data found in the literature on these questions, which are linked to the difficulty of setting up scientific protocols during events and associated with the predominant place occupied by the trail discipline, gave rise to the project in Clécy, Normandy, France.

To respond to this context, a consortium comprising several local (Centre Hospitalier Universitaire de Caen and laboratory COMETE U1075 Unit), national, and international research teams proposed to set up a common protocol to understand the kinetics of the psychophysiological mechanisms that contribute to performance during an ultratrail race, as well as the social determinants. To this end, measurements will be taken before, during, and after a trail of 156 km with 55 volunteers and experienced runners. This scientific study is the first in its format, with 55 participants over a long race with a positive elevation gain (6000 m) and bringing together 11 research laboratories for measurements in pre-, per- (6 standardized fixed points), and postrace (10 days of follow-up) variables.

Objective

The objective of this protocol was to study in situ the kinetics of the factors determining performance in an ultraendurance trail-running event. This main objective is broken down into several scientific disciplines, each of which includes subobjectives (Textbox 1).

Textbox 1. Objectives based on scientific disciplines.

Physiological exploration

- To study the relationship between thermoregulatory capacity and performance
- To quantify the degradation of the muscular and biomechanical determinants of performance, muscular function, locomotor function, and static and dynamic postural functions
- To study the variability of cardiorespiratory parameters, including heart rate, heart rate variability, and respiratory rate
- To analyze acute adaptations in cardiac volume, myocardial contractility, and relaxation using transthoracic echocardiography
- To study the per-effort and posteffort variations of biological markers of inflammation and cardiac, renal, and neurological functions
- To evaluate the impact of the ultratrail on the runners' glycemic balance
- To evaluate sleep before, during, and after an ultraendurance race

Biomechanical exploration

- To study the variation of the elastic and architectural properties of the gastrocnemius-Achilles tendon complex using ultrasound elastography
- To study the effects of fatigue on the biomechanics of trial running
- To study the relationship between shoe-related needs and the morphological, biomechanical, and sensory characteristics of the ultraendurance runner

Psychocognitive and sociological exploration

- To assess spatial cognition
- To determine the effect of exercise combined with sleep deprivation on response time, sustained attention, and sleepiness
- To study the psychological determinants of performance in an ultraendurance sport
- To study the link between the profile of confirmed or elite participants in ultraendurance and their ability to be attentive to self, others, and the world by mobilizing different indicators

Environmental exploration

- To study the evolution of air quality and its association with physiological parameters during an ultraendurance race

Methods

Recruitment

This experimental study included 55 volunteer participants, 43 (78%) men and 12 (22%) women, aged between 25 and 70 years. On the basis of the high range of abandonment (ie, 25% on an ultraendurance race), we estimated a cohort of finishers of 40 to 45 runners. Recruitment started in January 2021 until September 2021 with an announcement on the social networks of the Trail Scientifique de Clécy. If the runners met the inclusion criteria, they were invited to a videoconference exposing the entire protocol, with the consent letter being

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provided for reading. The runners were definitively included in the study on November 10, 2021, after a medical examination.

The medical examination was completed using electrocardiography and cardiac echography. If an anomaly was detected, the runner was excluded from the study.

A medical check-up was conducted 24 hours after the finish line or withdrawal and then 1 to 2 months after the race by teleconsultation.

Inclusion and Exclusion Criteria

To be eligible, participants had to verify all the defined inclusion and exclusion criteria (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Experienced runners voluntarily participating in the Trail Scientifique de Clécy (156 km/6000 D+)
- Participants who had already completed 2 ultratrail races (+160 km and −160 km), at least one of them in the past 24 months; the participants had to justify their events and rankings
- Participants affiliated with a social security system or those who were a beneficiary of such a system
- Participants who could speak and read the French language
- Healthy volunteers aged 25 to 70 years
- Participants with the ability to physically participate in the ultraendurance race
- Participants with the ability to provide written consent for participation in the study
- Participants whose usual place of residence is +2 hours or –2 hours from the Greenwich meridian
- Participants with a medical certificate of no contraindication to the practice of ultratrail for <1 year

Exclusion criteria

- Participants with cardiac or extracardiac contraindications to intense physical activity
- Participants who had run a mountain ultramarathon (160 km) after September 2, 2021
- Pregnant or breastfeeding women
- Minor participants
- Participants included in another biomedical research protocol during this study
- Participants who refused to participate or who had the inability to access or read the newsletter
- Participants with a swallowing disorder
- Participants with a chronic transit disorder, including Crohn disease and digestive cancer
- Participants with magnetic resonance imaging scheduled within 48 hours of the race
- Participants with a medical history of pulmonary pathology; cardiac pathology; arterial hypertension; or significant inflammatory, renal, cardiac, or neurological disease observed during the inclusion visit
- All runners undergoing medical treatment
- Participants with recent muscular and orthopedic injuries, limiting running for <15 days
- Participants with a history of ankle joint surgery (eg, arthrodesis)
- Participants with joint stiffness corresponding to ranges of <15° dorsal flexion and 35° plantar flexion
- Participants with a history of foot or ankle surgery
- Participants with significant sensory disturbances in the foot
- Participants with pathological asymmetry between the right and left feet
- Participants with lower-limb pathology or trauma
- Participants with central and peripheral neurological pathologies
- Participants who experienced a time difference of >2 hours in the month preceding the event (jet lag)

Selection of Variables Identified as Determinants of Performance

The selected variables were based on scientific work in an ultramarathon, trail running, or ultratrail (Table 1).

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Table 1. Parameters selected for our study, which have been reviewed in the literature.

Parameters	Studies
Muscle function	
Muscle strength and power	[25,26,29]
Neuromuscular fatigue	[30]
Thermoregulation	
Core temperature	[31,32]
Skin temperature	[31,32]
Regulation	[33]
Cardiac function	
Blood pressure	[11,21]
Ventricular volumes and function	[11,21]
Heart rate and heart rate variability	[22,34-37]
Sleep and sleep deprivation	
Before race	[38,39]
Nap	[39]
Sleep structure before, during, and after	[38-40]
Hallucination	[38]
Vigilance	[38,41]
Spatial cognition	
Posture	[20]
Balance	[20,42]
Shoes	
Pathologies	[43,44]
Foot volume	[43,45]
Running biomechanics	
Changes in kinetic parameters	[4,42,46-49]
Myotendinous activity of the ankle joint	
Stiffness and fatigue	[50-53]
Biological markers of inflammation	
Pro- and anti-inflammatory markers	[54-60]
Sepsis markers, metabolism markers, and renal function markers	[61-66]
Glycemia	
Control	[67]
Role of food	[68]
Psychology	
Motivation	[69,70]
Profile and personality traits	
Skills for attentive presence to oneself, others, and the world	[71]
Ability to project oneself in a future event	[71]
Anthropometry	
Body fat	[72]
Lean body mass	[25]
BMI	[73]

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Race

The start date was given as November 11, 2021, at 2:30 PM. The race was divided into 6 identical loops of 26 km and 1000 m D+ and was run in semiautonomy; each runner had to be self-sufficient in water and food between each refreshment point. At the end of each loop, runners had access to a refreshment station identical to that of a classic race. After this refueling, runners moved to the scientific zone, and the stopwatch was paused for the duration of the scientific tests. Once the tests were completed, the runners started a new loop and the stopwatch was restarted.

Time barriers were set up based on calculations from similar races to replicate the constraints of a real race (Table 2).

The measurements were conducted from 36 to 3 hours before the start of the race for the prerace measurements, at the end of each lap, and continuously during the race for the per-race measurements, and then at the finish and from 24 hours to 10 days after the race for the postrace measurements.

If a participant dropped out of the race, the time and distance covered were recorded. The participant was then required to participate in the postrace testing.

Once the race was over, the time was recorded, and postrace measurements were taken within an hour. Measurements at +24 hours were also taken and followed up for a week after the race.

Table 2. Time barrier per lap.

Date	Last start time (time of day)	Lap	Last finish time (time of day)	Maximum time per lap (hours)	Minimum speed per lap (km/hour)	Science time (hours)
November 11, 2021	2:30 PM	1	7:30 PM	5	5.2	1
November 11 and 12, 2021	8:30 PM	2	2:30 AM	6	4.3	1
November 12, 2021	3:30 AM	3	10:30 AM	7	3.7	1
November 12, 2021	11:30 AM	4	7:30 PM	8	3.25	1
November 12 and 13, 2021	8:30 PM	5	5 AM	8.5	3	1
November 13, 2021	6 AM	6	3 PM	9	2.8	1

Measures

Physiological Exploration

Anthropometry

Body mass was measured in kilograms using the BC545N (Tanita) scale. Body composition was assessed on the morning of the race and at the finish line using an mBCA 525 (Seca) impedance meter in the supine position to determine the proportion and distribution of fat, water, and muscle. It is a noninvasive technique validated against the gold standard [74].

Temperature

Body temperature analysis was performed by ingestion of an e-Celsius capsule (BodyCap). This is an ingested medical device that is noninvasive as it does not penetrate the skin or mucous membrane barrier and is connected to an external monitor that allows continuous measurement and recording of body temperature. The capsules are safe to ingest (17.7×8.9 mm, 1.7 g) and are eliminated through the natural route in 1 to 3 days in the stool. This device is valid, reproducible, and well-tolerated [6-9] and does not affect the athlete's performance. The e-Celsius capsule also has a high T° accuracy of 0.2 °C.

On the morning of the race, at breakfast, the participants swallowed an e-Celsius capsule that allowed continuous measurement of core temperature. An e-Celsius skin patch was placed on a waistcoat that the runners had to wear throughout the race to record their body temperature. In case of expulsion, new capsules were activated and ingested whenever necessary. The chosen acquisition rate was 1 data point per minute.

Ambient temperature and humidity were measured using 2 Air Quality Transmitter AQT530 (Vaisala) weather stations installed on the course at the scientific base (0 km) and the halfway point (13 km).

Muscular Strength and Power

- Measurement of the maximum isometric strength of the knee extensors:
  Participants were seated on a quadriceps chair in a standardized position: arms crossed, hands on the shoulders, back in contact with the backrest, gaze horizontal, and knee angulation at 90° in the beginning. They had 2 alternative trials per leg (ie, 1 maximum repetition on the left, then on the right, then on the left, and again on the right). This measurement was repeated the day before, on the morning of the race, at the end of each loop, at the end of the race, and 24 hours after the race.
- Measurement of the maximum isometric strength of the hip abductors:
  Participants were placed in a side-lying position and were required to abduct against an inelastic strap set in a neutral position. A cushion was placed between the legs to position the hip in a neutral position. The first strap around the waist held the pelvis on the table to limit compensation from the trunk. A second strap was used as the dynamometer and was placed 5 cm above the external malleolus of the evaluated leg. After 2 submaximal tests, the participants were asked to perform at least three trials at their maximum strength, spaced by 1 minute of rest. This measurement was repeated the day before, on the morning of the race, and at the end of each loop.

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- Measurement of the maximum isometric strength of the ankle plantar flexors:
  Participants were seated with their knees flexed at 90°. A rigid seatbelt strap was placed around the sole of the foot and secured to a step to provide resistance for the maximal test. The ankle position was maintained at 90° to ensure a stable ankle position with both the knee bent and straight. After 2 submaximal tests, the participants were asked to perform at least three trials at their maximum strength, spaced by 1 minute of rest. This measurement was repeated the day before, on the morning of the race, and at the end of each loop.
- Muscle power of the lower limbs:
  The day before the race, muscular power was evaluated using 3 squat jumps on a FD4000 force plate (Vald; 35 cm × 70 cm per plate). This measurement was repeated on the morning of the race, at the end of each lap, and at the end of the race. Each squat jump was separated by 30 seconds of rest. The instructions were as follows: "keep your hands on your hips and jump as high as possible during each repetition."
- Grip force measurement:
  Maximal grip strength was evaluated using a grip dynamometer (Grip, K-Invent) the day before, on the morning of the race, at the end of each loop, and at the end. Participants sat in a chair with their arms in 90° elbow flexion. The instructions were to squeeze the dynamometer as hard as possible for 5 seconds. The rest time between trials was 30 seconds.

HR Measurement, Respiratory Rate, and HR Variability

The participants were equipped with a Hexoskin Pro Physiological Waistcoat (Carre Technologies Inc) to measure HR, HR variability, and respiratory rate during the night before the race, during the race, and during the 10 nights following the race.

Electrocardiography and Transthoracic Echocardiography

Electrocardiography and transthoracic echocardiography were performed on all participants the day before the race and at the end of the race or retirement. A subgroup of 30 runners, comprising 13 (43%) female athletes and 17 (57%) age-matched male athletes, was selected for an additional transthoracic echocardiography evaluation at the end of each lap. Blood pressure was measured after each echocardiographic examination with respect to 10 minutes of quiet rest, using an automated monitor (Omron) with an appropriate-sized arm cuff.

Echocardiographic assessment of cardiac volumes and function was conducted according to the current guidelines [75,76] using a commercially available echocardiographic system (Philips Epiq 7 equipped with an ×5-1 xMATRIX-array transducer). The examination was performed on site for each participant in the left lateral decubitus position using a standardized echocardiographic protocol. All echocardiographic measurements acquired during a brief apnea were stored digitally for offline data analysis, which will be performed by a single operator blinded to the study time point (TOMTEC-Arena TTA2, TOMTEC Imaging Systems GMBH). The left and right ventricular and atrial dimensions will be assessed using 2D parasternal and apical views. 3D ventricular volumes and ejection fractions will be obtained using TOMTEC 4D-analysis software. Ventricular and atrial deformations will be based on speckle-tracking analysis. Left ventricular relaxation will be analyzed using Doppler indices [76]. Left ventricular diastolic intraventricular pressure gradient, a marker of left ventricular suction, will be estimated noninvasively from echocardiographic color Doppler M-mode acquisitions made along the left ventricular base to apex axis in the 4-chamber apical view, as described previously [77,78].

Blood Biology

On the morning of the race, at the end of each loop, at the end of the race, and 24 hours after the race, venipuncture was performed on participants in a sitting position. Blood samples (2 mL) were collected from the forearm in heparin and citrate tubes. The samples were centrifuged and aliquoted for further analysis. Coagulant-free serum, serum EDTA, and heparinized vacutainers allowed us to obtain serum and plasma for the following further analyses:

- Plasma levels of interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, protein S100, neuron-specific enolase, C-reactive protein (proinflammatory markers), and IL-4, IL-10, and IL-13 (anti-inflammatory markers)
- The parameters studied related to sepsis will be granzyme B, heat shock protein 70, IL-1α, IL-8, macrophage inflammatory protein 1 α, macrophage inflammatory protein 1 β, and matrix metalloproteinase-8
- The studied parameters related to metabolism will be ghrelin, gastric inhibitory polypeptide, glucagon-like peptide-1, glucagon, insulin, insulin leptin plasminogen activator inhibitor-1 (total), resistin, visfatin, C-peptide, cortisol, pancreatic polypeptide, insulin, and peptide YY
- The parameters studied related to inflammation will be soluble CD30, soluble epidermal growth factor receptor, soluble glycoprotein 130, soluble IL (sIL)-1 receptor type I, sIL-1 receptor type II, sIL-2 receptor type α, sIL-4 receptor, sIL-6 receptor, advanced glycosylation end product-specific receptor, soluble TNF receptor I, soluble TNF receptor II, soluble vascular endothelial growth factor (sVEGF) receptor 1, sVEGF receptor 2, and sVEGF receptor 3
- The parameters studied in relation to renal function will be blood count and blood ionogram with calcium, phosphorus, magnesium, urea, creatinine, neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, plasma, and urine lipocalin

Venous blood gas analysis was immediately performed using the Stat Profile Prime (Nova Biomedical) medical device, allowing hemoglobin measurement and hematocrit calculation.

Glycemia

The day before the race, the investigators placed a continuous interstitial glucose sensor (FreeStyle Libre Pro, Abbott) on the back of participants' arms. This sensor was used in masked mode; hence, the runners did not have live access to their blood glucose values, so as not to interfere with their usual running strategies. The sensor is self-calibrating and does not need to be manipulated once fitted. Blood glucose levels were estimated

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from interstitial glucose levels measured at 15-minute intervals from the time the sensor was fitted until it was removed 9 days after the race.

In addition, plasma glucose levels were analyzed from venous blood samples collected on the morning before the race, at the end of each loop, at the end of the race, and 24 hours after the race.

Sleep Exploration

A sleep questionnaire, adapted from the existing Spiegel, Epworth, and Vis-Morgen questionnaires, was administered to all participants before, during (if a nap was required), and after the race.

On the night before the race and the 7 nights after the race, the participants were equipped with the Hexoskin Pro Waistcoat, measuring sleep indirectly by actimetry.

Sleep was also recorded by electroencephalogram measurements using a Somfit (Compumedics Limited) for naps during the race and in the 7 nights following the race for a subgroup.

On the day before the race, the day of the start of the race, at the end of each loop, and at the end of the race or retirement, participants were asked to complete the Karolinska Subjective Sleepiness Scale.

Biomechanical Exploration

Elastic and Architectural Properties of the Gastrocnemius-Achilles Tendon Complex

Ultrasound examination was performed using a linear array transducer (EPIQ Elite with eL18-4 transducer ElastQ Imaging shear wave elastography, Philips Medical Systems). All participants were examined in the prone position, with the knee in the extended position and the ankle fixed in a neutral position. Both legs were assessed. The cross-sectional area of the Achilles tendon (in mm^2) was measured at the level between the malleoli [79]. Longitudinal panoramic sonographic images of the medial gastrocnemius muscle were obtained. Pennation angle and fascicle length were measured at the middle and distal parts of the muscle [80]. The elastic properties of the medial gastrocnemius muscle were measured in the longitudinal view at 30% of the muscle length using Young modulus values (in kPa) determined by shear wave ultrasound elastography [81]. The region of interest circle was placed in the muscle belly, and median elasticity, maximum elasticity, and average elasticity were collected. Measurements were performed before the race and repeated at the end of the second lap, the fourth lap, at the end or at retirement, and 6 hours after the race.

Running Kinetics and Kinematics

The data were collected on the day before the Trail Scientifique Clécy (10 minutes of warm-up before data collection for a few seconds for the kinematics); during the race; at the end of each loop; and 30 m before the end of a lap on a flat, paved, and covered portion.

The kinematics of the race were evaluated using a high-definition video camera and an Optojump system (Microgate) at the end of each loop. The characterization of foot strike patterns (rear foot, midfoot, and forefoot) using a video camera is a valid and accurate method of assessment [82-84]. The foot strike angle at the initial contact was also measured using a high-speed, high-definition camera at 240 frames per second. Step rate, step length, and ground and fly contact time were measured using an Optojump system comprising fixed sensors of 15 m × 1.5 m, which were positioned in an 18 m × 3 m tent on a level section. This instrument has been validated against an instrumented treadmill [85].

RunScribe sensors were used continuously throughout the run to measure the kinematic parameters of the stride. The variables of interest were the foot strike pattern, power, flight time, flight ratio, step rate, and ground contact time, which were previously found to be valid and reliable [86].

The loops were broken down into sections (ascent, descent, and flat) to isolate the variables and analyze the intermediate race times.

Shoes

The day before the race, information was collected on the trail shoes used by the participants (brand, model, size, weight, sole thickness and drop, torsional and longitudinal flexibility, motion control technologies, and the Minimalist Index [87]). A questionnaire was also administered to define their needs, expectations, and preferences regarding the footwear used.

Foot Measurement

Both feet were scanned using a photogrammetric 3D scanner (FeetBox3D, Corpus-e). A 3D model of the feet was reconstructed to observe the structural changes induced by the race (swelling).

This measurement was taken before the race and repeated at the end of each lap and at the end of the race or retirement.

Cognitive, Psychological, and Sociological Exploration

Vestibular System: Testing Sensory Organization and Measuring Spatial Orientation

We assessed verticality perception to evaluate the visuovestibular sensory preference with subjective vertical visual, dynamic subjective vertical visual, and the Rode and Frame test 4 hours before the race, at loops 1 and 3, at the end loop 6, and 24 hours after the race.

We measured the spatial strategy according to the egocentric (striatal network) versus allocentric (hippocampal network) response through the reverse T maze previously performed in rodents [88] and in healthy participants [49] before the race, at the end of loop 6, and at 24 hours after the race.

All tests were performed using a virtual reality headset setup (VRMaze [89]).

Postural Control

Postural control was measured 2 times for 50 seconds (open and closed eye conditions) on K-Force Plates (K-Invent).

This measurement was repeated 24 hours and 3 hours before the race, at loops 1 and 3, at the end of loop 6, and 24 hours

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after the race. Anteroposterior and lateral sway and stability scores were analyzed.

Cognitive Tests

On the day before the race, the morning of the race, at the end of each loop, and then at the end or at retirement, the runners were asked to assess a simple 5-minute serial response time test [90]. The number of mistakes termed *errors of omission* (eg, lapses of attention, historically defined as response time ≥500 milliseconds) plus *errors of commission* (eg, responses without a stimulus, false starts, or response time <100 milliseconds) are the primary outcome measures. The mean response times were also calculated. A measure of perceived sleepiness using the Karolinska Sleepiness Scale completed the objective assessment.

Psychomotivational Test

On the morning of the race, at the end of each loop, at the finish line, and 24 hours after the race, participants completed a motivational test.

The methodology comprised asking participants to perform 2 tests on a computer, each lasting approximately 3 minutes. A long version of these tests was described by Schmidt et al [91]. One was for physical effort, and the other was for mental effort. The short version was implemented during the Reunion ultratrail (Grand Raid).

In each test, participants were asked to try to win as much money as possible. The money was not real, as in a video game; however, the amount won is used to rank participants. Each trial had a coin or note (10c or 0.11c, €1 or US $1.06, or €10 or US $10.58) that one can win if they do their best. The maximum was specific to each participant and was measured during the prerace visit, which allowed instructions to be given.

Each test comprised 9 trials, 3 per incentive level, where the participant must either squeeze the handle as hard as possible or solve as many numerical comparisons as possible in a limited time. At the end of each trial, the participant was told his or her performance and the amount of money earned, calculated as the fraction of the incentive corresponding to the fraction of the maximum effort achieved. The maximum effort corresponds to the maximum muscular contraction produced during the calibration visit and the minimum time taken to complete 10 numerical comparisons.

Sociological Questionnaire

Before the race, the participants had to fill in a sociological questionnaire on their ability to be attentive to themselves, others, and the world using various indicators.

Environmental Exploration

To measure the air quality, we installed 2 sensors (Air Quality Transmitter AQT530, Vaisala) along the course of the trail of Clécy at a height of 1.70 m from the ground. The sensors were placed at 2 locations along the course. The first sensor was located at the center of the Pleine Nature Lionel Terray at the start of the race. This point was also the passage of each 26 km loop and the arrival of the race. This was the point of the course with the lowest altitude (50 m). The second sensor was located at the aid station at the 14th kilometer of the course, which was the point of the course with the highest altitude (254 m). The frequency of the measurement of the sensors was 1 measurement every 10 minutes.

These sensors measured nitrogen dioxide, nitrogen monoxide, carbon monoxide, ozone, and fine particles (particulate matter [PM]) with diameters <1 µm (PM1), <2.5 µm (PM2.5), and <10 µm (PM10). Environmental parameters such as temperature, humidity, and atmospheric pressure were also recorded.

Other Measures

Crosscall Core T4 tablets (France) with Quicktape Survey software (Canada) were used to merge the questionnaires of each scientific team.

Order of Tasks

To reduce the impact of one measure on another for the prerace measurements, the order of passage of the tasks was imposed. Therefore, no randomization was performed.

Figure 1 shows the sequence of the scientific part.

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Figure 1. Organization of scientific measurements.

Statistical Analysis

Data related to the primary and secondary objectives will be evaluated at the end of the study. For each studied parameter, the normality of the distribution will be examined using the Shapiro-Wilk test. Continuous quantitative variables will be expressed as mean (SD), discontinuous variables as median and IQR, and qualitative variables as percentages. The comparison of the values of the primary end point between the baseline and the end of the study will be performed using statistical tests for the paired series. In addition, to take into account repeated measures over time, we will analyze the primary end point as a function of time using appropriate mixed models for repeated data. Using the same statistical tests as for the primary end point, we will analyze the secondary end points. The threshold for statistical significance will be defined as P .05. Depending on the scientific team, we will use MedCalc Statistical Software (version 13.2.0) and JASP (version 0.16.1.0) or RStudio (version 1.2) to perform the statistical analyses.

Ethics Approval

The launch of the study was authorized on October 26, 2021, under trial number 21-0166 after a favorable opinion from the Comité de Protection des Personnes Ouest III (21.09.61/SIRIPH 2G 21.01586.000009).

Results

Overview

Of the 60 runners selected for the scientific trail, 56 (93%) showed up, and 55 (92%) were selected for the study, including 43 (72%) men (mean age 45.6, SD 14.6 years; mean height 1.76 m, SD 0.1 m; mean weight 70.3 kg, SD 7.8 kg; mean BMI 22.7, SD 2.0; and mean body fat 9.7%, SD 5.4%) and 12 (20%) women (mean age 43.8, SD 9.7 years; mean weight 53.5, SD 5.5 kg; mean BMI 19.7, SD 1.1; mean body fat 17.7%, SD 4.8%).

A woman was excluded from the study because of her participation in a 160 km ultramarathon 1 week before the protocol.

There were 14 participants who abandoned the study for the following reasons: perceived hypothermia (n=2, 14%), generalized exhaustion (n=5, 36%), gastric problems (n=4, 29%), and musculoskeletal pain (n=3, 21%).

We performed intermediate times over the entire race. Table 3 lists the values. Race time corresponds to the time taken to complete the 6 loops. Stop time corresponds to the time spent at the base of life (refueling and paramedical care). Science time refers to the time spent on various scientific measurements.

In a classic trail-running race, running and stopping times are part of the final timing. Here, this value is represented by the total time.

For finishers, the average time for science over the whole race was 320 (SD 56) minutes (ie, an average of 64, SD 13 minutes per lap; ie, 17.4%, SD 2.1% of the protocol time). As an indication, the time spent at the base of life for refreshments, a nap, foot care, and physiotherapy represented 8.6% (SD3.7%) of the protocol time.

For did not finish, the science time corresponded to 18.2% (SD 3.9%) of the protocol time, and 8.6% and SD 3.5%) of the protocol time was devoted to stops at the base of life.

The average time per loop is presented in Table 4 for all the runners, finishers, and did not finish.

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Table 3. Timing and split times.

Participants	Race time (hours)	Break time (hours)	Science time (hours)	Total time (race time+break time; hours)	Protocol time (total time+science time; hours)
Finishers, mean (SD)	23.3522 (3.5197)	2.1611 (1.3147)	5.3481 (0.9392)	1.4967 (4.5661)	30.8447 (5.2439)
First man	17.1839	0.6367	3.8969	17.8206	21.7175
First woman	19.7478	1.0992	4.8147	20.8469	25.6617

Table 4. Average time per lap (26 km and 1000 m D+) for the group, finishers, and nonfinishers (N=55).

Participants	Lap 1	Lap 2	Lap 3	Lap 4	Lap 5	Lap 6
Runners at each lap, n (%)	55 (100)	55 (100)	53 (96)	50 (91)	44 (80)	41 (75)
Time (all runners n=54), mean (SD)	3.0119 (0.3344)	3.5217 (0.4306)	3.9736 (0.6708)	4.2397 (0.6608)	4.4114 (0.9072)	4.6444 (0.9625)
Time for finishers (n=41), mean (SD)	2.9633 (0.35)	3.4528 (0.4197)	3.8631 (0.6214)	4.1261 (0.5825)	4.3144 (0.8425)	4.6444 (0.9625)
Time for did not finish, mean (SD)	3.1536 (0.2419)	3.7236 (0.4117)	4.3511 (0.7231)	4.7578 (0.78)	5.7367 (0.8175)	N/A[a]

[a]N/A: not applicable (there are no more runners in this category on lap 6 as they did not finish the race).

Undesirable Effects

No runner had to interrupt the race because of an undesirable effect of the protocol.

We noted a few lipothymia cases, which were not serious, during certain scientific tests, particularly those requiring prolonged standing.

We did not note any muscle damage related to the tests.

The venipunctures generated ecchymosis because of the difficulty of puncturing but also extravasation secondary to the rapid resumption of the race (strong and lasting compression not being possible).

Anecdotally, 8 punctures, 6 of which were during the race, were a major constraint.

Discussion

Principal Findings

The Trail Scientifique de Clécy allowed, for the first time, an integrative and multidisciplinary approach to better understand the performance of ultramarathons. The hypotheses based on the observations of the studies conducted in trail running go in the direction of degradation of many functions in the first one-third of the race before reaching a plateau in the last one-third of the race, suggesting that the differences in certain parameters of tiredness are no longer significant between the arrival of 100 miles or 200 miles in a mountain [3,4,20,41,42,48,92-94].

Thus, our initial hypothesis was that there is a significant degradation of all the studied functions under the effect of race-induced fatigue from the first one-third of the race before reaching a plateau on the third one-third. We assume that a difference or difference in the kinetics of the studied functions can lead to failure and abandonment.

Owing to its duration, a mountain ultramarathon induces night and day phases, which can induce a circadian effect on the fluctuation of physiological and cognitive functions. Our team is interested in verifying whether there is a circadian effect on the kinetics of the functions studied during the Trail Scientifique de Clécy, according to the running time and the time of day.

Our study population is representative of the real population of a classic ultratrail race. Our average age (45, SD 13.6 years) is in line with the recent observations, who reported that the average age of the different races of the Ultra Trail du Mont Blanc (Courmayeur Champex Chamonix and Orcières Champex Chamonix) from 2014 to 2018 for the 40 to 49 age group is the most represented [95]. Concerning the distribution of men and women, 21.8% of women against 9.8% of women are on the starting line for the Ultra Trail du Mont Blanc 2021 [95].

The downtime imposed to meet the requirements of the scientific protocol did not exceed 20% of the total time. These data allow us to justify that our scientific race model is closer to reality because of the reduced duration of the stopping time for scientific tasks compared with the duration of the race and voluntary stops.

Conclusions

The originality of this project is that it has allowed an integrative approach to the different parameters determining performance in ultraendurance. Our protocol allowed us to standardize the measurement points with a fixed and identical loop for each lap to collect fixed or continuous measurement points over the entire course, which is not the case in rare studies conducted in racing [5-26]. The loops can be compared with each other and will allow for splitting into sections to analyze each section 6 times in a row.

The first results for each scientific task are expected in June 2022.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Agence nationale de la recherche (ANR, or French National Research).
[PDF File (Adobe PDF File), 849 KB - resprot_v11i6e38027_app1.pdf]

Multimedia Appendix 2
Statement of expertise HAIS N°1.
[DOCX File , 33 KB - resprot_v11i6e38027_app2.docx]

Multimedia Appendix 3
Statement of expertise HAIS N°2.
[DOCX File , 26 KB - resprot_v11i6e38027_app3.docx]

Multimedia Appendix 4
Statement of expertise HAIS N°3.
[DOCX File , 27 KB - resprot_v11i6e38027_app4.docx]

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Abbreviations

HR: heart rate
IL: interleukin
PM: particulate matter
sIL: soluble interleukin
sVEGF: soluble vascular endothelial growth factor
TNF: tumor necrosis factor

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Protocol

Psychophysiological Reactions of Internet Users Exposed to Fluoride Information and Disinformation: Protocol for a Randomized Controlled Trial

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Abstract

Background: False messages on the internet continually propagate possible adverse effects of fluoridated oral care products and water, despite their essential role in preventing and controlling dental caries.

Objective: This study aims to evaluate the patterns of psychophysiological reactions of adults after the consumption of internet-based fluoride-related information and disinformation.

Methods: A 2-armed, single-blinded, parallel, and randomized controlled trial will be conducted with 58 parents or caregivers of children who attend the Clinics of Pediatric Dentistry at the Bauru School of Dentistry, considering an attrition of 10% and a significance level of 5%. The participants will be randomized into test and intervention groups, being respectively exposed to fluoride-related information and disinformation presented on a computer with simultaneous monitoring of their psychophysiological reactions, including analysis of their heart rates (HRs) and 7 facial features (mouth outer, mouth corner, eye area, eyebrow activity, face area, face motion, and facial center of mass). Then, participants will respond to questions about the utility and truthfulness of content, their emotional state after the experiment, eHealth literacy, oral health knowledge, and socioeconomic characteristics. The Shapiro-Wilk and Levene tests will be used to determine the normality and homogeneity of the data, which could lead to further statistical analyses for elucidating significant differences between groups, using parametric (Student *t* test) or nonparametric (Mann-Whitney *U* test) analyses. Moreover, multiple logistic regression models will be developed to evaluate the association of distinct variables with the psychophysiological aspects. Only factors with significant Wald statistics in the simple analysis will be included in the multiple models ($P<.2$). Furthermore, receiver operating characteristic curve analysis will be performed to determine the accuracy of the remote HR with respect to the measured HR. For all analyses, $P<.05$ will be considered significant.

Results: From June 2022, parents and caregivers who frequent the Clinics of Pediatric Dentistry at the Bauru School of Dentistry will be invited to participate in the study and will be randomized into 1 of the 2 groups (control or intervention). Data collection is expected to be completed in December 2023. Subsequently, the authors will analyze the data and publish the findings of the clinical trial by June 2024.

Conclusions: This randomized controlled trial aims to elucidate differences between psychophysiological patterns of adults exposed to true or false oral health content. This evidence may support the development of further studies and digital strategies, such as neural network models to automatically detect disinformation available on the internet.

Trial Registration: Brazilian Clinical Trials Registry (RBR-7q4ymr2) U1111-1263-8227; https://tinyurl.com/2kf73t3d

International Registered Report Identifier (IRRID): PRR1-10.2196/39133

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(JMIR Res Protoc 2022;11(6):e39133) doi:10.2196/39133

KEYWORDS

fluoride; disinformation; randomized controlled trial; social media; internet

Introduction

Dental caries in children is still a significant public health challenge in distinct populations, affecting 532 million infants worldwide, mainly in socially disadvantaged families [1,2]. Its contemporary management focuses on improving personal dietary and oral hygiene habits, as it is a sugar- and biofilm-driven disease resulting from consecutive dental demineralization processes [2,3]. In this context, fluoride-containing oral care products and drinking water play an important role in preventing dental demineralization and promoting remineralization [4-6]. Nevertheless, false or misleading content on the internet continually propagates the discouragement of fluoride usage because of possible adverse health effects [7], which supports the development of dental beliefs that could negatively impact parental oral health behaviors [8]. At the same time, fluoride refusal is a growing concern observed in pediatric dental offices, probably driven or reinforced by internet-based disinformation [9].

Indeed, diverse aspects such as innovative messages, information overload, and predisposed personal characteristics such as pre-existing beliefs, ideological motivations, and political polarization influence the spread of false or misleading web-based content [10-13]. Concurrently, digital users tend to interact with posts associated with their interests uncritically, reinforcing the emergence of echo chambers on social media [13-15]. On the other hand, people may also be susceptible to persuasive information slightly misaligned with their current motivations and behaviors (eg, falsehoods formulated to deceive called disinformation) [16,17]. This process of cognitive dissonance can cause different emotional reactions starting from discomfort or stress to a counterreaction depending on the threat to the individual's freedom, a response known as psychologic reactance [16,18,19]. Interestingly, people with motivations more aligned to the values of persuasion messages exhibit less physiological arousal than less-aligned individuals [16]. Additionally, American adults likely to believe in conspiracy theories have more stressful life events and more significant perceived stress [20]. Nevertheless, the users' emotional reactions during the consumption of internet-based oral health information and disinformation remain uncertain.

Therefore, this study aims to evaluate the patterns of psychophysiological reactions of adults after the consumption of internet-based fluoride-related information and disinformation. The hypothesis (H_1) for this randomized controlled trial indicates that there are differences in the psychophysiological reactions of adults exposed to oral health information and disinformation.

Methods

Trial Design

A 2-armed, single-blinded, parallel, and randomized controlled trial (trial registration number: U1111-1263-8227) will be conducted with 58 parents or caregivers of children who attend the Clinics of Pediatric Dentistry of the Bauru School of Dentistry, considering an attrition of 10% and a significance level of 5%. The participants will be randomized into test and intervention groups, being respectively exposed to fluoride-related information or disinformation presented on a computer, with simultaneous monitoring of their psychophysiological reactions, such as heart rate (HR) and 7 facial features (mouth outer, mouth corner, eye area, eyebrow activity, face area, face motion, and facial center of mass). Then, the participants will respond to questions about the utility and truthfulness of content, their emotional state after the experiment, eHealth literacy, oral health knowledge, and socioeconomic characteristics. The Shapiro-Wilk and Levene tests will be used to determine the normality and homogeneity of data, which could lead to further statistical analyses for elucidating significant differences between groups using parametric (Student *t* test) or nonparametric (Mann-Whitney *U* test) analyses. Moreover, multiple logistic regression models will be developed to evaluate the association of distinct variables with the psychophysiological aspects. Only factors with significant Wald statistics in the simple analysis will be included in the multiple models ($P<.2$). Furthermore, receiver operating characteristic (ROC) curve analysis will be performed to determine the accuracy of F_9 (remote HR) concerning F_8 (measured HR). For all analyses, $P<.05$ is considered significant.

This protocol is written according to the SPIRIT (Standard Protocol Items for Clinical Trials) guidelines. Figure 1 depicts the study design synthesis [21]. The peer review reports are available in Multimedia Appendices 1 and 2.

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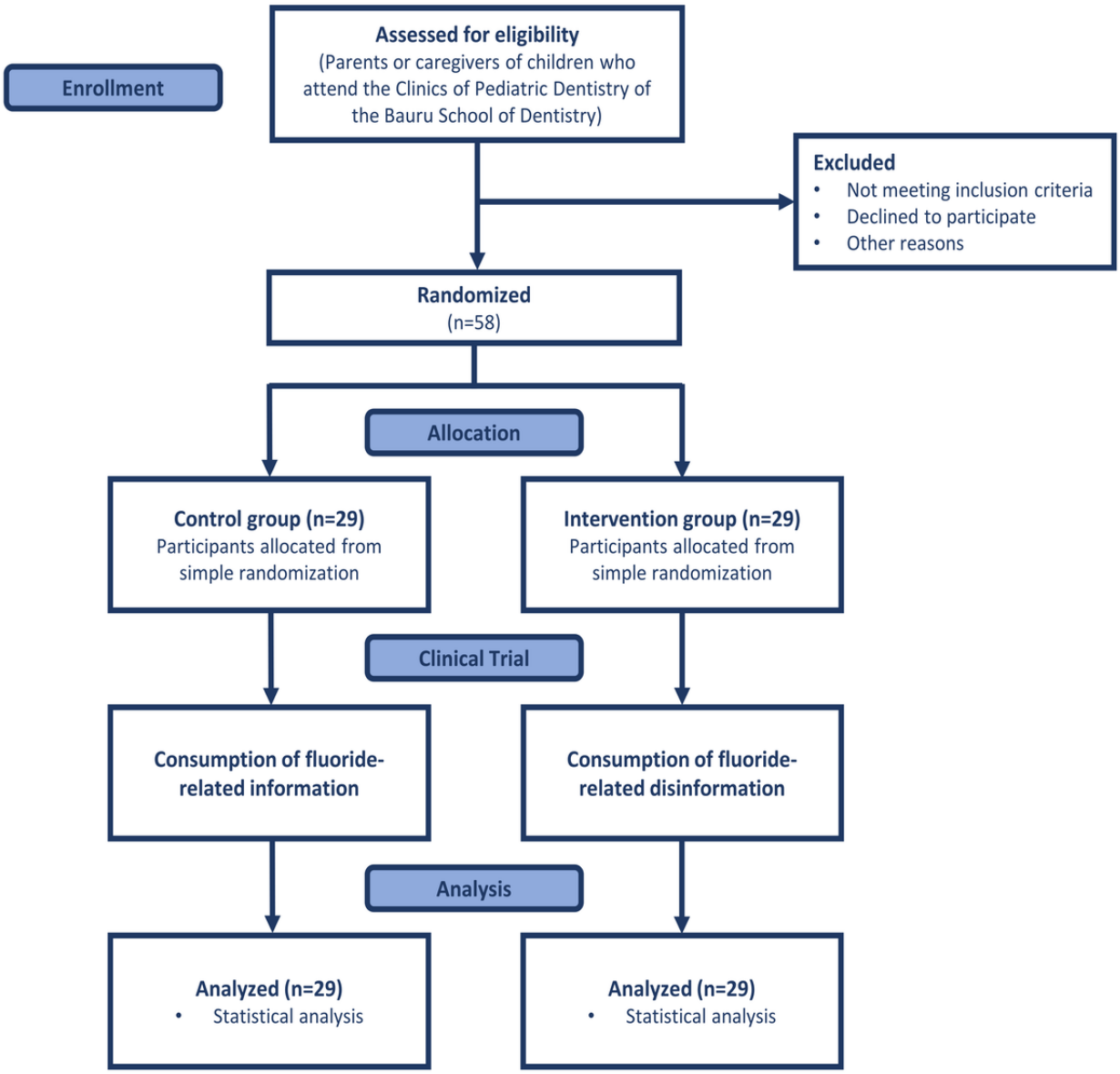
Figure 1. Study flowchart.



Participants, Intervention, and Outcomes

Study Setting

The study will be conducted in a reserved and silent room in the Department of Pediatric Dentistry at the Bauru School of Dentistry in the University of São Paulo, Brazil. The parents and caregivers of children who attend the Clinics of Pediatric Dentistry will be invited to participate in the study.

Eligibility Criteria

The participants will be recruited according to the following inclusion criteria: (1) should be parents or caregivers of children who attend the Clinics of Pediatric Dentistry of the Bauru School of Dentistry, (2) should be native Brazilians, (3) should be literates, (4) should have regular access to the internet, and (5) should agree with terms and sign the free consent form. On the other hand, people who decide to withdraw the previously signed free consent form will be excluded from the study.

Intervention

The experiments will be conducted based on the methodology described by Kirkwood and Minas [22]. After agreeing with the terms and signing the free consent form, the participants will be led to a silent room and will sit in front of a computer. At this moment, the researcher will instruct the participants about the test functioning (consumption of fluoride-related digital content), highlighting the presentation format and time and explaining the technical issues regarding the capture of psychophysiological reactions, besides encouraging them to persist until the end of the activity, and maintain the sitting posture during the process. To monitor the HR (1 Hz), the participants will be asked to wear 2 digital sports watches (Polar Ignite 2 and Polar Verity Sense) positioned at 7 cm away from their wrists. The HRs captured by Polar Ignite 2 will be used in the analyses, whereas the HRs captured by Polar Verity will be recorded as backup measurements.

Throughout the experiments, a camera (Canon Vixia HF R800 Full HD) will record the participants' facial expressions. The

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camera will be placed on a tripod to remain slightly slanted upward and placed to face people at approximately 0.6 m. The video will be recorded in color at 60 frames per second (fps) with a resolution of 1920 × 1080 pixels and saved in the AVCHD-HD format. In addition, a spotlight will be positioned 1.6 m from participants and 45 cm above the camera level to avoid shadows on their faces during the recording. To standardize the recording of the videos, a white photographic background will be positioned approximately 60 cm behind the participants.

Initially, the psychophysiological reaction of participants will be monitored for 150 seconds while they watch a relaxing video with a classical music piece playing in the background (baseline). Next, the monitor will show 25 messages containing fluoride-related information (control) or disinformation (test) in a 6.25-minute slide presentation (15 seconds to read each message).

Each slide will show a short and straightforward message (maximum of 200 characters) for 15 seconds, which is sufficient for the participants to read and understand it [23]. The slides will be developed with a white background and contain messages in black font. By default, the messages will be aligned at the center of the slides. Additionally, the messages will be related to the main issues that emerged from a previous characterization of false or misleading fluoride-related posts on social media [24]. In this regard, we will format the original content of false or misleading posts (intervention group) to ensure a better simulation of the digital environment. Despite the difficulties in classifying distinct information disorder types, the intervention group participants will only receive disinformation because they are intended to deceive individuals intentionally [17].

At the end of the experimental session, the same video used to collect baseline data will be made available to participants for an additional 150 seconds to measure the variations in the psychophysiological parameters.

Questionnaires

The participants will respond to a questionnaire containing 6 questions about the self-perception of the emotional state besides the utility and truthfulness of messages, as detailed in Table 1.

Furthermore, as it is expected that age, levels of education, electronic health literacy, and oral health knowledge can influence the ability of participants in acquiring and criticizing digital content [25,26]; these outcomes will be determined through specific questionnaires.

eHealth literacy is defined as the ability of a person to search, find, understand, and evaluate digital health information and apply the acquired knowledge to address or solve a health issue [27]. It will be measured by the Brazilian version of the eHealth Literacy Scale (eHEALS) [28]. This instrument consists of 8 items linked to the consumption of health information on the internet, as demonstrated in Textbox 1. Participants must answer each question according to their self-perception using a 5-point Likert scale that has options varying from “completely agree” to “completely disagree,” with a total score ranging between 8 and 40 points [28].

The participants’ oral health knowledge will be assessed using the questionnaire proposed by Vilella et al [29], which measures knowledge related to topics of interest in pediatric dentistry, such as breastfeeding, sugar intake, bottle feeding, oral hygiene, and use of fluoride toothpaste (Textbox 2). Questions will be answered using a 3-point Likert scale, categorized as “completely agree,” “neither agree nor disagree,” and “completely disagree.” It should be noted that only the “completely agree” option is precise. Hence, the participants receive a point for each correct answer, with a final score ranging between 0 and 9.

Moreover, the participants will answer questions about their sociodemographic characteristics, self-perception of their oral and general health, and use of internet-based health information.

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Table 1. Questionnaire about self-perception of the emotional state of participants, as well as the utility and truthfulness of messages after the consumption of fluoride-related content.

Question category	Answer options
Emotional state	
1. After consuming these messages, I am feeling...	Calm
	Hectic
2. After consuming these messages, my feeling is...	Positive
	Negative
Utility	
3. Are these messages useful for your own health or for your family's health?	Yes
	No
4. Are these messages important to other people to make their health decisions?	Yes
	No
Truthfulness	
5. Have you already read or heard about these messages before this research?	Yes
	No
6. How do you classify most of these messages?	True
	False

Textbox 1. Brazilian version of the eHealth Literacy Scale questionnaire presented in English.

1. I know how to find helpful health resources on the Internet.
2. I know how to use the Internet to answer my questions about health.
3. I know what health resources are available on the Internet.
4. I know where to find helpful health resources on the Internet.
5. I know how to use the health information I find on the Internet to help me.
6. I have the skills I need to evaluate the health resources I find on the Internet.
7. I can tell high-quality health resources from low-quality health resources on the Internet.
8. I feel confident in using information from the Internet to make health decisions.

Textbox 2. Questionnaire about oral health knowledge of parents or caregivers.

1. The child who is breastfeeding does not need to eat any other type of food until the six months old.
2. Up to six months old, even breastfeeding, the baby also needs to ingest water.
3. After six months old, the baby should eat foods other than maternal milk.
4. After six months old, the baby should no longer drink breast milk.
5. After one year, the baby can taste foods containing sugar.
6. The best way to give teas and juices to babies is using a bottle.
7. After six months old, the baby can be bottle-fed overnight or as much as you want.
8. While the child has baby teeth, it should wear a piece of diaper moistened with filtered water for clean teeth.
9. Babies under two years of age can use the same toothpaste as the adults.

Note: Questionnaire proposed by Vilella et al [29]

Outcomes

The primary outcomes will be obtained by comparing the psychophysiological reactions and self-reported emotional states of participants, as well as the self-perception of the utility and truthfulness of the content between the 2 groups.

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The secondary outcomes will be related to sociodemographic characteristics, eHEALS scores, and oral health knowledge of the participants, and these are considered possible confounding factors of primary outcomes.

Participant Recruitment Timeline

The participants will be recruited from June 2022 to December 2023. As all data will be collected simultaneously, the enrollment process will require only 1 visit from each participant.

Sample Size

Based on previous HR variability outcomes reported by Kirkwood and Minas [22], the sample will be composed of 58 participants, considering an effect size of 2.074 (P=.04) when a subject believes that an article is true, an attrition level of 10%, and a significance level of 5%.

Recruitment

The research team will invite the 58 parents or caregivers in person to participate in the study when they attend the Clinics of Pediatric Dentistry to their children's dental care.

Allocation: Sequence Generation and Concealment Mechanism

The study participants will be randomized with randomly selected block sizes using the Sealed Envelope website [30]. For this process, an operator (AMR) will generate a sequence of randomly selected block sizes to randomize participants equally into the test and intervention groups. The allocation sequence will be blinded using opaque, sealed, and consecutively numbered envelopes to ensure allocation confidentiality.

Implementation

A researcher not involved in the experiments (TSM) will invite the parents or caregivers to participate in the study, taking them directly to the experimental room. Before starting the intervention, the envelopes indicating the group allocated to the participants will be taken to the pretrained examiner (ML) by another operator (OSJ). Then, the allocated group will be known only to the trained examiner (ML), who will open the envelope alone immediately before starting the experiment. He will conduct the experiments, including collecting the informed consent forms and administering the questionnaires.

Blinding

The parents or caregivers, researchers not involved with the experiments (TSM and OSJ), and the data analysts (TC and FB) will be blinded to the participants' allocation groups.

Data Collection, Management, and Analysis

First, the HR data of the participants will be exported from Polar Ignite 2 and Polar Verity Sense to Microsoft Excel (Microsoft Corporation) as.csv files. Further, the sociodemographic, oral health knowledge, self-perception about information, and eHEALS data will be manually entered into Excel sheets. Moreover, the videos will be exported from the camera and stored in a closed repository for further analysis, according to the findings of Bevilacqua et al [31,32]. Notably, the features were designed based on previous reports regarding the potential to distinguish participants' emotional states [31-34]. As a result, 9 psychophysiological features will be calculated, with 7 related to facial activity and 2 to HR, as summarized in Table 2.

Table 2. Description of the psychophysiological characteristics to be measured in the clinical trial.

Feature number	Facial landmark	Description
F_1	Mouth outer	Monitor the zygomatic muscle
F_2	Mouth corner	Monitor the zygomatic muscle
F_3	Eye area	Monitor the orbicularis oculi muscle (eg, blinking)
F_4	Eyebrow activity	Monitor the corrugator muscle
F_5	Face area	Monitor facial movement to and away from the camera
F_6	Face motion	Describe the total distance the head has moved in any direction in a short period
F_7	Facial COM[a]	Describe the overall movement of all 68 facial landmarks
F_8	Measured HR[b]	Measurement of HR using Polar Ignite 2 and Polar Verity Sense
F_9	Remote HR	Estimated measurement of HR using the rPPG[c] technique

[a]COM: center of mass.

[b]HR: heart rate.

[c]rPPG: remote photoplethysmography.

Features F_1 to F_7 are grounded on 68 facial landmarks automatically detected using constrained local neural fields (CLNFs) and are calculated using the Euclidian distance between those facial landmarks [31,32]. However, subjects have unique facial shapes and characteristics, which could prevent their comparison. Thus, we will first calculate a normalization coefficient for the Euclidian distance between the upper and lowermost anchor landmarks to mitigate this problem [31]. Additionally, feature F_9 is based on remote estimations of HR performed using the established remote photoplethysmography

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(rPPG) technique [35]. This is an extremely resilient technique when estimating the HR under challenging conditions and could be combined with the disinformation consumption scenario.

Statistical analysis will be performed using Stata 17.0 software (StataCorp LLC, College Station, TX, USA). The questionnaire and psychophysiological data will be expressed through descriptive analysis (mean, SD, median, minimum, maximum, and percentage of variation). Moreover, the Shapiro-Wilk and Levene tests will be performed to analyze the normality and homogeneity of data to determine significant differences between groups by the Student *t* test (parametric analysis) or Mann-Whitney *U* test (nonparametric analysis). Further, multiple logistic regression models will be developed to evaluate the association of distinct variables with the psychophysiological aspects. Only factors with significant Wald statistics in the simple analysis will be included in the multiple models ($P<.2$). Furthermore, ROC curve analysis will be performed to determine the accuracy of F_9 concerning F_8. For all analyses, $P<.05$ will be considered statistically significant.

It is noteworthy that anonymized data will be shared in a public repository after the end of this study.

Monitoring

Data Monitoring

The authors will assume responsibility for independent regulation of data collection, management, and analysis.

Hazards

People can feel confused about the trustworthiness of the consumed content and consequently develop negative oral health beliefs. Thus, after the intervention, the trained examiner will clarify all aspects of the information and disinformation for each individual. In this way, they will resolve the doubts and possible misunderstandings regarding fluoride consumption, whether in terms of oral hygiene or drinking water. As a result, the present study also serves as a health education measure for the participants.

Auditing

Data management and analysis will be conducted by 1 statistical expert from the research team (TC). If necessary, data inconsistencies will be verified, corrected, and registered.

Ethics and Dissemination

Research Ethics Approval

This study was reviewed and approved by the Council on Ethics in Human Research from the Bauru School of Dentistry (CAAE: 53483821.0.0000.5417), registered in the Brazilian Clinical Trials Registry (RBR-7q4ymr2) and assigned with the universal trial number U1111-1263-8227.

Consent and Assent

Informed consent will be provided and assigned by the participants.

Confidentiality

Identification numbers will be used to ensure participant confidentiality during data analysis.

Availability of Data

All raw data will be available in an open repository.

Ancillary and Posttrial Care

This study is also intended to serve as an oral health education strategy. Thus, participants in the test group will be informed about the falsehood provided, aiming to avoid the development of negative health beliefs. Moreover, all questions about the content consumed will be clarified for all the participants. In addition, participants are expected to observe how disinformation can be harmful in managing their health.

Dissemination Policy

The findings will be reported in high-impact dental or medical informatics journals.

Results

From June 2022, parents and caregivers who frequent the Clinics of Pediatric Dentistry at the Bauru School of Dentistry will be invited to participate in the study and will be randomized into 1 of 2 groups (control or intervention). Data collection is expected to be completed in December 2023. Subsequently, the authors will analyze the data and publish the findings of the clinical trial by June 2024.

Discussion

Principal Findings

To the best of our knowledge, it is the first study that will evaluate the differences in psychophysiological reactions of internet users exposed to or not exposed to disinformation. Given the proposed hypothesis, we expect that individuals exposed to fluoride-related disinformation will present more psychophysiological reactions during the experiments because of stressors provided by the consumption of novel content. Additionally, those who disagree with the content due to previous health beliefs tend to show more psychophysiological reactions, also considering the cognitive dissonance process [16]. Moreover, it is expected that younger adults with higher levels of eHealth literacy and oral health knowledge probably will feel less persuaded by disinformation than their older counterparts. Finally, we hope to obtain promising results pertaining to the comparison of F_9 (remote HR) to F_8 (measured HR), enabling remote validation and measurement of this parameter in future studies on information disorder.

Comparison to Prior Work

Notably, the proposed analysis proved effective in detecting remote emotions in experiments with games [31], but it is still necessary to understand its strengths and limitations in the information disorder context. Nevertheless, it could be a precursor to developing artificial intelligence models to detect false health content automatically and prevent consumption in digital environments. In addition, the results can help people who are more susceptible to believe in fluoride-related false messages found on the internet better understand such information.

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Furthermore, the present methodology adds a new perspective to the study of information disorder. Currently, this research field focuses on internet-based surveillance of falsehoods on social media to formulate public health measures and policies [24,36,37], besides proposing definitions and taxonomies for a better understanding of this phenomenon [17,38,39]. In this context, previous studies have detected the high prevalence of false or misleading fluoride-related content on distinct social networks [7,24,40,41]. On the other hand, investigations about disinformation concerning the user perspective are still lacking.

Strengths

Although desirable, the mitigation of false or misleading messages from computational detection measures that screen and remove posts on social media does not seem to be enough to end the consumption and spread of digital falsehoods [42]. Indeed, the overload of information on internet channels makes data screening difficult because existing artificial intelligence–based systems cannot cover all health issues [11,43]. Considering this scenario, the proposed methodology is advantageous because it investigates the information disorder phenomenon in terms of the users' reactions, instead of only analyzing it from a content perspective. Furthermore, it is possible to validate the collection of HR data from psychophysiological facial reactions using neural network modeling, which would enable remote monitoring of users through an ordinary camera using a computer [31]. Thus, people would have an additional tool to avoid consuming disinformation.

Limitations

The measurements of HR and psychophysiological reactions using specialized technical equipment can be uncomfortable for participants during the experiments, which would influence their stress levels. Despite this, we will use equipment that can provide greater comfort, such as a sports watch that will be attached to the wrist instead of a chest heart reader, besides providing a comfortable air-conditioned experimental room.

Conclusions

Our randomized controlled trial aims to determine if there are identifiable differences in the psychophysiological reactions among individuals who consume true or false fluoride-related digital content. The evidence produced can support the development of further studies and digital strategies, benefiting research, businesses, and communities.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from São Paulo Research Foundation - Part 1.
[PDF File (Adobe PDF File), 275 KB - resprot_v11i6e39133_app1.pdf]

Multimedia Appendix 2
Peer-review report from São Paulo Research Foundation - Part 2.
[PDF File (Adobe PDF File), 561 KB - resprot_v11i6e39133_app2.pdf]

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Abbreviations

CLNF: constrained local neural field
eHEALS: eHealth Literacy Scale
HR: heart rate
ROC: receiver operating characteristic
rPPG: remote photoplethysmography

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Protocol

Supporting People Who Have Lost a Close Person by Bereavement or Separation: Protocol of a Randomized Controlled Trial Comparing Two French-Language Internet-Based Interventions

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Abstract

Background: Internet-based interventions (IBIs) are as efficient as face-to-face psychotherapy for a variety of mental health disorders, including complicated grief. Most evidence stems from guided IBIs. However, recent research indicates that the benefit of guidance is lower in more interactive IBIs. As such, providing guidance only to people requiring it (guidance on demand) appears a cost-effective solution. This is particularly important to develop given the recent rise in grief symptoms in the context of the COVID-19 pandemic. This paper presents the protocol of a randomized controlled trial comparing the efficacy and adherence rate of 2 IBIs for grief-related symptoms after the loss a close one following death or romantic separation, using a guidance on demand framework. LIVIA 2.0 was developed based on theoretical and empirical findings on grief processes and IBIs, and it will be compared to LIVIA 1 that has already demonstrated its efficacy.

Objective: Our main hypotheses are that LIVIA 1 (control condition) and LIVIA 2.0 (experimental condition) increase participants' well-being and decrease their distress at posttest and at follow-up, that LIVIA 2.0 is more efficient than LIVIA 1 for all outcomes, and that LIVIA 2.0 has less dropouts than LIVIA 1.

Methods: Outcomes will be assessed at pretest, posttest (12 weeks later), and follow-up (24 weeks later). We will recruit 234 participants through a variety of means, including social media and contacts with the press. Primary outcomes are grief symptoms, depressive symptoms, and eudemonic well-being. Secondary outcomes are anxiety symptoms, grief coping strategies, aspects related to self-identity reorganization, and program satisfaction. LIVIA 2.0 participants will additionally undergo a weekly mood and grief symptom monitoring, allowing us to explore the short-term efficacy of the sessions.

Results: The creation and development of the content of LIVIA 2.0 was completed during the first phase of the project. Participant recruitment will begin in May 2022 and will last until January 2023.

Conclusions: This study will emphasize the relevance of the innovations included in LIVIA 2.0 regarding the efficacy and dropout rate of IBIs for grief symptoms and will allow investigations on how these changes impact the demand for guidance. In the current postpandemic times, developing and assessing IBIs targeting grief symptoms are particularly critical given the rise in grief-related symptoms.

Trial Registration: clinicaltrials.gov NCT05219760; https://tinyurl.com/3dzztjts

International Registered Report Identifier (IRRID): PRR1-10.2196/39026

(JMIR Res Protoc 2022;11(6):e39026) doi:10.2196/39026

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KEYWORDS

internet-based interventions; grief; bereavement; separation; divorce; identity; digital health; mental health; psychotherapy

Introduction

Background

Internet-based interventions (IBIs) offer numerous efficient prevention and treatment programs for a variety of psychological difficulties [1,2]. Generally based on methods originating from empirically supported face-to-face psychological interventions for people reporting complicated grief symptoms [3,4], IBIs for grief-related symptoms are also effective [5,6].

Offering guidance to participants is one of the most commonly cited means to improve IBI effectiveness [7], including grief-related symptoms [5]. However, recent evidence indicates that the benefits of guidance are lower in more interactive internet interventions [8]. Moreover, when given the choice, not all participants request guidance. Additionally, the efficacy of guidance on demand is similar to standard weekly guidance [9-11]. Finally, including specific and individualized principles, such as the Motive-Oriented Therapeutic Relationship (MOTR), in the guidance appears feasible and useful for IBIs [12,13]. Thus, MOTR-based guidance on demand appears as a cost-effective alternative to mandatory guidance. Other elements can also improve adherence rate and efficacy: (1) using automated reminders [14]; (2) providing interactivity in the tasks and exercises [15-18]; (3) promoting personal resources to cope when problematic experiences arise [19,20]; (4) tailoring the intervention to the participant's characteristics and timing the content in accordance with the participant's characteristics [21-24].

LIVIA 2.0 was developed as an alternative IBI to LIVIA 1, the original program, for grief-related symptoms after bereavement or separation [25], which was tested in German via a randomized controlled trial (RCT) [26] and in French via a noncontrolled trial [27]. Indeed, fundamental research has pointed to the many similarities between these kinds of losses [27,28]; moreover, studies on LIVIA 1 have proved that the same intervention can be provided to both populations [26,29]. LIVIA 2.0 implements different factors to improve patient adherence and program efficacy. Specifically, it includes automated emails, increased interactivity (quizzes, video files, and audio files), personal resource assessment and promotion, and the freedom to choose the session order combined with an individualized recommendation. The content is based on the Dual Process Model (DPM) of bereavement recovery and proposes an oscillation process mimicry [30,31] with an alternation of loss-focused and restauration-focused sessions. Finally, LIVIA 2.0 includes a module focused on identity and memory processes that play a key role in adapting to loss [32,33] as well as novel emotion regulation tools [34,35].

In detail, the development of LIVIA 2.0 and its innovations were based on the theoretical and empirical literature about grief and romantic dissolution. On the theoretical level, we relied on one of the most influential models of coping with loss, the DPM of Coping with Bereavement [30,31]. According to it, after loss, instead of going through consecutive phases, people oscillate between a focus on the loss and a focus on the restauration from the loss. This model postulates that oscillation is a natural and necessary movement to cope with loss. Moreover, DPM-based interventions are more efficient than classic ones [36]. Hence, LIVIA 2.0 imitates the oscillation process by alternating between loss- and restauration-focused sessions. Additionally, LIVIA 2.0 integrates recent loss-related empirical findings into its content and exercises. For example, the Emotion module proposes self-compassion exercises, as self-compassion has been shown to predict better grief recovery [37,38]. Moreover, LIVIA 2.0 includes a newly developed module based on empirical cognitive psychopathological knowledge and focused on identity processes, which play a key role in adaption to bereavement [32,33]. Addressing identity factors, such as fostering an independent sense of identity by focusing on adaptive specific autobiographical memories and future projections, could improve existing cognitive-behavioral programs for grief.

LIVIA 2.0 also integrates recent developments in IBIs [16,20]. First, a series of changes are designed to improve participant autonomy by sending automated emails [14], providing individualized recommendations about the order in which to complete the modules [22], promoting and encouraging the use of personal resources [20], and augmenting the interactivity of the website [15-18]. Finally, the emails exchanged with the participants within the guidance on demand framework will be based on the MOTR [12].

Objectives

Our main hypotheses are the following: (1) LIVIA 1 and LIVIA 2.0 increase participants' well-being and decrease their distress at posttest and follow-up. (2) LIVIA 2.0 is more efficient than LIVIA 1 for all outcomes. (3) LIVIA 2.0 has less dropouts than LIVIA 1.

Moreover, we will conduct the following exploratory analyses. First, we will compare the guidance requirements of the participants (ie, number of participants requiring guidance and number of exchanged emails) in LIVIA 2.0 with those of the LIVIA 1 participants and explore which session triggers more requests for guidance. Second, we will examine in LIVIA 2.0 the short-term effectiveness of each module on the participants' weekly moods, feelings of loneliness, and grief symptoms. Third, we will compare participant satisfaction in the 2 versions of LIVIA. Fourth, we will explore the role of multiple measures (attachment style, type of loss, interpersonal closeness to the lost person, and symptom severity) as moderators of the program's effectiveness. Finally, we will investigate the semantic content of the responses to the LIVIA 2.0 exercises [39] to explore its relationship with improvement over the evaluation period.

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Methods

Study Setting

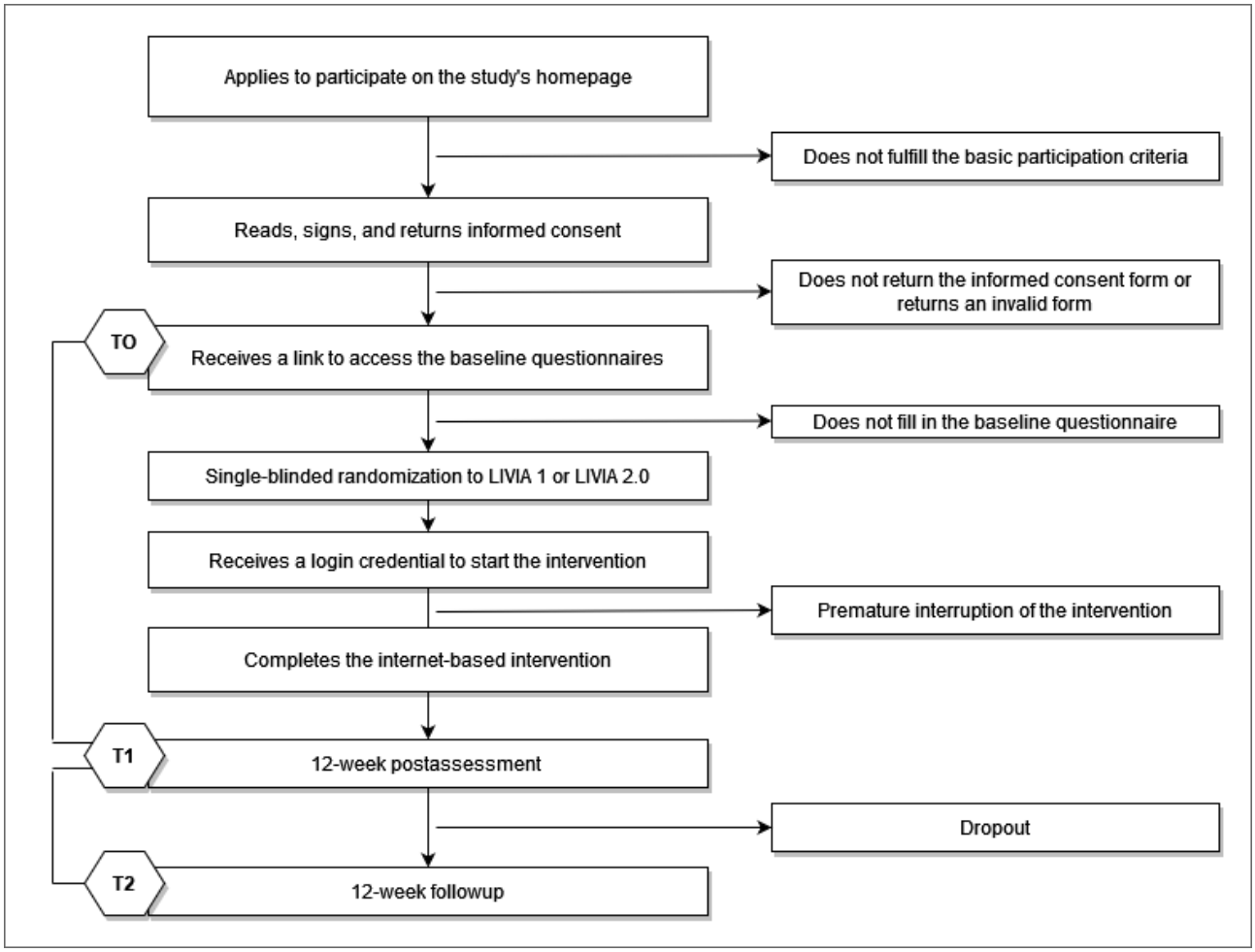
This is a study of an IBI in French. We will recruit participants in Switzerland, but participation will be open to French-speaking people across the world.

Design and Procedure

This study is a monocentric, single-blinded, 2-arm RCT comparing the efficacy of 2 versions of an IBI—namely LIVIA 1 and LIVIA 2.0—aimed at relieving distress and augmenting the well-being of people suffering from prolonged grief symptoms. There will be three measurement points: a pretest (T0), posttest (T1), and follow-up (T2). The flowchart of the study design is presented in Figure 1.

This self-help intervention is embedded in a larger project on life-span vulnerabilities and strengths conducted by the LIVES Centre [40].

Figure 1. Flowchart of the study design. T0: assessment at baseline; T1: assessment at posttest; T2: assessment at follow-up.



Study Conditions

LIVIA 1: Control Condition

LIVIA 1 is a self-help intervention for coping with prolonged grief symptoms after the death of a loved one or romantic separation/divorce, developed at the University of Bern by Brodbeck and colleagues [25]. Participants are encouraged to work through 1 session per week and complete the exercises provided. Each session takes approximately 60 minutes to complete. The sessions must be completed in the prescribed order. Details of the session contents can be found elsewhere [25].

LIVIA 2.0: Experimental Condition

LIVIA 2.0 is a psychological IBI composed of 10 sessions (see Table 1). These include an introductory session, a closing session, and 8 sessions in between belonging to 4 modules. Theoretically anchored in the DPM [30,31], each module comprises a session focused on loss and another on restoration. The modules have the following main themes: cognitions, emotions, behaviors, and identity. The sessions involving these modules are composed of psychoeducational information and exercises. In each session, participants can choose between 3 variants of the exercise (eg, some exercises vary in their themes or length). They are expected to complete 1 exercise per session but can complete all 3 available exercises if they wish to. LIVIA 2.0 also contains texts, audio and video files, and interactive quizzes.

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Table 1. Summary of the sessions and main content of LIVIA 2.0[a].

Session	Module	Theme	Content
1	Introduction	Psychoeducation; assessment of resources and goals	Information about the self-help intervention, grief reactions, predictors, and treatment of complicated grief; assessment of individual resources and goals in pursuing the intervention
2	Cognition-focused	Loss-oriented session	Information about the impact of negative thoughts on well-being and the typical negative thoughts experienced during difficult grief; cognitive restructuration exercises
3	Cognition-focused	Restoration-oriented session	Information about secondary stressors and related thoughts; importance of building positive thoughts as resources; exercise to promote focus on positive aspects of one's own life
4	Emotion-focused	Loss-oriented session	Information about the central role of emotions in the grieving process; assessment of own emotional state; self-compassion exercises
5	Emotion-focused	Restoration-oriented session	Importance of experiencing positive emotions, even if only briefly; hypnosis-like exercises to promote positive emotions
6	Behavior-focused	Loss-oriented session	Information about the typical vicious circle of avoidance in grief and the importance of confronting the avoided situations; confrontation exercises
7	Behavior-focused	Restoration-oriented session	Importance of behavioral activation in line with one's own values; assessment of values; preparation of behavioral activation in line with one's own values
8	Identity-focused	Loss-oriented session	Psychoeducation about identity formation and the way it is affected by grief; exercise aimed at revisiting memories and the relationship with the lost person; developing an independent sense of identity
9	Identity-focused	Restoration-oriented session	Psychoeducation about the importance of autobiographical memory for the individual's sense of self and ability to generate images of future events; exercise aimed at focusing on specific adaptive autobiographical memories and future projections to foster an independent sense of identity
10	Conclusion	Assessment of the individual's experience of the intervention; relapse prevention	Promoting reflection on one's own journey through the program (what was learned, what still needs to be done); identification of vulnerable moments and strategies to deal with the latter

[a]Modules 2 to 9 can be completed in the order chosen by the participants.

Navigation in the LIVIA 2.0 Program

The participants will first complete the introduction module. In this module, they will answer a questionnaire for allowing the program to automatically suggest an order of completion for the main modules (sessions 2 to 9, see Table 1), based on each participant's priorities (eg, "It is important for me to avoid being taken over by negative thoughts" or "It is important for me to experience more positive emotions"). Nevertheless, participants will be able to choose the completion order freely. Each module consists of a (1) short introduction, (2) loss-related session, and (3) restauration-related session. Participants will mandatorily complete the module in this order. Once they have completed the 4 modules, they will complete the program with the conclusion session.

The following are the rules governing content access: (1) Once a session is opened, only that session is available for the next 7 days. After that, the following session is available, or if starting a new module, participants can choose the next module they wish to work on. (2) Within a session, participants can only access the content of that session or content that has already been completed. (3) Once they have reached the end of a session within a module, they can choose to do another exercise. (4) At the end of the intervention (12 weeks after starting it), they will have access to all the content.

Additional Resources

To assist participants as they complete the program, a toolbox will be provided with the content shown in Textbox 1.

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Textbox 1. Toolbox provided to the participants during the program.

Favorites

Participants will be able to add parts of the program that they particularly appreciate to their favorites.

Individual resources of the participant

Participants can access the assessment of their personal resources with AERES (a self-assessment scale for resources) during the first session (Bellier-Teichmann et al [20]).

Soothing techniques for emotionally difficult times

Short exercises, such as breathing exercises or tools to anchor attention in the present moment, will be available.

Key scientific references

We will provide the main references of the content of each session so that participants may deepen their knowledge on a specific domain, should they wish to.

Automated emails

To encourage participation, emails will automatically be sent (1) when a new session becomes available and (2) if the participant has not accessed the program for 7 consecutive days.

Assignment of Interventions

To assign participants to the LIVIA 2.0 (experimental) or LIVIA 1 (control) condition, we will use the randomization module in REDCap (Research Electronic Data Capture [41,42]), which will automatically generate a 1:1 randomization. We will apply a single-blinded randomization strategy stratified according to the gender and loss type (bereavement vs separation) of the participants. Due to the nature of the study, double-blinded randomization is not possible.

Participants

Sample Size

We will conduct a power analysis with G*Power (Version 3.1.9.2 [43]) for ANOVA of repeated measures involving within-between interactions that would enable us to compare the efficacy of the 2 interventions. Based on a probability level of 0.05 and a power of 0.8, to detect a small effect size of $f=0.1$ (as we expect small differences between the 2 programs), a sample size of 164 participants is needed. Expecting a dropout rate of 30% at the 3-month follow-up, we aim to have 234 participants at posttest.

Recruitment

To maximize recruitment, the following strategies will be applied: (1) contacting grief and divorce-related associations as well as other potentially interested associations (eg, senior citizens' associations), (2) contacting radio and television channels as well as newspapers, (3) distributing flyers in churches, beauty salons, and health-related institutions, (4) promoting the project in church administrations, (5) sending emails to large groups of university students, (6) promoting the study through social media, and (7) publishing an advert on research facility websites. To ensure an ongoing flow of participants until we reach the desired number of participants, we will continuously revise and rerun our recruitment strategy.

Eligibility Criteria

Participants meeting all the following inclusion criteria will be eligible for the study: (1) have experienced bereavement or separation, (2) either events must have happened more than 6 months prior to participating in the study, (3) feel the need for support to cope with the loss (a diagnosis of complicated grief is not necessary), (4) aged 18 years or older, (5) have regular access to the internet, (6) fluent in French, and (7) have approved the informed consent form.

The presence of any of the following exclusion criteria will preclude individuals from participating in the study: (1) moderate to acute current suicidality (Suicidal Ideation Attributes Scale score>19] [44,45]) (Note that participants having a Suicidal Ideation Attributes Scale score between 13 and 19 will undergo a telephonic interview to accurately assess their suicidal risk and will be excluded from the study if the risk is assessed as important [46]), (2) severe psychological or somatic disorders that need immediate treatment, (3) concomitant psychotherapy, (4) prescription or change in dosage of psychoactive drugs in the month prior to or during the self-help intervention, (5) inability to follow the study procedures (eg, due to comprehension problems), and (6) enrolment of the investigator, their family members, employees, and other dependent people.

Security During the Procedure

During the intervention, participants will receive a biweekly assessment of the occurrence of a serious adverse event. Additionally, they will be able to contact the investigation team at any time through a contact form available in both the IBIs. An automatic reply will be sent informing that their message will be processed within 3 working days and that they can contact the emergency numbers that will be provided. This will enable the participant to make contact and be attended to at any moment if necessary. We will then discuss with them the reason for contacting us and if a serious adverse event is occurring. If this is the case, the participants will be contacted, and their situation will be evaluated. If necessary, alternative treatments will be proposed.

Measures

The calendar for obtaining the measures from the participants can be found in Multimedia Appendix 1.

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Primary Outcome Measures

Grief symptoms will be assessed with the French version of The Traumatic Grief Inventory-Self-Report prepared by Cherblanc and Zech (unpublished work, 2021), an 18-item self-report measure assessing the presence of symptoms described in each item on a 5-point scale ranging from 1 (never) to 5 (always) [47]. This inventory is designed to assess symptoms of persistent complex bereavement disorder as described in the Diagnostic and Statistical Manual of Mental Disorders (5th edition [48]) and prolonged grief disorder in the International Classification of Diseases (11th edition) [49]. It has shown good reliability and validity to recognize people at risk of prolonged grief disorder.

Depression symptoms will be assessed with the Patient Health Questionnaire-9 [50], a 9-item measure of depression with adequate reliability and validity [51,52]. It assesses various depressive symptoms in the previous 2 weeks on a scale ranging from 0 (never) to 3 (almost every day).

Well-being will be measured with the French version [53] of the Flourishing Scale [54], a brief 8-item summary measure of the respondent's self-perceived success in important areas such as relationships, self-esteem, purpose, and optimism. As such, it measures eudemonic well-being, a larger conception of conventional well-being measures. Participants will answer questions such as "I lead a purposeful and meaningful life" on a scale ranging from 1 (strongly disagree) to 7 (strongly agree).

Secondary Outcome Measures

Anxiety symptoms will be assessed with the Generalized Anxiety Scale [55] in its validated French version [56]. The scale has 7 items (eg, "Feeling nervous, anxious, or on edge") assessing the frequency of symptoms over the previous 2 weeks rated on a 4-point Likert scale (0=not at all; 3=nearly every day).

Grief coping strategies will be measured with the Coping with Bereavement Questionnaire [57]. It consists of 14 items relating to loss orientation, such as "I take time to think about the things that I have experienced with the lost person" and 12 items relating to restoration orientation, such as "I try to accept living on without the lost person." These items correspond to a list of coping strategies (thoughts, behaviors) for which the respondent must estimate the frequency of use during the previous month (1=almost never [less than once a month]; 5=all the time [several times a day]; 0=not applicable [this statement does not apply to the context of my life]).

Aspects related to identity will be measured with 3 scales. First, the 12-item French version [58] of the Self-Concept Clarity Scale [59] will assess the extent to which self-beliefs are clearly and confidently defined, internally consistent, and stable. Participants will answer questions such as "In general, I have a clear sense of who I am and what I am," rated on a 5-point scale (1=strongly disagree to 5=strongly agree). Second, the Centrality of Event Scale [60] will assess the extent to which a memory for a distressing life event becomes a reference point for personal identity and for the attribution of meaning to other experiences in the person's life (eg, "I feel that this event has become a central part of my life story."), rated on 5-point scale (1=totally disagree to 5=totally agree). The French version of the Centrality of Event Scale was developed by Ceschi et al (unpublished work). Finally, 3 items will assess self-continuity [61]: "I am the same person as I always was," "With time a lot of things have changed, but I'm still the same person," and "I am a different person than I was in the past." These items will be evaluated on a 5-point scale (ranging from 1=does not apply to me at all to 5=fully applies to me).

The feelings of loneliness will be measured with the University of California Los Angeles Loneliness Scale [62,63] contains 10 positive (eg, "I feel in tune with the people around me") and 10 negative (eg, "I lack companionship") items. Participants will respond to each item using a 4-point scale (1=never to 4=often).

Program satisfaction will be measured with a translated version of the Client Satisfaction Questionnaire adapted to IBIs [64]. The questionnaire will assess satisfaction with the theoretical content, practical content (exercises), structure, design, and overall assessment of the intervention. It contains 15 items rated with a scale ranging from 1 (no) to 4 (yes) and 4 open-ended questions.

Additionally, we will monitor the mood of the LIVIA 2.0 participants on a weekly basis using a single item: "How would you describe your current mood" on a scale ranging from 0 (very bad) to 6 (very good). Moreover, we will monitor weekly grief and solitude symptoms on a scale ranging from 0 (strongly disagree) to 7 (strongly agree) with the following items: "During the past 24 hours, (1) I have felt negative emotions; (2) I have had negative images or thoughts; (3) I felt blocked in my behavior (what I do, my activities); (4) I felt lonely; (5) I had a very clear vision of myself." We will also assess the linguistic behaviors in the exercises of LIVIA 2.0 where the participants are required to describe a loss-related situation. More specifically, we will analyze indicators of verbal immediacy (use of first-person pronouns and present-tense words) and so-called "we-talk" (first-person plural pronouns [39]). Finally, we will assess the degree of guidance required in each group (number of participants requiring guidance and number of emails exchanged).

Predictors and Moderators

The following variables will be assessed only at baseline (T0) and their moderating role in the efficacy of the intervention will be explored: (1) demographic characteristics (31 items); (2) relationship quality prior to death or separation, measured with adapted items from the Dyadic Adjustment Scale-4 [65,66]. The Dyadic Adjustment Scale-4 will only be used if the person lost was a romantic partner. It has 4 items, with 3 items (eg, "In general, how often do you think that things between you and your partner are going well?") rated on a 6-point scale (from 0=all the time to 5=never) and a 4th item rated on a 7-point scale (from 0=extremely unhappy to 6=perfectly happy); (3) adult attachment style, measured with the Experiences in Close Relationships–Short Form scales [67,68]. This 12-item measure captures variability along two attachment dimensions: avoidance and anxiety. Participants will rate the extent to which they agreed with each statement using a 7-point scale (1=strongly disagree to 7=strongly agree); (4) interpersonal closeness with

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the person lost measured with the Inclusion of Other in the Self scale [69]. Respondents will be required to select 1 out of 7 Venn-like diagrams depicting their relationship with the lost person.

Data Collection and Management

Study data will be collected and managed using REDCap electronic data capture tools hosted at the Lausanne University Hospital [41,42]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data assessment, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources. Data integrity is enforced through several mechanism (ie, referential data rules, valid values, range checks, and consistency checks).

Moreover, data on the use of the self-help sessions will be collected within the platform, as well as the entries of the participants in LIVIA 2.0 (exercises, quizzes, questions, etc). All data will be saved anonymously, identified only by a random code. The servers are protected by high-end firewall systems. The participant code list will be saved on an internal Network-Attached Storage. Only the researchers directly involved in the study will have access to the data.

Statistical Analysis

Primary analyses will be performed using SPSS (IBM Corporation) and R (R Foundation for Statistical Computing) after the participants complete the study. Primary follow-up analyses will be conducted 3 months later. Intermediate analyses during data collection will be done. We will perform intention-to-treat analyses [70]. We will develop multilevel mixed effects models with repeated measures data in SPSS to evaluate the efficacy of LIVIA 2.0 compared to LIVIA 1 and the stability of the effects. These models have the advantages of considering the dependency of the data and accounting for the correlation of repeated measures within individuals. Moreover, they rely on all available data of every participant and estimate parameters of missing values [71].

We will explore the potential moderating effect of different variables on the intervention effects by conducting analyses of covariance for repeated measures. To explore the short-term efficacy of each module, we will use multilevel modeling whereby each participant's monitoring data are nested within participants. These analyses will be conducted with Mplus [72] or R. Additionally, we will analyze qualitatively the satisfaction questionnaire using the thematic content analysis method [73]. Finally, we will analyze the semantic content of the exercises included in LIVIA 2.0 [39] and test if some categories (eg, "we-talk") are associated with the efficacy of the program. We will rely on a significance level of a 2-sided α=.05 or smaller. We will use the Bonferroni correction to adjust for multiple testing.

To handle missing data and dropouts, we will conduct the analyses relying on the intention-to-treat paradigm. We will first analyze the magnitude of missing data, explore the missing data patterns, and determine the pattern of missing data (missing completely at random, missing at random, and not missing at random). If the missing mechanism is missing at random, we will use multilevel regression analyses, which allow for nonindependent observations and for different numbers of measurement points per participant and are thus less sensitive to missing data [71].

Monitoring of the Study

The Clinical Trial Unit of the Centre de Recherche Clinique (CTU/CRC) of the Lausanne University Hospital will monitor the study. This includes (1) a monitoring preparation meeting; (2) an initiation visit whereby before starting the study, the CRC team and the investigation team will go over the entire procedure of the clinical trial; (3) intermediary visits whereby the CTU/CRC will control the available data and write reports on a regular basis; and (4) a close-out visit whereby upon study completion, the CRC team and the investigation team will meet 1 last time and revise all the study materials.

Ethics Approval and Consent to Participate

The protocol (trial registration: NCT05219760) has been approved by a federally acknowledged ethics committee (Commission cantonale d'éthique de la recherche sur l'être humain, CER-VD, BASEC reference number: 2021-D0086) and by the Swiss Agency for Therapeutic Products (reference number: 102667545) in accordance with the Swiss Ordinance 810.306 on Clinical Trials with Medical Devices. We will obtain informed consent from all participants in the study (see Multimedia Appendix 2), codify their data, and ensure secure storage of the data.

Results

The project started in February 2019. Throughout the initial years of the project, the website and the content of the LIVIA 2.0 intervention were developed, pretested [74], and corrected according to the obtained feedback. Additionally, the LIVIA 1 intervention was transferred to a new digital platform and the study materials were selected and prepared. Moreover, the required approvals by the ethics committee and the competent authority (Swissmedic) were prepared and obtained. At the time of the submission (April 2022), the website and research materials were ready, but no data had been collected. The recruitment will begin in May 2022, once the monitoring authority provides approval and will last until January 2023 (the recruitment period might be prolonged if necessary). The findings will be disseminated using different methods, including peer-reviewed journals, academic and public conferences, and other verbal and digital channels (eg, through the blog tab of the study's webpage or using the social media accounts of the study).

Discussion

In this study, we aim to investigate how a newly developed IBI for grief-related symptoms (LIVIA 2.0) compares to one that has already been tested and validated (LIVIA 1 [26,29]) for people who have lost a close one either by bereavement or separation. This will inform about the efficiency of incorporating different empirically based innovations.

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Strengths and Limitations

The treatment gap in mental health care is a global reality [75], and we can expect the COVID-19 crisis to have aggravated it [76]. Moreover, because of the increased deaths and obstacles to social contact due to the distancing measures during the pandemic, it is particularly crucial to make IBIs available for general purposes [77] and for grief symptoms in particular [78]. To our knowledge, this study will be the first one to test an IBI targeting grief symptoms in French. As such, it will contribute toward facilitating access to high-quality IBIs for the French-speaking population. Additionally, research on IBIs using a guidance on demand framework is rare [10,11]. Hence, this study will contribute to knowledge about this method that may provide a promising outlook from human resource and economical perspectives. This project will thus contribute toward expanding the possibilities to offer accessible and cost-efficient interventions to people in need.

Some potential limitations can be anticipated. First, the self-selection of the sample may result in participants that have higher education levels and a higher proportion of women than the targeted population of people experiencing grief symptoms after bereavement or romantic separation [79]. However, the study will provide valuable information about the efficacy of LIVIA 2.0 for the targeted population. Second, because participants will have considerable freedom in the way they navigate through the program (ie, choosing the order of the modules and selecting the exercises they want to complete in each session), all the participants will not have taken the same path to complete LIVIA 2.0. However, this will provide them with more choices and higher individualization. Finally, we cannot confirm accurately if the participants respect the exclusion criteria of not undergoing face-to-face psychotherapy while doing the program. This would not be ethically nor practically feasible. However, as the participants are randomized to both programs, this potential bias should be equal in both study arms.

Conclusions

IBIs contribute to closing the so-called treatment gap, which refers to the difference between the number of people needing psychological treatment and those who actually undergo it [80,81]. This is particularly true in the case of interventions targeting grief symptoms, as a significant proportion of people reporting the need for support after bereavement do not get it [82,83]. Additionally, psychotherapists often lack the competences to deal optimally with this affection [84,85]. Finally, the COVID-19 pandemic crisis has contributed to the increased risk of suffering complicated grief symptoms [86,87]. Hence, developing, assessing, and offering IBIs for grief-related symptoms seems particularly crucial in the current times [78,86]. The results of this RCT will give insight into the relevance of the present developments in outcome improvement and dropout diminution for adults who experience grief symptoms. Besides, the study design will allow for conducting additional analyses that can provide a deeper and more fine-grained understanding of the mechanisms of change in IBIs. For example, we will be able to analyze the effect of specific modules on the weekly mood and symptom monitoring, assess the effect of some moderators (eg, attachment style or closeness to the lost person at pretest), or study the linguistic behaviors in the exercises where participants are required to describe a loss-related situation [39].

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Data Availability

The data sets that will be generated during the current study will be available in the Zenodo repository. They will be password-protected to ensure correct use of the data, but the data will be made available from the corresponding author upon reasonable request.

Authors' Contributions

AD and VP conceived the study. AD, LE, MK, LB, and VP developed the LIVIA 2.0 intervention content and selected the questionnaires.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Calendar of the participants' measures.
[PDF File (Adobe PDF File), 138 KB - resprot_v11i6e39026_app1.pdf]

Multimedia Appendix 2
Feedbacks from Fonds National Suisse Schweizerischer Nationalfonds (SNSF, Swiss National Science Foundation) reviewers.
[PDF File (Adobe PDF File), 263 KB - resprot_v11i6e39026_app2.pdf]

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Abbreviations

DPM: Dual Process Model
IBI: internet-based intervention
MOTR: Motive-Oriented Therapeutic Relationship
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

A Mobile Phone App Intervention to Promote Healthy Salt Intake Among Adults: Protocol for a Randomized Controlled Study

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Abstract

Background: There is sound evidence associating high salt intake and a greater risk of cardiovascular and noncardiovascular diseases. High salt intake has been observed in several populations worldwide. Therefore, promoting healthier salt consumption has been encouraged as a low-cost strategy to reduce this risk factor. However, these strategies need to be sound, built on theoretical and methodological bases, and consider the target population's context.

Objective: This protocol aims to describe a mobile phone app intervention to promote healthy salt intake among adults.

Methods: This is an experimental and longitudinal study protocol conducted in three modules. Module 1 refers to the planning of the intervention based on the Behaviour Change Wheel framework. Module 2 is the development of the mobile phone app intervention based on the date of module 1. In module 3, the intervention will be evaluated using a randomized controlled study, with three steps of data collection in a 2-month follow-up in a sample of 86 adults (43 participants for each group: the control group and intervention group) recruited from the primary health care centers of a Brazilian town. The discretionary salt intake questionnaire will assess salt consumption, the app usability will be assessed using the System Usability Scale, and psychosocial variables (habit, intention, and self-efficacy) will also be measured.

Results: Recruitment began in October 2021, and the follow-up will end in August 2022. The results of this study are expected to be published in 2023.

Conclusions: Results from this study will help people to control salt intake when cooking at home, will stimulate self-care, will work as an alternative or supportive method in the relationship between health care professionals and patients, and will contribute to implementing the app intervention to promote healthy salt intake on a large scale.

Trial Registration: The Brazilian Clinical Trials Registry RBR-4s8qyyq; https://ensaiosclinicos.gov.br/rg/RBR-4s8qyyq

International Registered Report Identifier (IRRID): DERR1-10.2196/37853

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KEYWORDS

mHealth; intervention; sodium chloride; dietary; behavior change; mobile health

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Introduction

It is estimated that salt consumption is high worldwide [1,2], and there is sufficient evidence to associate high salt intake with the development and worsening of cardiovascular diseases [3-7]. A population-based study in a Brazilian town was conducted to characterize salt intake using biochemical and self-report methods, and according to sociodemographic and clinical variables, and found a mean of salt intake based on a 24-hour urine excretion of 10.5 g/day. Most of the salt is derived from the salt added during cooking [8]. It means consuming more than twice the daily recommendation of salt, which is less than 5 grams per day (2300 milligrams of sodium per day) [9,10], and it is the critical salt consumption behavior that should be reduced.

Plans and guidelines conducted by international and governmental agencies [7,11,12] encourage the promotion of a healthy intake of this nutrient in several countries, but changing people's behavior is not a simple task for educators, researchers, health professionals, and those responsible for creating and implementing public policy strategies. Isolated educational campaigns or population awareness campaigns are insufficient. On the other hand, the results are effective when we associate behavior change interventions based on theoretical models in promoting healthy salt consumption [12-17].

A global systematic review [12] investigated 22 studies related to the impact of behavior change interventions to reduce salt consumption in the population and found that health education at the population level and awareness-raising interventions can improve salt-related behaviors and reduce their salt intake. In the analysis of the interventions developed based on methodological frameworks or models, all studies have shown success in improving the behavior or reduction of salt intake [12]. Thus, reducing salt intake is not a simple behavior to achieve, requiring more specific initiatives with the aid of consistent and effective methodological frameworks to change people's dietary patterns [12,18,19].

One of the frameworks used to design a behavior change intervention is the Behaviour Change Wheel (BCW). The BCW is a validated synthesis of 19 frameworks of behavior change linked to a broad model that can be applied to any behavior in any setting [20]. At the center of the BCW is the Capability, Opportunity, Motivation, and Behaviour (COM-B) model, which recognizes that the behavior is a complex interaction of all these components, and its variant, the Theoretical Domains Framework (TDF), which synthesizes key theoretical constructs from the 33 behavior change theories [20]. The components of COM-B and the domains of TDF together give a more detailed diagnosis of the behavioral analysis. The BCW has been applied successfully in intervention development in various health-related contexts, including changing eating behaviors [19].

In addition to using a consistent tool to design the intervention, there is the choice of an appropriate way to deliver this intervention. Given advances in information technology, increasing smartphone users, easy internet access, and the use of mobile apps, health care app-based interventions have become a growing area for the promotion and self-monitoring of users' health because of their cost-effectiveness by encouraging self-care [21], the flexibility in information delivery, and the breaking down of barriers that have been associated with traditional interactions [22,23].

As a result of a low cost and easy access, behavior change interventions through apps have increased considerably in several areas, such as physical activity–related behaviors [24,25], smoking [26], medication adherence [27,28], and depression [29,30] as well as chronic diseases such as diabetes [31] and asthma [32]. Based on this perspective, we set out to promote healthy salt consumption through the app.

Thus, the objective of this protocol is to describe a randomized pilot study aimed at assessing the efficacy of an app intervention to promote healthy salt intake based on the BCW in a Brazilian population and assessing the usability of the app.

Methods

This study will be conducted in three modules: (1) intervention development using the BCW, (2) elaboration of the mobile phone app, and (3) evaluation of the intervention (Figure 1).

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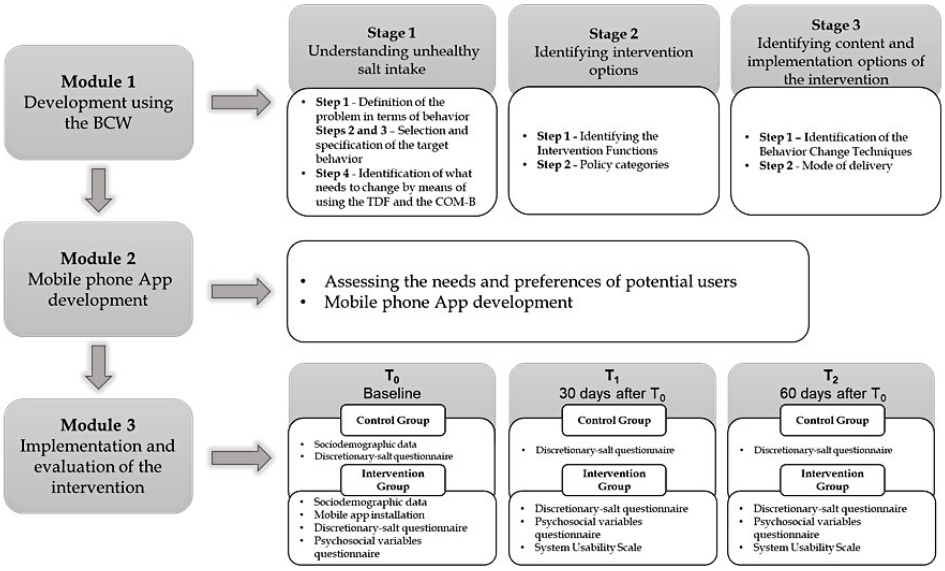
Figure 1. Intervention flow diagram. BCW: Behaviour Change Wheel; COM-B: Capability, Opportunity, Motivation, and Behaviour; TDF: Theoretical Domains Framework.



Module 1: Intervention Development Using the BCW

Module 1 will follow the BCW stages: understanding unhealthy salt intake, identifying intervention options, and identifying the content and implementation options of the intervention [20].

Stage 1: Understanding Unhealthy Salt Intake

Stage 1 includes four steps: (1) definition of the problem in terms of behavior (unhealthy salt intake), (2) selection of the target behavior, (3) specification of the target behavior, and (4) identification of what needs to change using the TDF [33] and the COM-B model.

Steps 1, 2, and 3 will be developed based on previous studies on salt intake among the Brazilian population [8]. In step 4, the TDF and the COM-B model, proposed by Michie and collaborators [20], will be used to identify the behavioral determinants targeted by the intervention. The TDF is an integrative framework developed from a synthesis of psychological theories to provide a comprehensive approach to identifying determinants of behavior [33].

Stage 2: Identifying Intervention Options

The first step is called intervention functions. From these functions, it is possible to assess which of these types of intervention give the best results and may be able to change the behavior. The intervention functions will be selected after identifying TDF and COM-B components. There are nine functions described in the BCW: (1) education, (2) persuasion, (3) incentivization, (4) coercion, (5) training, (6) restriction, (7) environmental restructuring, (8) modeling, and (9) enablement.

After selecting functions, we will apply the Affordability, Practicability, Effectiveness/cost-effectiveness, Acceptability, Side-effects/safety, Equity (APEASE) criteria that is used for designing and evaluating interventions [20]. In our study, the APEASE criteria will be by an experts committee formed by two professionals with experience in theories of behavior change, development, and implementation of the intervention; a research professional with knowledge of the BCW guide; a clinician with experience in patient counseling for salt consumption; and a researcher with knowledge of salt consumption and behavior change techniques (BCTs) [34].

The next step in this stage is the policy categories. This step refers to the inclusion of policy makers in the implementation and execution of an intervention. This step is optional. Due to the difficulty of contacting these policy makers in the research development region, they will not participate in this study.

Stage 3: Identifying Content and Implementation Options of the Intervention

In stage 3, BCTs and the mode of delivery of the intervention are defined.

In step 1, after identifying the intervention functions, the expert committee will determine the most appropriate BCTs based on the intervention functions selected in stage 2. A BCT is an "observable, replicable, and irreducible component of an intervention designed to change behavior and a postulated active ingredient within the intervention" [20]. This step also requires the application of the APEASE criteria to select the BCTs that will be used in the intervention.

The last step corresponds to the mode of delivery. Driven by recent advances in the use of mobile apps and their use as a health promotion tool delivering beneficial results to users in many areas [24-32] and the current scenario of a pandemic caused by SARS-CoV-2, in which it is necessary to socially distance, we will choose to use the mobile phone app as a remote administration mode. For this choice, a delivery taxonomy was consulted [20].

Module 2: Mobile Phone App Development

Module 2 aims to develop the mobile phone app, which requires data collection from participants who are potential users of the app.

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Study Design

To develop the mobile phone app, we will conduct an exploratory study aiming at assessing the needs and preferences of potential users regarding the use of an app for reducing salt.

Potential users will be interviewed to assess their preferences regarding receiving the intervention by the app in an attempt to absorb this empirical reality, which is continually changing, either due to sociocultural diversity, epidemiological dynamics, or technological changes [35].

Participants and Recruitment

Potential users were defined as any person interested in using an app for reducing salt. To be eligible, they should be aged between 20 and 59 years (classification of the Brazilian Institute of Geography [36] for adults, the same age group used in a previous study to choose the target behavior), speak Portuguese, have a mobile phone that supports mobile apps, have skill in handling a cell phone, and consent to participate in the study.

Participants will be recruited from a primary health center in an urban Brazilian town, Artur Nogueira, with 56,247 inhabitants, located in a metropolitan region of Sao Paulo, Brazil [36]. A research assistant will be present in the waiting room of the Basic Health unit of the clinical site to meet patients and offer them the opportunity to participate in the project.

Data Collection

We will conduct semistructured interviews with potential users to explore participants' needs (eg, content) regarding the mobile app, their preferences (eg, features and settings) regarding the mobile app, their current use (if any) of or search for health care apps, and their perception of an app for controlling and monitoring salt addition in meal preparation, as we are proposing.

At the beginning of the interview, each participant will be invited to sign a consent form. The interviews will last 30 to 45 minutes and will be recorded.

Sample Size

The interviews will be conducted with a convenience sample of potential users of the app. According to Guest and collaborators [37], data saturation occurred within the first 12 interviews. Considering this, we planned to collect data from at least 12 participants while ensuring data saturation.

Data Analysis

Audios will be recorded in transcripts and used to extract the information related to factors cited in the Data Collection section and any other relevant information from the interviews. The extracted data will be processed and used to guide the following mobile app development phase.

Procedure for Mobile Phone App Development

The mobile app will be developed based on the previous phases/steps and qualitative exploration. We will follow the guidelines for describing health interventions using mobile phones (the mHealth evidence reporting and assessment checklist [38]). The app will be developed by a software engineer using the Android operating system, and it will be written in JavaScript using the React Native framework. After its elaboration, the mobile app will be evaluated by experts to assess its content and layout.

Module 3: Implementation and Evaluation of the Intervention

Study Design

To evaluate the efficacy of the intervention, we will conduct a randomized controlled study, with three waves of data collection in a 2-month follow-up. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline was followed in the description of this module.

Eligibility Criteria

The study population is adults living in a Brazilian town (described in module 2). To be eligible to participate in this study, they should be aged between 20 and 59 years, have access to a mobile phone that supports the mobile app, speak Portuguese, and consent to participate in the study.

Sample Size and Recruitment

According to the quantitative outcomes, the sample size was calculated considering the objective of comparing the two groups (control group [CG] and intervention group [IG]) in the three periods of time. The methodology of a sample calculation for a repeated-measures ANOVA model was considered to perform this calculation. In this calculation, a significance level of 5%, a test power of 80%, and an effect size of 0.25 were assumed, which, according to Cohen [39], can be considered a medium degree effect size. The first calculation resulted in a sample of 86 participants, but a 20% rate for possible losses was considered, which resulted in a sample of 108 participants (54 participants per group).

Recruitment will occur in primary health care centers of a Brazilian town, with the help of the community health agent of the unit that is linked to each resident of its microarea; the individual will be approached and will invite a resident at home who meets the inclusion criteria to participate in the study. Participants will be selected in a randomized way and will be divided between groups (IG and CG), considering a randomization scheme by blocks of random size. The randomization scheme was generated online [40].

Outcomes

System Usability Scale

The scale was created in 1986 by Brooke [41] to measure the usability of products and services, including hardware, software, mobile devices, websites, and applications. It consists of a 10-item questionnaire with five response options for respondents that range from *strongly agree* to *strongly disagree* [41]. This scale will be used to assess the usability of the app.

Primary Outcome

Discretionary Salt Questionnaire

The discretionary salt questionnaire was validated in a previous study [42,43] on the Brazilian population. Participants will report their regular monthly salt consumption (number of 1 kg packages of salt consumed per month), the number of persons

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who ate meals at home, the age of each person, and the number of meals that each person eats per week at home to correct the salt consumption per person. Children younger than 3 years will not be considered in the calculation, and the meals of children younger than 10 years will be regarded as half meals. The following steps will be used to calculate the salt intake per person: divide the amount of salt (grams) used per month at home by 30 and multiply the quotient by 7 (=grams of weekly salt intake at home), divide this amount of weekly salt intake by the total number of weekly meals (=grams of salt intake/meal), multiply the amount of salt used per meal by the number of meals eaten per week by the participant, and divide the total weekly salt intake of the participant by 7, resulting in the estimated quantity of individual daily added salt. The discretionary salt questionnaire will be used to evaluate the efficacy of the intervention.

Secondary Outcomes

Habit

The first psychosocial variable interferes with the adoption of behavior and will be evaluated through the mean of 10 items [44] assessed on a 5-point scale (1, definitely not, to 5, definitely yes). The guiding phrase for the investigation of the habit will be “Using more than one level teaspoon of salt/day (ie, more than 3 g of salt) during cooking is something that I do...” The items will be “I do it frequently”; “I do it automatically”; “I do it without having to remember to do it consciously”; “If I don’t, it make me feel strange”; “I do it without thinking”; “It would take effort not to do it”; “It is part of my day-to-day”; “I start doing it without realizing that I’m already doing it”; “I would find it difficult not to do”; and “I've been used to doing this for a long time.” The higher the response score, the greater the individual’s favorability of not restricting the amount of salt used during cooking.

Self-Efficacy

The second psychosocial variable will be estimated through the mean of 5 items [44] rated on a 5-point scale (1, completely disagree, 5, completely agree. The higher the score, the greater the perception of self-efficacy to perform the behavior. The statements were “I trust my ability to use 1 level teaspoon of salt a day during cooking,” “I can use 1 level teaspoon of salt a day during cooking,” and “I am sure that I can use 1 level teaspoon of salt a day during cooking.”

Intention

The last psychosocial variable will be estimated through the mean of 6 items [44] rated on a 5-point scale. A high score indicates a high intention to perform the behavior. “I am planning to use 1 level teaspoon of salt a day during cooking” (1, definitely not, 5 definitely yes), “I will try to use 1 level teaspoon of salt a day during cooking” (1, definitely not, 5, definitely yes), “I want to use 1 level teaspoon of salt a day during cooking” (1, I totally disagree, 5, I totally agree). “I hope to use 1 level teaspoon of salt a day during cooking” (1, unlikely, 5, very likely), “How likely are you to use 1 level teaspoon of salt a day during cooking” (1, unlikely, 5, very likely).

Data Collection

Data collection will be performed in three steps (T0, T1, and T2), considering a period of 1 month between them. At the first step (T0), participants will be informed about the research, the study’s relevance, and the need to return to the next meeting, and will sign the informed consent form. Sociodemographic data, the discretionary salt questionnaire, habit, self-efficacy, and intention will be evaluated; the mobile app will be installed on their phone and guidance will be given on using the mobile app. Both groups will be assessed at T1 (1 month after T0) and T2 (1 month after T1) for the discretionary salt questionnaire, habit, self-efficacy, and intention variables. The usability of the mobile app (System Usability Scale) will be evaluated in the intervention group in T1 and T2. At the end of the study, participants in the CG will have the right to have the app installed on their cell phones if they wish and receive instructions on how to use it.

Data Analysis

Qualitative data will be described using frequencies and percentages, and quantitative data as measures of central tendency (mean and median) and dispersion (SD, maximum, and minimum). Correlation tests (Spearman or Pearson coefficient) will test the relation between habit and self-efficacy with intention at T0. Regression analysis using generalized linear models will be used to verify if habit, self-efficacy, and intention at T0 predict the discretionary salt questionnaire at T1 and T2.

To evaluate the efficacy of the intervention, comparisons between groups and times about the discretionary salt questionnaire will be performed using a linear regression model via generalized estimating equations modeling [45].

A significance level of 5% will be adopted. Statistical analyses will be performed using SAS, version 9.4 (SAS Institute).

Ethics and Dissemination

Participants from the data collection of phases 1 of module 2 (user needs assessment) and module 3 (implementation and evaluation of intervention) will provide written informed consent. At this moment, complete and adequate information about the study’s nature, purpose, and possible risks and benefits are given to the participants, confirming that they understand the study requirements according to the local ethics committee that approved the study (Process No. 10937419.0.0000.5404).

Results

Module 1

The development of module 1 has been completed, and the results are described in the following sections.

Recruitment began on October 1, 2021. The trial will complete the recruitment phase in June 2022, and the follow-up phase will end in August 2022. The publication of results is anticipated in 2023.

All steps of stage 1 (understanding unhealthy salt intake) have been entirely detailed.

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Step 1 of Stage 1: Definition of the Problem in Terms of Behavior (Unhealthy Salt Intake)

Due to the high salt consumption evidenced in the previous study in the same town where this project will be developed and considering the health risks and harms resulting from this consumption, there was a need to promote the healthy consumption of this nutrient not only to specific groups but also at the population level.

Step 2 of Stage 1: Selection of the Target Behavior

Perin et al's [8] study also demonstrated that, regarding the sources of salt intake, 24% came from the intrinsic sodium assessed from a 24-hour dietary recall and 7.3% from ultra-processed foods with high sodium content, and the addition of salt in food preparation was the behavior that contributed to 59.1% of the overall salt intake in the population. Thus, reducing salt addition in food preparation was selected as the target behavior of the intervention.

Step 3 of Stage 1: Specification of the Target Behavior

In this step, it is essential to have a specific behavior because, according to Michie and collaborators [20], the clearer the behavior, the better your behavioral analysis. Thus, the salt added to food preparation will be monitored daily at home by the person or by the person helping them cook.

Step 4 of Stage 1: Identification of What Needs to Change (the TDF and COM-B Model)

First, we selected the TDF using the determinants described in Cornélio et al's [46] study. This study applied an extended version of the Theory of Planned Behavior among Brazilian individuals with hypertension and found that self-efficacy and habit were significant determinants of intention, explaining 62% of the variability of intention to add less than 4 g of salt per day in food preparation, and the intention, on the other hand, explained 22% of the variability of this behavior [46]. Thereby, the domains of the TDF were mapped from these three determinants—intention, self-efficacy, and habit—to identify what needed to change. In the second process, we identified the components of the COM-B model from the TDF domains, which could be physical capability, psychological capability, social opportunity, physical opportunity, reflective motivation, and automatic motivation. The findings are described in Table 1.

From this process, we are capable of developing stage 2: identifying intervention options.

Table 1. Linking of the determinant of the TPB[a], the domain of the TDF[b], and the COM-B[c] model based on Michie and collaborators [20].

Determinant of TPB (based on Cornélio et al [46])	Domain of TDF (definition)	Component of COM-B (definition)
Intention	Intentions (a conscious decision to perform a behavior or a resolve to act in a certain way)	Reflective motivation (reflective processes involving plans [self-conscious intentions] and evaluations [beliefs about what is good and bad])
Self-efficacy	Beliefs about capabilities (acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)	Reflective motivation
Habit	Behavioral regulation (anything aimed at managing or changing objectively observed or measured actions)	Psychological capability (knowledge or psychological skills, strength, or stamina to engage in the necessary mental process)

[a]TPB: theory of planned behavior.

[b]TDF: Theoretical Domains Framework.

[c]COM-B: Capability, Opportunity, Motivation, and Behaviour.

Step 1 of Stage 2: Intervention Functions

The intervention functions that met the APEASE criteria were education (increasing knowledge or understanding), persuasion (using communication to induce positive or negative feelings, or to stimulate action), incentivization (creating an expectation of reward), modeling (providing an example for people to aspire to or imitate), enablement (increasing means or reducing barriers to increase capability or opportunity), and training (imparting skills).

Finally, after identifying intervention functions, we achieved stage 3: identifying content and implementation options.

Step 1 of Stage 3: Behavior Change Techniques

The selection process of the techniques resulted in 31 BCTs after removing duplicates. In conclusion, after applying APEASE criteria, we had a list of 16 BCTs: goal setting (behavior), problem solving, goal setting (outcome), action planning, commitment, feedback on behavior, self-monitoring of behavior, social support (unspecified), social support (practical), instruction on how to perform the behavior, information about health consequences, demonstration of the behavior, prompt/cues, behavioral practice/rehearsal, credible source, and adding objects to the environment.

Discussion

Expected Findings

We have described our innovative protocol for an intervention to promote healthy salt intake using the BCW, a guide to designing behavior change interventions. The design of this protocol study has considered the evidence on the efficacy of changing eating behaviors using the BCW [19], the advances in the use of the technology of mobile apps in various areas of health (mainly in eating behaviors [47]), and the dietary

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recommendations to reduce salt intake for the prevention of cardiovascular diseases [48].

To our knowledge, there is only one study available in the literature that evaluated the effect of an app intervention to reduce salt consumption using BCW; however, the study was focused on people with arterial hypertension and not on the general population [49].

We expected that this theory- and evidence-based mobile app intervention would effectively promote healthy salt intake when cooking at home since this behavior is the primary source of consumption of this nutrient among the Brazilian population. We also hope that mobile apps as the mode of delivering the intervention will encourage and facilitate people's self-care and work as an alternative or supportive method in the relationship between health care professionals and patients. Finally, it is expected that the study will inform the potential scalability and transferability of this intervention for achieving a broader public health impact.

The next phase of this research is to complete the development of module 2, the semistructured interviews with the potential users of the mobile app, and the mobile app. After that, we will implement and evaluate the intervention (module 3) using a randomized controlled study.

The results of this study will be published in peer-reviewed scientific journals and presented at scientific events in the thematic area. They will also be communicated to research participants and the public involved in the study through face-to-face presentations at the health services participating in the research.

Strengths and Limitations

Our protocol intervention has some strengths. First, a behavioral analysis guided by the BCW was carried out to gain a theoretical understanding of the specific behavior of salt consumption and the factors that influence it. Besides that, we involve potential users in the development process, which will make it possible to tailor the app to the target audience. This will allow a robust design to be created to increase the efficacy of the intervention. Last, this is the first time that an intervention will be developed to help monitor salt addition in meal preparation for the Brazilian population through a mobile app. A new approach in this area, regarding the recent advances in the field of mobile apps, has been showing its use as a health promotion tool with beneficial results in other areas, including depression, diabetes, medication adherence, respiratory diseases, and physical activities [24,25,27-32].

This study also has limitations. First, we did not consider the political levers in developing our intervention because we did not have access to them. Second, the choice of the intervention delivery mode using a mobile app was based on the evidence of success in previous studies.

Conclusions

This protocol details a theory- and evidence-based intervention to promote healthy salt intake behavior among Brazilian adults. The steps of the BCW were successfully applied through a systematic process to identify the behavioral determinants and select the intervention options and the BCTs. A mobile phone app was chosen as the mode of intervention delivery.

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Data Availability

Due to its proprietary nature and ethical concerns, supporting data cannot be publicly available. The supporting data of this study will be stored in the Research Data Repository of the University of Campinas [50]. Data may also be available after publication of the study results and upon reasonable request to the corresponding author.

Authors' Contributions

MSP and MEC conceived and developed the study. TSJ, TTA, MCBJG, and RCMR contributed to the methodological design. All authors contributed to the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APEASE: Affordability, Practicability, Effectiveness/cost-effectiveness, Acceptability, Side-effects/safety, Equity
BCT: behavior change technique
BCW: Behaviour Change Wheel
CG: control group
COM-B: Capability, Opportunity, Motivation, and Behaviour
IG: intervention group
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TDF: Theoretical Domains Framework

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Protocol

A Case Management Program at Home to Reduce Fall Risk in Older Adults (the MAGIC Study): Protocol for a Single-Blind Randomized Controlled Trial

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Abstract

Background: Individual case management programs may be particularly effective in reducing fall risk as they can better identify barriers and facilitators to health recommendations.

Objective: This paper describes the protocol for a single-blind, parallel-group randomized controlled trial that aims to investigate the effectiveness and cost-effectiveness of a home-based multifactorial program targeting fall risk factors among people aged 60 years and over who have fallen at least twice in the past 12 months (the MAGIC trial).

Methods: Older people with a history of at least 2 falls in the last year will be divided into 2 groups. The intervention group will receive case management at home for reducing the risk of falls, including a multidimensional assessment, explanation of fall risk factors, and elaboration and monitoring of an individualized intervention plan based on the identified fall risk factors, personal preferences, and available resources. The control group will be monitored once a month. Assessments (clinical data, fall risk awareness, physical and mental factors, safety at home, feet and shoes, and risk and rate of falls) will be carried out at baseline, after 16 weeks of the intervention, and at the posttrial 6-week and 1-year follow-up. After 16 weeks of the intervention, satisfaction and adherence to the intervention will also be assessed. Economic health will be evaluated for the period up to the posttrial 1-year follow-up.

Results: Data collection started in April 2021, and we expected to end recruitment in December 2021. This case management program will address multifactorial assessments using validated tools and the implementation of individualized intervention plans focused on reducing fall risk factors.

Conclusions: This trial may provide reliable and valuable information about the effectiveness of case management for increasing fall risk awareness and reducing fall risk in older people.

Trial Registration: Brazilian Clinical Trials Registry (ReBec) RBR-3t85fd; https://ensaiosclinicos.gov.br/rg/RBR-3t85fd

International Registered Report Identifier (IRRID): DERR1-10.2196/34796

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KEYWORDS

accidental falls; risk management; aged; fall prevention

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Introduction

One of the challenges of aging is the social and health costs arising from falls—a major cause of disability and death among older adults. The economic impact of falls affects family, community, and society [1]. Between 2011 and 2015, 43,400 fall-related deaths and 240,000 fall-related hospitalizations occurred among older Brazilian people [2,3]. In general, falls result from multiple risk factors. Reducing risk factors for falls through an intervention based on case management may be particularly beneficial for preventing falls in older adults [4].

Case management interventions allow professionals to develop and implement individualized plans for preventing falls and consequences [5,6]. The case manager ensures follow-up of the plans in accordance with the older adult and family, identifies barriers to their implementation, and motivates the older person to adhere to the program [5]. Moreover, in a cross-sectional study, the preference of the older people in relation to different formats of programs for falls was verified. Older people with a greater concern about falls and disposition to participate in some program prefer participating in personalized and home-delivered programs based on their individual characteristics, difficulties, and limitations when compared to programs conducted in groups [7].

A Cochrane systematic review has shown that integrated multifactorial assessments and individualized interventions are effective in reducing the rate of falls [8,9]. Although these studies provide good evidence for fall prevention, there is a lack of trials investigating multifactorial interventions based on individualized fall risk factors, such as case management interventions. In addition, there is a need for studies that assess acceptance and adherence to multifactorial programs for reducing fall risk [8,9], taking into consideration monthly falls monitoring and the presence of managers within the work team.

There is a scarcity of randomized controlled trials involving case management for reducing fall risk. Individual case management programs may be particularly effective in reducing fall risk, as they can better identify barriers and facilitators to health recommendations. This model of care can offer physical, psychological, and social assistance that goes beyond the traditional models of health care for fallers.

Considering the aforementioned discourse, we designed a home-based multifactorial program targeting fall risk factors among people aged 60 years and over who have had a fall at least twice in the past 12 months. The proposed intervention program consists of individualized management of fall risk factors. This study protocol details the MAGIC trial, outlining the design of the study, describing their objectives, methodology, and overall organization of the research to be carried out.

Methods

Trial Design and Setting

A parallel-group, single-blind randomized controlled trial with a block randomized design (allocation ratio 1:1) will be carried out. The trial will be performed in São Carlos, Brazil, and surrounding cities, where 16% of the local population is aged 60 years and over (Multimedia Appendix 1).

Study Population

Participants will be recruited through health and social services, open registration via telephone, and a volunteer database of the research group. The study will be promoted via leaflets, posters, social networks, and local radio and television.

Eligible people will be community older adults aged 60 years and over, be residents of São Carlos and surrounding regions, be noninstitutionalized, and have a history of falls in the last year. Inclusion criteria will be having a history of at least 2 falls in the last year, being willing to participate in the interventions and assessments, being able to walk with or without walking devices, and being available to be contacted by telephone. Exclusion criteria will be having severe and uncorrected visual or auditory disorders that affect communication during assessment and intervention, having active inflammatory and neurological diseases that severely interfere with balance performance (advanced Parkinson disease—stage 5 on the modified Hoehn and Yahr Scale and not being regular users of antiparkinsonian medications, multiple sclerosis, Huntington disease, dementia, uncontrolled vestibulopathy, epilepsy, traumatic brain injury, and severe motor sequelae of stroke), or participating in regular and systematic physical activity for a total duration of ≥150 minutes per week.

Randomization and Blinding

A randomization sequence will be created by an external researcher with Random Allocation software (Windows Inc) with a 1:1 allocation using random block sizes. The allocation sequence will be concealed from the external researcher enrolling participants in sequentially numbered, opaque, sealed, and stapled envelopes. Corresponding envelopes will be opened after assessment at baseline by another independent researcher, who will be responsible for advising participants of their allocation by telephone.

Assessors will be blinded to randomization until the end of the study. Owing to the nature of the trial, the researchers responsible for the intervention and the volunteers will not be blinded to randomization.

Intervention

The intervention protocol follows all protective measures recommended in response to the COVID-19 pandemic. The intervention group (IG) will receive a remote case management intervention at home over 16 weeks, once a week by video or a telephone call. Volunteers who have regular access to the internet and a smartphone or computer made weekly calls through video, while those with limited access were contacted by telephone. The control group (CG) will be followed by monthly telephone calls. The intervention will be carried out by 2 trained researchers, scheduled to start in April 2021.

Case managers are responsible for monitoring the volunteers and their families among the intervention proposals to reduce each of the modifiable fall risk factors in the initial assessment. These managers are trained gerontologists who, in addition to having pre-established proposals, hold discussions fortnightly

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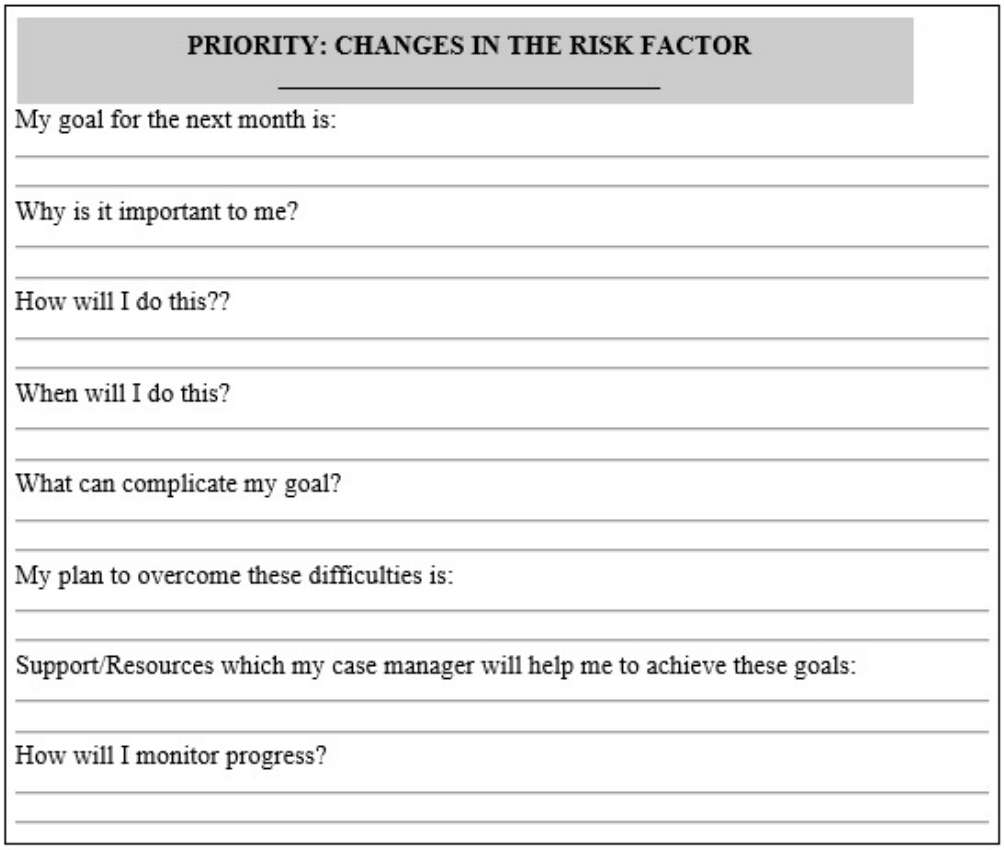
to discuss cases with the entire intervention team, ensuring the best guidelines for volunteers and the alignment of manager´s actions. According to the Brazilian Society of Geriatrics and Gerontology, gerontologists have training in different areas of knowledge (psychology, social work, nutrition, occupational therapy, law, etc), so they are able to plan, coordinate, and evaluate health actions related to older people; in addition, they can deliver biopsychosocial care.

In the first week, for the IG, a multidimensional fall risk assessment will be applied (Multimedia Appendix 2) [10]. In the second session, the case managers will discuss and explain the identified fall risk factors to the participant and his or her caregiver. An individualized intervention proposal based on the identified fall risk factors will be devised considering participants' preferences and priorities. All IG volunteers will be encouraged to carry out a home-based multicomponent physical exercise program delivered through recorded videos, guidelines, or printed booklets. The exercise program will consist of trunk and lower limb muscle–strengthening, aerobic conditioning, gait, and balance and stretching exercises at moderate intensity, performed twice per week (30-60 minutes per session) with individualized progression every 2 weeks. The exercise program is based on a previous protocol [11] and in line with the recommendations of the American College of Sports Medicine [12], having been adapted for community older adults in the primary health context. Volunteers who agree to participate in the intervention with physical exercises will have to present a medical certificate before carrying out the activities.

In the third session, an individualized intervention plan will be developed with the volunteer and his or her caregiver, taking into consideration priority of the identified fall risk factors, personal preferences, and available resources. During the 16 weeks of the intervention, the case manager, the volunteer, and his or her caregiver will implement the previously agreed plan, which includes recommendations and guidelines, dialogue with suppliers, and referrals for specialized programs. If needed, the plan will be monitored and reviewed by weekly telephone or video calls. During the monitoring, the manager will check if the participant has any difficulty in carrying out the requested activities and will identify what assistance should be offered and what possible changes are needed [5,6]. All cases will be discussed with case managers and 2 specialists in the field. All recommendations, in case of resistance, will be facilitated for better adhesion based on support materials and personal preferences. If there is still refusal, awareness and maintenance of daily risk behaviors will be prioritized so that no accidents happen.

After 16 weeks of the intervention, all volunteers will undergo 6 weeks of detraining (follow-up) in which they will be asked to carry out their usual activities. At the end of the study, all volunteers will receive a booklet of recommendations for reducing fall risk (Figure 1). If positive results are identified, older adults of the CG will be invited to undertake the intervention.

Figure 1. Recommendations for reducing fall risk.



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Outcome Measures

Overview

Assessments will be conducted at participants' homes at baseline, after 16 weeks of the intervention, and at 6 weeks and 1 year post trial completion. The volunteers will be instructed to wear comfortable clothing, closed shoes, not to perform vigorous exercises the day before the assessment, and to wear hearing or visual aids if needed.

Baseline assessments include sociodemographic measures (age, sex, race, marital status, years of schooling, living alone, and income) and general health (BMI; medication use; morbidities; foot problems including dryness of skin, calluses, fissures, open ulcers, and deformities; history of falls, hospitalizations, level of physical activity measured with the Modified Baecke Questionnaire for the Elderly; general health assessed with the Self-Rated Health questionnaire; functional activities evaluated with the Lawton-Brody Scale; and risk of fracture measured with the Fracture Risk Assessment Tool—FRAX).

Primary and secondary outcomes will be reassessed after 16 weeks of the intervention and at the posttrial 6-week follow-up. In addition, after 16 weeks of the intervention, satisfaction and adherence to the intervention will also be assessed among the IG participants. Prospective falls will be collected from baseline to 1-year follow-up. The economic health assessment will be carried out for the period up to the posttrial 1-year follow-up.

Primary Outcome Measure

The primary outcome is fall risk awareness and behavior change, which will be assessed using the Falls Risk Awareness Questionnaire (Brazil). A score range from 0 to 32 points and higher scores indicate greater knowledge about fall risk factors [13].

Secondary Outcome Measures

Secondary outcomes are falls, physical function (muscle strength of lower limbs, balance, and mobility), mental functions (cognition, depressive symptoms, and fear of falling), fall risk, safety at home, feet and footwear, satisfaction with and adherence to the intervention, and health care costs.

Prospective falls will be collected from baseline to 1-year follow-up using falls calendars and monthly telephone calls. Muscular strength of hip, knee, and ankle joints will be evaluated using the Lafayette dynamometer. In addition, muscle strength, mobility, and balance will be assessed with the Brazilian version of the Short Physical Performance Battery (SPPB). The SPPB consists of 3 tests: Balance Test, Gait Speed Test, and Chair Stand Test [14]. The scores range from 0 to 4, and the total ranges from 0 to 12 points, with higher scores indicating better lower limb function [14]. Balance will also be assessed with the MiniBest test, which has a total score of 28 points, and higher scores indicate better balance [15].

Cognition will be assessed with Addenbrooke's Cognitive Examination-Revised screening battery, which has a maximum score of 100 points, with a score of ≤78 points indicating cognitive impairment [16]. Digit Span Forward will be used to assess attention and immediate memory deficits (indicated by scores less than 6 points) and Digit Span Backward for measuring attention and working memory deficits (indicated by scores less than 4 points) [17]. To assess depressive symptoms, the Geriatric Depression Scale will be used. Higher scores on this 15-point scale indicate a greater risk of depressive symptoms. The Falls Efficacy Scale-International will be used to assess fear of falling [18]. A total score of ≥23 points is associated with occasional falls, and a score of >31 is associated with recurrent falls [18].

Fall risk will be assessed with the Falls Risk Assessment Tool. The score varies from 0 to 5 points, with a score of 3 or more points indicating a high risk of falls [19]. Regarding home safety, the Home Falls and Accidents Screening Tool will be used. The maximum score is 25 points, and higher scores are indicative of a greater risk of falls and home accidents [20].

For feet and footwear, the Manchester Foot Pain and Disability Index will be used. A total score of ≥2 points indicate disability associated with foot pain [21]. The tactile sensitivity of feet will be assessed using the 10-gram Semmes-Weinstein monofilament on hallux, the second and fifth metatarsals, 3 points of the forefoot, and 1 point of the midfoot and heel. Flexibility (dorsiflexion and plantar flexion) will be assessed by a goniometer. The characteristics of footwear that the volunteers usually wear at home and when they get up at night will be documented.

After 16 weeks, adherence to the case management program will be assessed by diary entries. Adherence of ≥70% to recommendations will be considered satisfactory [22,23]. In addition, questionnaires will be used to assess reasons for adhering or not adhering to treatment. The prevalence of each recommendation offered in the case management and adherence to these recommendations will also be assessed, using a 3-point scale (total adherence, partial adherence, and nonadherence) [24]. To assess satisfaction of the intervention after 16 weeks, a questionnaire based on the Short Assessment of Patient Satisfaction will be used [25]. A question will be added about the satisfaction of overall care ("How would you rate the health care you received in the past 16 weeks?"), with scores ranging from 0=worst possible care to 10=best possible care.

For economic analyses, the incremental cost effectiveness ratio will be calculated as the difference between the total cost of the IG and that of the CG. Furthermore, the use of health services will be analyzed. The EuroQol-5D is used in many cost-effectiveness studies, which allows the comparison of effects generated by interventions for any disease. Its score ranges from 1 to 3 for each item, allowing 243 different health profiles [26,27].

Power and Sample Size

For the primary outcome (fall risk awareness), the sample size was calculated using the G*Power 3.1 software, based on type of study design (2-way ANOVA), type I error of 5%, statistical power of 80%, moderate effect size (0.20), and number of groups (n=2). This revealed that a total sample size of 42 is required. Allowing for 20% dropout, we will recruit a sample size of 60 people.

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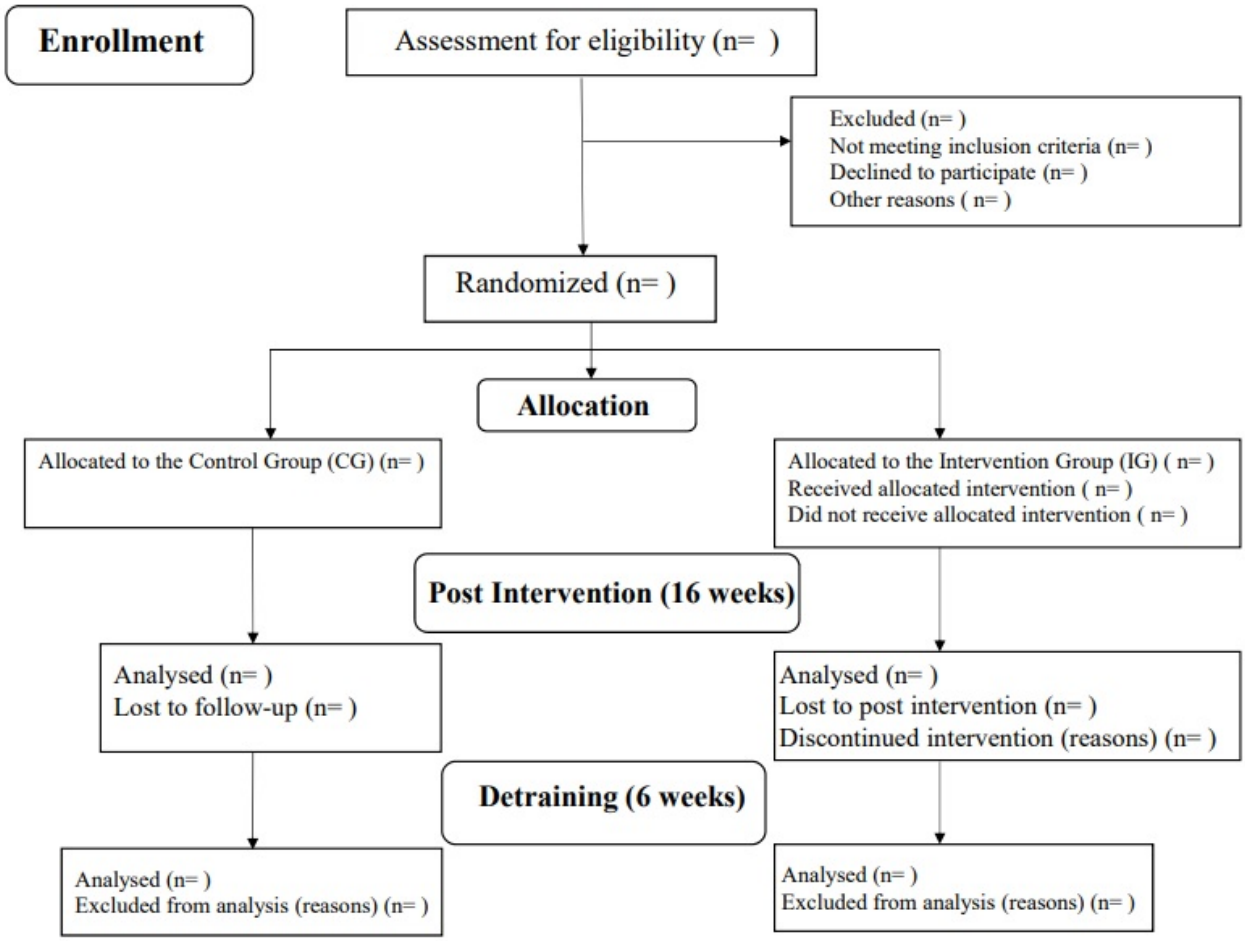
Statistical Analysis

For statistical analysis, a significance level of 5% will be adopted, and SPSS (version 22.0; IBM Corp) will be used. The analysis will be performed by intention to treat. The Kolmogorov-Smirnov normality test will be applied for all continuous variables to verify data distribution. To compare groups with regard to clinical and sociodemographic characteristics, the chi-square association test and the independent samples *t* test will be used. To test the interaction between groups and assessments, a 2-way, repeated measures ANOVA will be used. If an interaction is identified, simple main effects analyses will be performed, with adjustment for multiple comparisons (Bonferroni correction). To verify which factors influence adherence to the intervention (frequency of ≥70%), a univariate logistic regression analysis will be used. To check which factors influence satisfaction with the intervention, a simple linear regression analysis will be applied.

Ethics Approval, Monitoring, and Dissemination

The trial was approved by the research ethics committee of Federal University of São Carlos (CAAE: 34350620.7.0000.5504). Regarding monitoring, the researchers will be responsible for making decisions related to any need for changes to the assessment and intervention in the presence of adverse effects during the research. Data will be used only for scientific purposes with the utmost confidentiality and will not be transferred to any person or entity outside of the research team. Participant data will not be released. There will be no personal expenses or any benefits for the participant. If there is any damage resulting from the research, compensation will be guaranteed. The participant will have the right to withdraw from the study at any time, if they will, without prejudice to them. If necessary, at all stages of the study, participants will have access to the researchers for further enquiries (Figure 2).

Figure 2. CONSORT flowchart 2010.



Results

This is a protocol for a single-blind, parallel-group randomized controlled trial funded in July 2021 by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; grant code 001), Approved by Registro Brasileiro de Ensaios Clínicos (ReBEC; RBR-3t85fd), with data collection started in April 2021 and expected to end in December 2021. The number of recruited volunteers as of submission of this manuscript is 52.

Discussion

The MAGIC trial aims to provide rigorous direct evidence about the effectiveness and cost-effectiveness of a home-based multifactorial program targeting fall risk factors among people

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aged 60 years and over who have fallen at least twice in the past 12 months. We hypothesize that the IG presents better awareness of fall risk and positive behavior change in reducing fall risk factors identified by case management, thus decreasing new episodes of falls with an increasing volume of physical activity after the 16-week intervention compared to the CG; in addition, we expect that community older people in the IG will continue to show the positive results obtained after the 6-week follow-up compared to the CG.

The strengths of this MAGIC study are the follow-up of individualized case management that offers greater attention to the older people in the home environment and includes the family or caregiver in the action plan for behavior change in order to reduce the identified risk factors for falls. In addition, the program offers monitoring of the older people by a physical therapist to implement a protocol for safe physical activities at home.

The researchers may encounter some limitations during this randomized controlled trial, including difficulties in recruitment, restrictions on home visits owing to the COVID-19 pandemic, and poor compliance with the recommendations proposed by the case managers. If needed, potential solutions will be the use of remote assessments by video and telephone calls and the inclusion of additional recruitment sites.

The findings of this study may provide reliable and valuable information about the effectiveness of case management for increasing fall risk awareness and reducing fall risk in older people. This study protocol detailed the design and methodology of the research to support the transparency of results. This may also assist the design of future studies.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Table 1: Description of Study Period.
[DOCX File , 16 KB - resprot_v11i6e34796_app1.docx]

Multimedia Appendix 2
Table 2. Intervention plan sheet, including modified STRIDE Intervention risk factors and priorities [12].
[DOCX File , 18 KB - resprot_v11i6e34796_app2.docx]

Multimedia Appendix 3
Peer Review Reports from the Auxílio à Pesquisa Regular - Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), The São Paulo Research Foundation (Brazil).
[PDF File (Adobe PDF File), 1148 KB - resprot_v11i6e34796_app3.pdf]

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Abbreviations

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CG: control group
CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico
FAPESP: Fundação de Amparo à Pesquisa do Estado de São Paulo
IG: intervention group
ReBEC: Registro Brasileiro de Ensaios Clínicos
SPPB: Short Physical Performance Battery

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Protocol

Promoting Physical Activity Among University Students During the COVID-19 Pandemic: Protocol for a Randomized Controlled Trial

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Abstract

Background: Since the beginning of the COVID-19 pandemic, sanitary context and e-learning have greatly modified student lifestyles and led to deteriorations in their mental health. An increase in anxiety and depressive symptoms and sedentary behaviors, reduction in physical activity, and a stronger tendency to move toward unhealthy diet have been demonstrated. This finding highlights the need for innovative interventions to promote healthy lifestyle among students.

Objective: This research protocol aims to evaluate the effects of an intervention program on the lifestyle and psychological state of students.

Methods: Students from University of Nîmes were recruited and randomly assigned to 1 of 2 following conditions: an intervention group and a control group. Participants in the intervention group were engaged in an 8-week physical activity program. Prior to the start of the program, design-based innovative workshops were conducted with participants to ensure that the program was co-constructed by the users and met their specific needs. Students in the control group did not receive any intervention. For each group, measures of physical activity, sedentary time, anthropometric data, sleep, physical condition, and psychological variables (eg, anxiety, depression, motivation, body appreciation, perceived control, well-being) were conducted at baseline and 9 weeks later.

Results: A total of 110 participants were initially included. Reporting of the results is projected for the spring of 2022.

Conclusions: It is anticipated that this innovative intervention co-constructed by pairs will promote a healthier lifestyle and psychological health in students. There is every reason to believe that a mobilized co-construction approach is a promising strategy to limit unhealthy habits and promote physical activity while increasing motivation. The development and evaluation of interventions to address the specific needs of university students is essential and could be transferred to other vulnerable populations such as people with chronic diseases or older people.

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International Registered Report Identifier (IRRID): DERR1-10.2196/36429

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KEYWORDS

physical activity; psychological factors; university student; COVID-19

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Introduction

Background

The COVID-19 pandemic is one of the most profound crises of our time. The socioeconomic impact of the crisis has been devastating, as have the repercussions on the well-being of the populations. In France, the general population has undergone 3 confinements (March 17 to May 10, 2020; October 30 to December 15, 2020; and April 3 to May 3, 2021). Since the beginning of the COVID-19 pandemic, university students have not been spared and have faced many challenges. They have had to adapt to many constraints (eg, reduced number of students in classrooms, wearing masks) and significant changes in teaching (eg, distance and/or hybrid education). It was only at the beginning of the academic year September 2021 that the university has returned to an almost normal functioning (ie, almost all face-to-face teaching with the full complement of students but with the wearing of masks maintained). However, the re-increase in COVID-19–positive cases since November 2021 suggests that students' conditions could be affected again in the coming weeks.

Students are among the population for whom the pandemic has had the most negative impact on their lives [1]. Even before the pandemic, university students were identified as a population with unhealthy lifestyles and habits, notably reflecting unhealthy diet [2], poorer mental health than their nonstudent peers [3], high levels of sedentary behavior (SB), and low levels of physical activity (PA) [4,5]. During the pandemic, and more specifically during the first lockdown, this unprecedented sanitary crisis clearly had a massive impact on the lifestyle and mental health of university students around the world [6], and French students have not been spared [7,8]. Studies conducted during the first lockdown have shown an increase in unhealthy lifestyles as evidenced by their high levels of SB [9,10] and their low levels of PA [8,11,12]. In the same vein, high levels of anxiety and depressive symptoms among university students were reported during the first lockdown in different countries around the world [13-15], just like in France [7,16]. The few longitudinal studies conducted during the following lockdown attest to a maintenance of the difficulties or even a worsening of them [7,17-19]. The authors suggest that adverse health effects will persist long after the COVID-19 pandemic and note the need for long-term interventions [20,21]. In this perspective, interventions in PA appear particularly appropriate. Indeed, even if this was already known before, this pandemic reinforces the protective role of PA on physical and mental health [22,23]. This has led many governments and sports science societies to provided recommendations on PA and SB during the COVID-19 pandemic, particularly to prevent the occurrence or worsening of chronic diseases [24-26]. Despite these recommendations, very few interventional studies to promote PA and reduce SB have been conducted.

As noted above, students were particularly affected by the COVID-19 pandemic and were already a vulnerable population before the pandemic. Therefore, they are a prime target for this type of intervention. It is essential to conduct interventional studies with university students to accompany them in this (even more) complex period and prevent the deterioration of student health in a COVID-19 context. However, getting students to engage in health promotion interventions is often difficult. Indeed, many students do not seek help [27] due to barriers such as stigma or lack of information [28]. Therefore, it is essential to go beyond traditional interventions and provide more innovative and accessible interventions to achieve real student engagement. This is especially important because if we don't implement interventions to which students adhere, we may see lasting alterations in their lifestyles and, more broadly, in their health.

Study and Protocol Aim

This study is conducted in order to reduce or prevent deterioration of the health of university students related to the COVID-19 pandemic. Specific objectives of this study are to measure the impact of this innovative program on physical capacities, lifestyle, and psychological issues. We hypothesized that our program can have beneficial effects on university students' physical capacities, improve their motivation to engage in PA, reduce their SB, and improve psychological issues.

To this end, students from the University of Nîmes have benefited from an innovative intervention aimed to improve their motivation to engage in PA and reduce sedentary lifestyle. First, co-construction workshops were conducted with participants to define the modalities of the expected PA program. Once the program was co-constructed between pairs, they participated in the new program. This paper aims to describe the protocol of this study.

Methods

Context

The COVID-19 pandemic has increased unhealthy lifestyles of students that were already prevalent before the pandemic. Their difficulty in engaging in PA programs justifies the need for innovative interventions to address their specific needs. First, in February 2021, our team conducted a pre-study to evaluate the effects of a PA program conducted by students for other students to promote PA and social interactions. However, the restricted access of students in the university to minimize COVID-19 propagation did not permit us to obtain a large sample size. In order to conduct a larger study, we have developed a research project called Cov'Etu. It was submitted in April 2021 in the framework of a call for proposals about COVID-19 (AAP Résilience–COVID-19) managed by the French research agency (Agence Nationale de la Recherche) and approval was granted. The Cov'Etu project includes 2 axes of research. The first axis aims to identify the role of individual factors (eg, symptoms of COVID-19, health concerns) on students' psychological health (eg, anxiety and well-being) and lifestyle (eg, SB, alcohol) over the course of the pandemic. The second axis of research evaluates the health effects of 2 programs. Our research protocol refers to one of these programs as it is called in French, UNIMES EN FORME.

Population and Study Design

This study was conducted among students from the University of Nîmes. Nîmes is a midsize city in the southern part of France

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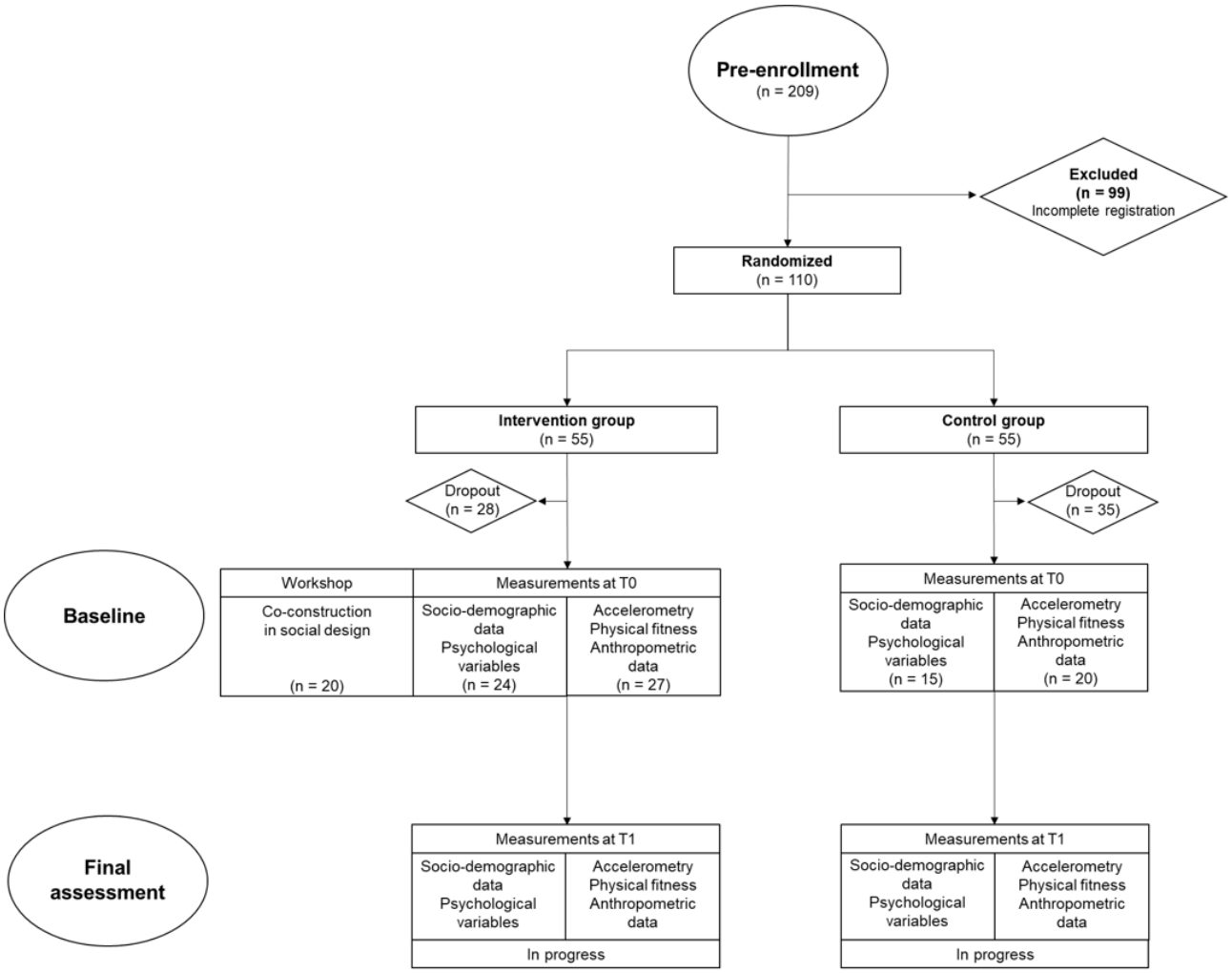
that has 4 university campuses. In academic year 2021/2022, 5201 students were registered at this university, of which approximately 4000 are on the main university campus named Vauban. This campus site is located in the heart of the city and includes the administrative and sports infrastructures in addition to auditoriums and classrooms. The inclusion criteria were as follows: (1) have their courses mainly on the Vauban campus (this campus site includes students in the bachelor and master levels mainly in psychology, law, and art/design); (2) be aged 18 years or older; (3) have never benefited from any intervention in the field of PA; and (4) sign a consent form to participate in the study. Three principal exclusion criteria were established: (1) with physical diseases that prevent PA practice (eg, cardiovascular disease), (2) in sport sciences, and (3) not signing the consent form to participate in the study.

The study was designed as a randomized controlled trial with 2 groups. The first was the intervention group including participants who have benefited from a co-construction workshop and an innovative PA program based on their workshop. The second was the control group, which included students who had not benefited from any intervention. In total, 110 university students agreed to participate in the program, with 55 students in the intervention group and 55 in control group and randomization by age and gender. The number of students enrolled and chronological stages of the study are reported in the flowchart (Figure 1).

Figure 1. Flowchart of the study.



Ethics Approval

An ethics review was not applicable for this study because all personal data was collected anonymously and the program evaluated has been integrated into the University Service of Physical and Sports Activities at the Université de Nîmes (governed by decree No. 2018-792 of September 13, 2018 relating to university common services) established by the Ministry of Higher Education, Research and Innovation.

The recruitment of the students was done with the approval of the Université de Nîmes health service to ensure good physical condition of the participants and was available to students throughout the program. Participants agreed to participate in this study after reading a consent form. They were informed that their personal data would remain anonymous, their participation was voluntary, and they could withdraw at any time. The study was conducted in accordance with the Declaration of Helsinki.

Procedure

First, a workshop with the participants of the intervention group was realized to co-construct the PA program in order to remove barriers to the practice of PA. The aim of co-construction with

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users was to obtain better adherence to the program by being based on needs of the users themselves and not imposed by others. Second, the co-constructed PA program was conducted with them for 8 weeks with sessions twice per week.

For both groups, during September/October 2021, baseline assessments (T0) were conducted: measurements of PA and sedentary time (ST; with an accelerometer), physical fitness and body composition (face-to-face measurement), and psychological variables (online assessment). The final assessments (T1) were conducted in December 2021.

Variables Measured

Physical Activity and Sedentary Time

The levels of PA and ST were measured in baseline and final assessments with the tri-axis accelerometers in the GT3X activity monitor (ActiGraph LLC) as a valid objective measure [29,30]. Participants wore the accelerometer on the right side of the hip, adjusted with an elastic belt, during 7 consecutive whole days including day and night. They removed it only during the shower and aquatic activities. ActiLife Lite Pro software (version 6.13.4, ActiGraph LLC) was used to extract PA and ST values. Data were downloaded in 10-second epoch to measure PA and ST.

Data collection was performed over 5 weekdays and 2 weekend days, and the first day of measure was excluded from the analysis. Corresponding to the French cultural schedule, PA and ST were analyzed for the whole day (6:00 AM to 11:59 PM) for weekdays and weekend days. Non–wear time during this period was excluded from the analysis, and the Choi algorithm was used to define non–wear time during the whole day as it is more adapted for the adult population [31]. This algorithm identified as non–wear time an activity of 0 counts over a period of at least 90 minutes, allowing a quota of time 1 to 2 minutes of no activity counts detected both in the 30 minutes before and after this interval. A 10-second epoch was then used to detect more accurately the changes in PA intensities [32,33]. To establish the different intensity categories (with step count and time spent in each category), the Freedson algorithm was used [34]: ST 0-99 counts per minute, light PA 100-1951 counts per minute, moderate PA 1952-5724 counts per minute, vigorous PA 5725-9498 counts per minute, very vigorous 9499 or more counts per minute.

According to the optimal methodological approach for accelerometry, 2 conditions had to be met concerning the minimum wear time required to be considered as a valid measure: (1) participants had to wear the accelerometer at least 80% of the time between 6:00 AM and 11:59 PM and (2) 70% of participants had to wear the monitor during this period [29]. To estimate usual PA and ST levels, wear-time had to be sufficient for a least 3 weekdays and 1 weekend to be considered valid [30]. All the data were processed with the ActiLife software. We focused on 7 variables for the whole day in weekdays and weekend days: number of sedentary breaks occurring in the day, ST (minutes), light PA (minutes), moderate PA (minutes), moderate to vigorous PA (minutes), vigorous PA (minutes), very vigorous PA (minutes), and number of steps.

Sleep

The ActiGraph GT3X activity monitor was used to measure sleep patterns. These measurements were conducted over the same period of time as the PA and ST. Participants were asked to wear the accelerometer on the right side of the hip even during the night. Sleep data were validated and analyzed if the total sleep period time was above 160 minutes per night with an estimated 90% wear time [35,36]. Data were analyzed only for participants having 3 nights validated on weekdays and 1 night validated on weekend days [35]. Raw data were downloaded in 10-second epochs using the ActiLife software and reintegrated to 60 seconds to perform sleep pattern analysis. We then applied the Tudor-Locke algorithm developed automatically by the ActiLife software and validated [37]. In contrast to previous algorithms, The Tudor-Locke algorithm provides a more accurate estimation of sleep duration and captures total sleep time from sleep onset to sleep offset, including the number and time of awakening. We focused on 7 variables for weekdays and weekend nights: total sleep time (time scored as sleep during the sleep period of the night, expressed in minutes), wake after sleep onset (time scored as wake occurring after sleep onset and before sleep offset, expressed in minutes), and sleep efficiency (total sleep time divided by sleep period time, expressed in percentages).

Physical Fitness

Participants in the control and intervention groups performed tests for physical fitness at preintervention (T0) and postintervention (T1). During 15 consecutive days, 180 sessions of 1-hour duration from 9:00 AM to 6:00 PM were dedicated to these measurements. The first 8 days were allocated to test the participants in the intervention group, and the last 7 days were reserved for the participants in the control group. At T1 (ie, after the intervention program), this organization was switched in order to have 8 weeks between the first and second assessments for the participants in each group. Assessments were conducted individually in a quiet university classroom. Two research engineers conducted the measurements in absolute confidentiality. Upon arrival, participant blood pressure, heart rate, and body composition were measured. Physical fitness tests were performed in order to measure balance, flexibility, lower limb strength, and cardiovascular fitness. The organization and rank of the tests was similar for the 2 groups of participants.

Balance

In the unipedal stance test, participants stood barefoot and held the position in a single-legged balance for 1 minute [38]. The time spent in the unipedal position was recorded in seconds. If the participant did not achieve the full minute in the balance position, the precise time spent in this posture was reported; if participant achieved it completely, the maximum time of 60 seconds was reported.

Flexibility

Participants completed a traditional sit-and-reach test to measure lower back and hamstring flexibility [39]. In a seated position with legs extended, participants reached as far as possible along a measured line with hands on top of each other or side by side.

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Measurement was reported 3 times with performance recorded in centimeters.

Lower Limb Strength

For assessment of muscular strength, participants were seated on a dynamometric chair (LegControl V2.0, Mtraining) with a 90° hip angle, 90° knee angle, and straps fixing the hip and thighs. The axis of the dynamometer was aligned with the anatomical knee axis. A lever, connected to the calibrated load cell, was positioned against the right leg 5 cm proximally to the medial malleolus. After a familiarization consisting of 5 submaximal isometric contractions, participants performed 3 maximal voluntary contractions of 3 seconds, separated by 1 minute each. Specifically, they were asked to contract the knee extensors as hard as they could for 3 seconds. Participants were given strong vocal encouragement during each maximal voluntary contraction. The maximum value was used for statistical analyses.

Cardiovascular Fitness

Participants completed a YMCA 3-minute step test [40]. Participants stepped up and down 24 steps per minute without stopping and with a frequency indicated by a metronome set to 96 beats per minute. Once the test completed, participants sat down immediately. After 5 seconds, the recovery heart rate was monitored 5 seconds during 1 minute and this last heart rate was reported to assess cardiovascular fitness [40,41]. The score was then reported on age-adjusted standards based on guidelines for gender, in 1 of 7 categories (very poor, poor, below average, average, above average, good, excellent).

Body Composition

Baseline standing height (cm) was recorded to the nearest 0.1 cm using a portable stadiometer (Leicester HR001, Tanita). Body weight (kg) was measured using a calibrated scale (780 MA-S, Tanita) to the nearest 0.1 kg. BMI (kg/m^2) was calculated using height and body weight measurements. Variables were assessed through a bioelectrical impedance analysis method using a 780 MA-S (Tanita) body composition analyzer/scale such as body fat, body muscle, body water expressed in mass (kg) and percentage (%), and visceral fat rating expressed on a scale from 1 to 60. A score from 1 to 12 is considered healthy and a score from 13 to 60 excessive.

Questionnaire

Measurements were made before and after the intervention using an online questionnaire via an online survey designed with Qualtrics software (Qualtrics). The questionnaire can be found in Multimedia Appendix 1.

Sociodemographic and Situational Factors

Sociodemographic factors such as age, gender, level of education, and field and year of study were collected. In addition, situational factors on a Likert scale (0 to 100) were collected such as the extent to which participants felt that lockdown was compromising their future job prospects; the extent to which university studies were essential to participants; participants' level of concern about their relatives' health due to the COVID-19 crisis; participants' level of concern about their health due to the COVID-19 crisis; and others on dichotomous answer (yes or no) such as the presence or absence of COVID-19 symptoms and the presence or absence of COVID-19 symptoms in their relatives.

Subjective PA

The validated French version of the International Physical Activity Questionnaire–Short Form was used to assess participant PA over the last 7 days. Seven items of the questionnaire evaluated the number of days participants performed moderate-intensive PA, walking activities, and the time (hours and minutes) spent per day in performing the exercises at those intensities. The variable was the total PA expressed as metabolic equivalents of task in minutes per week (METs/week), which is calculated as the sum of 3 PAs such as walking and moderate-intensive PA. For the categorical division into the 3 activity levels (low, moderate, and high), definitions from published evaluation guidelines were used.

Motivation for PA

To assess participant motivations for PA, the French version of the Echelle de motivation envers l'activité physique en contexte de santé [42] was used. This questionnaire contains six 3-item subscales assessing intrinsic motivation, integrated regulation, identified regulation, introjected regulation, external regulation, and amotivation. Participants responded on a 7-point Likert scale (1=strongly disagree to 7= strongly agree).

Subjective Sleep Quality

Sleep quality was assessed with the French adaptation of the Pittsburgh Sleep Quality Index [43]. Participants indicated their usual bedtime, how long it took them to fall asleep, their usual waking time, and their usual hours of sleep per night, as well as responding to different questions on a 4-point Likert scale (0=not during the past month to 3=three or more times a week). Algorithms were used to generate 7 component scores and a global total score (for scoring algorithms, see Buysee [44]).

Body Image

Assessment of body image was measured with the Body Appreciation Scale–2 [45]. The scale comprises 10 items rated on a 5-point Likert scale (1=never to 5=always), with higher total scoring indicating more positive body appreciation.

Eating Behaviors

Assessment of eating behavior was measured with the French version of the Eating Attitudes Test [46]. This questionnaire is a self-administered questionnaire that reveals abnormal eating behaviors. It consists of 26 items with 6 components scored on a 4-point Likert scale (0=never to 3=always). The total score ranges from 0 to 78, and a score ≥20 is considered to represent abnormal eating attitudes or behaviors.

Anxiety and Depressive Symptoms

Assessment of anxiety and depressive symptoms was measured with the French version of the Hospital Anxiety and Depression Scale [47]. This 14-item self-report questionnaire assesses anxiety symptoms and depressive symptoms (7 items for each dimension) with labels varying from one item to the next. Scores range from 0 to 21 for each dimension, with higher scores reflecting higher levels of anxiety or depressive symptoms.

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Social Support

Assessment of social support was measured with the French validation of the Social Provisions Scale–10 item [48]. The 10 items are rated on a 4-point Likert scale (1=strongly disagree to 4=strongly in agreement). This self-report scale captures 5 dimensions of social support (2 items per dimension of support): emotional support or attachment, social integration, reassurance of worth, tangible help, and orientation.

Well-being

Assessment of well-being was evaluated with the French validation of the Psychological Well-being Scale [49]. The 18 items are rated on a 6-point Likert scale (1=disagreement to 6=agreement). This self-report scale captures 6 components of well-being (3 items per component): autonomy, control of the environment, personal development, positive relationships, giving meaning to life, and self-acceptance.

Perceived Fatigue

Assessment of perceived fatigue was evaluated with the French validation of the Multidimensional Fatigue Inventory–20 item [50], a brief self-report instrument that assesses 5 dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Respondents indicate their level of agreement with fatigue-related statements on a 5-point Likert scale (1=yes, that is true to 5=no, that is not true). Possible scores for each dimension range from 4 (no fatigue) to 20 (maximum fatigue). The primary outcome measure for this study will be the total of 4 subscales (general fatigue, physical fatigue, reduced activity, and reduced motivation).

Perceived Control

Assessment of perceived control was evaluated with the French validation of the Pearlin Self-Mastery Scale–Perceived Control [51]. This questionnaire consists of 7 items designed to assess 1 aspect of psychological coping resources on a 7-point Likert scale (1=strongly disagree to 7=strongly agree). Higher scores correspond to higher mastery.

Intervention Program

During the first week, participants from the intervention group were invited to a meeting to co-create a PA program. Two workshops (10 participants per group) were organized in order to clarify the students' expectations. The objectives of these workshops were as follows: (1) understand their motivations to engage in PA and/or sports, (2) understand the barriers and levers to these engagements, (3) determine the types of sports and/or PA that particularly interest both athletic and nonathletic people, and (4) determine their understanding and perception of communication supports on these topics.

The PA program was established according to these workshops. It consisted of weekly sessions (on the day of the participant's choice) less than an hour in length. Activities such as cross-training and cardioboxing make up most of the program sessions. Table 1 provides an example of cross-training and cardioboxing sessions. Cross-training consisted of exercises organized in circuit training with kettlebells, swissballs, slamballs, battle rope, suspension straps, and elastic bands. Cardioboxing consisted of exercises such as shadow boxing, kickboxing, and muay Thaï sequences organized in several rounds. Once a week, a team sports event was organized (volleyball, baseball, tchoukball, spikeball, etc). The PA program was designed to develop strength, endurance, and flexibility/mobility in each session. Participants participated in at least 1 session a week and had a privileged access to all on-campus sports activities without registration. To communicate with participants about the program, the schedule, or any other important information, a group was created on the Discord social media platform with a subgroup for each main topic.

Table 1. Examples of the main physical activities.

Parts of the training session	Cardioboxing	Cross-training
Warm-up	A progressive warm-up was proposed with boxing moves, athletic moves, and running in order to prepare participants for the sequences of the session.	A progressive warm-up was proposed in circuit on each exercise without any weights and then with weights, fitting the level and skills of each participant.
First part	Participants were in pairs and started either with gloves or punching pads. They then changed places. They performed the sequences with a fixed work time and rest time.	Participants were invited to choose an exercise to start the circuit. They then performed each exercise with a fixed work time and rest time.
Second part	A new sequence and a new fixed work time and rest time was proposed, with either the work time increasing or the rest time decreasing.	Jumps, slamball shots, or mainly cardio exercises were proposed as a challenge in the remaining time. The main goal was to achieve the highest number of repetitions possible.
Mobility and flexibility	Participants were invited to either use foam rollers combined with mobility and flexibility exercises or to relax with Jacobson progressive muscle relaxation.	Participants were invited to either use foam rollers combined with mobility and flexibility exercises or to relax with Jacobson progressive muscle relaxation.

Statistics

To further analyze changes in anthropometric values, physical fitness, objective and subjective PA and ST, sleep, and psychological variables, statistical comparisons might include (but will not be limited to) *t* tests, analysis of variance, Mann-Whitney *U* test, Kruskal-Wallis test, Pearson/Spearman correlation analyses, or linear and multiple regression analyses. Analyses will be performed using JASP software (version 0.14.1, JASP Team).

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Results

For this trial, it was hypothesized that the intervention program would improve physical capacities, increase engagement in PA, decrease SB, and improve psychological issues among the intervention group versus the control group. A total of 110 participants initially agreed to participate in the study, with a distribution of 55 participants per group. At baseline, in the intervention group (mean age 22.5 [SD 3.2] years), only 49% (27/55) of participants completed the fitness tests and only 44% (24/55) completed the questionnaire via the internet. In the control group (mean age 21.8 [SD 6.6] years), fitness test and questionnaire completion rates were lower, at 36% (20/55) and 27% (15/55) participants, respectively. Table 2 outlines key aspects of participant characteristics.

Table 2. Characteristics of survey respondents (n=51).

Characteristics	Value, n (%)
Sex	
Female	37 (73)
Male	14 (27)
Other	0 (0)
Level of education	
Undergraduate	35 (69)
First year	7 (14)
Second year	15 (29)
Third year	13 (26)
Master's	15 (29)
Fourth year	12 (24)
Fifth year	3 (6)
PhD	0 (0)
Undefined	1 (2)
Subject	
Psychology	24 (47)
Languages	2 (4)
History/geography	3 (6)
Sciences	3 (6)
Art/design	8 (16)
Law/economics/management	6 (12)
French literature	1 (2)
Mathematics	2 (4)
Others	2 (4)
Positive COVID-19 test or symptoms	
Yes	4 (8)
No	35 (69)
Undefined	12 (24)
Relative with positive COVID-19 test or symptoms	
Yes	21 (41)
No	18 (35)
Undefined	12 (24)

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Discussion

Expected Results

This protocol paper describes the methodology processes of an innovative intervention, encompassing both PA and psychosocial components, designed to help university students. We expect that our intervention based on a co-construction program will lead to an improvement in students' motivation to engage in PA, reduce their SB, and have positive effects on their psychological states, which appears to be even more essential during and after COVID-19 pandemic.

Indeed, the COVID-19 pandemic has profoundly influenced our behaviors in terms of PA and SB at all ages of life [28], especially among university students [52]. This study is in line with a recent systematic review on PA and physical capacities among students [53] that revealed it is crucial to get their awareness and have them maintain a satisfactory level of PA and physical fitness.

Moreover, unlike most studies that conduct conventional PA programs without taking into consideration the expectations of the participants [54], our study includes an innovative protocol based on users' preferences. In this study, the co-construction of a PA program was used as a creative way to re-engage students in PA and modify their lifestyles, which have been deteriorated during the COVID-19 pandemic.

This approach seems particularly interesting because it has been shown that a co-constructed participative workshop was efficient to promote healthy eating habits in a socioeconomically disadvantaged population [55] and for children [56,57]. Engaging in a chosen and desired recreational PA could maintain active behaviors through healthy lifestyle habits [58].

Finally, while most studies mobilize either objective or subjective measures, our protocol proposes to cross the two in order to provide as many insights as possible on the effects of our program. For illustration, our research protocol includes several objectives measures (eg, anthropometric values, flexibility, strength) and subjective measures (eg, psychological variables) but also double measures (accelerometry and questionnaires) for PA and SB as well as sleep in order to compare the measures with this population.

Limitations

Despite the inclusion of 110 participants, the loss of participants was substantial even before the program began. This can be partly explained by the lack of time at the beginning of the academic year or the fear of doing a PA with others during a pandemic period. It may also be due to the requirement to complete different assessment sessions (physical fitness and questionnaires, at approximately 30 minutes each) and 5 days of accelerometer wearing for baseline and T1 measurements. However, it is important to note a high adherence of participants to the PA program, suggesting that the engagement of the students who remained in the program was high.

Conclusion

To the best of our knowledge, there have been no comparable protocols conducted on students, even more so during COVID-19. The pandemic has highlighted the need to pay more attention to the physical and psychological health of students. For this, the development and evaluation of innovative interventions to address their specific needs is essential and could be transferred to people with chronic diseases or older people. In the future, this co-construction approach could be used later by organizations and universities in order to limit unhealthy habits and promote PA while increasing motivation.

Acknowledgments

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Authors' Contributions

EC led the global research for Cov'Etu. AG ran the physical activity intervention, UNIMES EN FORME. AG and EC developed the study concept. AG, MD, BG, AGP, CB, KK, and EC contributed to the study design. KK and MN coordinated the physical activity program. AG and MD analyzed the data. AG, CB, and KK wrote the original draft and all authors wrote, reviewed, and edited the final manuscript. All the authors read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[PDF File (Adobe PDF File), 503 KB - resprot_v11i6e36429_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Agence Nationale de la Recherche (ANR).
[PDF File (Adobe PDF File), 378 KB - resprot_v11i6e36429_app2.pdf]

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Abbreviations

PA: physical activity
SB: sedentary behavior
ST: sedentary time

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Protocol

Feasibility of a Combined Neuromodulation and Yoga Intervention for Mild Traumatic Brain Injury and Chronic Pain: Protocol for an Open-label Pilot Trial

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Abstract

Background: Mild traumatic brain injury (mTBI) and chronic pain often co-occur and worsen rehabilitation outcomes. There is a need for improved multimodal nonpharmacologic treatments that could improve outcomes for both conditions. Yoga is a promising activity-based intervention for mTBI and chronic pain, and neuromodulation through transcranial magnetic stimulation is a promising noninvasive, nonpharmacological treatment for mTBI and chronic pain. Intermittent theta burst stimulation (iTBS) is a type of patterned, excitatory transcranial magnetic stimulation. iTBS can induce a window of neuroplasticity, making it ideally suited to boost the effects of treatments provided after it. Thus, iTBS may magnify the impacts of subsequently delivered interventions as compared to delivering those interventions alone and accordingly boost their impact on outcomes.

Objective: The aim of this study is to (1) develop a combined iTBS+yoga intervention for mTBI and chronic pain, (2) assess the intervention's feasibility and acceptability, and (3) gather preliminary clinical outcome data on quality of life, function, and pain that will guide future studies.

Methods: This is a mixed methods, pilot, open-labeled, within-subject intervention study. We will enroll 20 US military veteran participants. The combined iTBS+yoga intervention will be provided in small group settings once a week for 6 weeks. The yoga intervention will follow the LoveYourBrain yoga protocol—specifically developed for individuals with TBI. iTBS will be

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administered immediately prior to the LoveYourBrain yoga session. We will collect preliminary quantitative outcome data before and after the intervention related to quality of life (TBI-quality of life), function (Mayo-Portland Adaptability Index), and pain (Brief Pain Inventory) to inform larger studies. We will collect qualitative data via semistructured interviews focused on intervention acceptability after completion of the intervention.

Results: This study protocol was approved by Edward Hines Jr Veterans Administration Hospital Institutional Review Board (Hines IRB 1573116-4) and was prospectively registered on ClinicalTrials.gov (NCT04517604). This study includes a Food and Drug Administration Investigational Device Exemption (IDE: G200195). A 2-year research plan timeline was developed. As of March 2022, a total of 6 veterans have enrolled in the study. Data collection is ongoing and will be completed by November 2022. We expect the results of this study to be available by October 2024.

Conclusions: We will be able to provide preliminary evidence of safety, feasibility, and acceptability of a novel combined iTBS and yoga intervention for mTBI and chronic pain—conditions with unmet treatment needs.

Trial Registration: ClinicalTrials.gov NCT04517604; https://www.clinicaltrials.gov/ct2/show/NCT04517604

International Registered Report Identifier (IRRID): DERR1-10.2196/37836

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KEYWORDS

concussion; mild traumatic brain injury; chronic pain; neuromodulation; transcranial magnetic stimulation

Introduction

Background

The World Health Organization estimates that the yearly incidence of mild traumatic brain injury (mTBI) is 600 per 100,000 persons and is even higher in military populations [1,2]. Although most patients are expected to recover from mTBI within 1 week to 3 months [3], a subset of patients with mTBI experience a host of poor rehabilitation outcomes, including impairments in cognition, physical health, and psychological health [4] that lead to poor quality of life (QoL) [5]. Worsening this clinical picture, 75% of individuals with TBI have comorbid chronic pain [6,7], defined as pain in the muscles, bones, ligaments, tendons, or nerves that persists for more than 6 months [8]. In addition, recent research indicates that mTBI is strongly associated with increased pain interference—a measure of the extent to which pain hinders QoL [9,10]. There are many established nonpharmacological treatment options for the sequelae of mTBI or chronic pain as individual diagnoses, including patient education, rehabilitation, and psychological interventions [11-14]. However, evidence regarding the efficacy of nonpharmacological interventions for people with co-occurring mTBI and chronic pain (mTBI+chronic pain) is lacking [15]. Further, clinical practice guidelines recommend against opioid treatment for people with mTBI+chronic pain due to an increased risk of adverse outcomes; yet, this patient cohort remains at increased risk of receiving short- and long-term opioid therapy [16]. Clinical practice guidelines for the treatment of chronic pain alone also recommend against the long-term use of opiates owing to the risk versus benefit profile [17]. The lack of sufficient evidence for any nonpharmacological intervention for mTBI+chronic pain in combination with the ongoing opioid epidemic demonstrates the strong need for effective nonpharmacological interventions for this patient population.

Rationale

Yoga, Pain, and mTBI

Yoga is a mindfulness-based intervention that may be a promising alternative treatment for mTBI+chronic pain sequelae. Clinical trials of yoga interventions most commonly utilize hatha-based yoga, which is comprised of breathing exercises (*pranayama*), physical postures (*asanas*), and meditation [18]. Studies of yoga for chronic pain have found yoga to be the most effective for improving headaches and low back pain relative to pain in other areas of the body; headaches and low back pain are the most common types of chronic pain sequelae after mTBI [6,15,19-26]. The effects of yoga on various outcomes among individuals with mTBI have previously been assessed [27]. A systematic review and meta-analysis of 20 studies on yoga for mTBI revealed significant improvements in fatigue, depression, physical health, cognitive performance, and QoL [27]. One specific adaptive yoga program, LoveYourBrain yoga, is a hatha yoga program created and tested specifically for TBI and designed to be modifiable to serve people of all ability levels [28]. LoveYourBrain yoga is a manualized 6-session group-based yoga intervention that incorporates breathing exercises, physical postures, meditation, and TBI-tailored psychoeducation. LoveYourBrain yoga has been shown to be feasible in people with TBI [28-30]. Further, preliminary evidence suggests that participating in LoveYourBrain yoga leads to improvements across other outcomes, including QoL, among people with TBI of all severities [28-30]. Preliminary evidence suggests that yoga-based programs may be feasible and acceptable for individuals with mTBI+chronic pain [31]. However, the impact of yoga in general, as well as the impacts of LoveYourBrain yoga, on pain outcomes in the mTBI+chronic pain population is yet to be tested.

Neuromodulation and Pain

Neuromodulation through transcranial magnetic stimulation (TMS) is another promising noninvasive, nonpharmacological treatment for mTBI+chronic pain. A recent systematic review of repetitive TMS (rTMS) for chronic pain [32] and a

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meta-analysis of rTMS for neuropathic pain [33] demonstrated that high-frequency rTMS (>1%) applied to the motor cortex effectively reduces pain. Additionally, high-frequency rTMS applied to the left motor cortex of patients with mTBI-related headaches resulted in reductions in headache symptoms [34]. Collectively, these studies indicate that high-frequency excitatory rTMS applied to the motor cortex is beneficial for alleviating pain and can be safely and effectively applied to populations with TBI.

Intermittent theta burst stimulation (iTBS) is a type of patterned, excitatory rTMS. A practical advantage of iTBS over rTMS is that iTBS protocols are typically 3 minutes in duration instead of 30 minutes. The short duration makes this intervention ideally suited for people with chronic pain who may be unable to tolerate prolonged TMS. Research on iTBS as a treatment for pain and TBI is in its infancy. A recent trial of a single session of iTBS applied to the motor cortex of patients with chronic orofacial pain demonstrated significant, yet transient, improvement in self-reported pain [35]. These promising results may be improved with repeated provision of iTBS treatments over time. Furthermore, evidence suggests that iTBS applied to the dorsolateral prefrontal cortex may significantly decrease the frequency, duration, and severity of headaches [36], which are the most common types of chronic pain after mTBI [6,19]. Another randomized controlled trial conducted among patients with multiple sclerosis and lower spastic paraparesis examined the effects of iTBS versus high-frequency rTMS (20 Hz) on spasticity. Although researchers found that high-frequency rTMS resulted in better short-term outcomes, iTBS resulted in longer lasting improvements in outcomes [37]. These positive findings in other neurological conditions suggest that iTBS may be a promising intervention for mTBI.

At the time of publication, a single case study utilizing iTBS as a potential treatment for mTBI has been reported. The study outlined a 3-week iTBS intervention combined with rehabilitation that resulted in improvements in balance performance, motor recovery, step length, and walking speed [38]. This case study in combination with a systematic review of TMS for mTBI suggests that iTBS can be safely used among individuals with mTBI [39,40]. However, more research is essential to understanding whether this noninvasive, nonpharmacological intervention may be beneficial as a wide-scale treatment option for this population.

iTBS as a "Primer" for Other Interventions

What makes iTBS a unique and particularly promising intervention is that it induces a window of enhanced neuroplasticity, making it ideally suited to be paired with other interventions (eg, yoga) to magnify the effects of those interventions provided after it [41,42]. iTBS increases the excitability of the motor cortex [43] during and up to 60 minutes after the cessation of the treatment; during this time, the other intervention can be provided [43]. For example, iTBS provided prior to high-frequency (10 Hz) rTMS to the motor cortex provided greater analgesia than rTMS alone (without iTBS priming) among patients with chronic neuropathic pain [41]. In terms of pairing with behavioral interventions, iTBS was successfully combined with cognitive behavioral therapy to promote smoking cessation [42]. Collectively, this emerging evidence suggests that iTBS shows promise to prime the brain for combined interventions and may magnify the impacts that these interventions would have when used alone.

In this study, we will test the idea that for people with mTBI+chronic pain, the beneficial effects of yoga can be magnified if yoga is provided immediately after the provision of iTBS ("iTBS+yoga"). Yoga is an ideal intervention to pair with iTBS for this patient population for several reasons. A yoga program that was created specifically for TBI already exists and has been validated [28,29]. Further, comorbid mental health conditions are common in the veteran mTBI+chronic pain population owing to trauma exposure [10]. Mindfulness-based interventions such as yoga have well-established benefits for those with trauma-associated mental health sequelae [44]. Lastly, yoga is an intervention that can be easily continued independently at home after the study is complete. To the authors' knowledge, at the time of publication, no studies have explored iTBS+yoga in any population despite burgeoning evidence in support of both of these individual interventions for a multitude of diagnoses.

Objectives

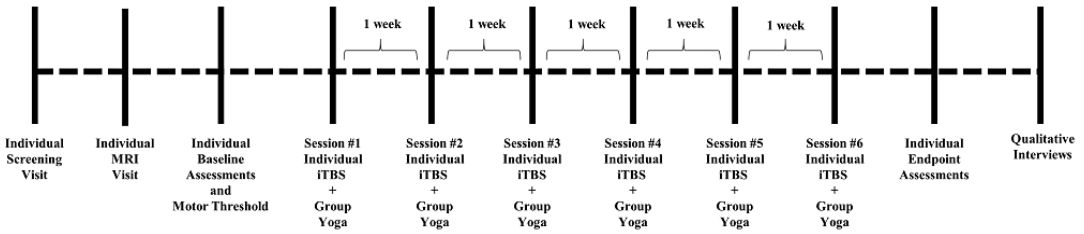
The objectives of this pilot study are to (1) develop a combined iTBS+yoga intervention targeting chronic pain among veterans with mTBI+chronic pain, (2) assess the intervention's feasibility and acceptability, and (3) gather preliminary clinical outcome data on QoL, function, and pain that will guide future studies.

Methods

Study Design

This study will be a single-group, exploratory, mixed methods design, wherein all participants will receive iTBS+yoga (Figure 1). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations were referenced when developing this protocol [45].

Figure 1. Study visit timeline. iTBS: intermittent theta burst stimulation; MRI: magnetic resonance imaging.



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Ethics Approval and Dissemination

This study protocol was approved by Edward Hines Jr Veterans Administration Hospital Institutional Review Board (Hines IRB 1573116-4) and was prospectively registered on ClinicalTrials.gov (NCT04517604). This study includes a Food and Drug Administration Investigational Device Exemption (IDE: G200195). A 2-year research plan timeline was developed (Table 1).

Table 1. Research plan timeline.

Task	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study team role identification	✓							
Develop intervention	✓	✓						
Participant enrollment (n)			5	5	5	5		
Study procedures			✓	✓	✓	✓		
Data analyses							✓	✓
Dissemination								✓

Participants

We will target recruitment of 20 veterans aged 22 years or older with mTBI+chronic pain over the course of 12 months. Veteran participants must perceive themselves as able to participate in gentle physical movements and will be cleared for gentle exercise by a study team physician. mTBI will be defined according to the Veterans Affairs (VA)/Department of Defense clinical practice guidelines [46] utilizing the mTBI symptom attribution and classification algorithm (SACA) [47]. Chronic pain will be operationally defined as pain in the muscles, bones, ligaments, tendons, or nerves that persists for >6 months and is of moderate-to-severe intensity as indicated by a score of >5 on specific items on the Brief Pain Inventory [8,48]. For safety, we will exclude persons with contraindications to TMS or magnetic resonance imaging (MRI). We will not exclude participants with major depressive disorder and other psychological disorders; these diagnoses will be documented as potential covariates. We will not exclude participants based on gender, ethnicity, or race. All participants will provide written informed consent in accordance with the World Medical Association Declaration of Helsinki. Each participant is eligible to receive compensation for participation. The inclusion and exclusion criteria are listed below (Textbox 1).

Textbox 1. Inclusion and exclusion criteria for the participants.

Inclusion criteria

- 22+ years of age
- Can read and speak English
- Perceive themselves as able to participate in gentle physical movements and cleared by study physician to do so.
- Mild traumatic brain injury (mTBI) criteria: Symptom Attribution and Classification criteria for mTBI (without requirement of clinical neuropsychological impairment)
- Chronic pain: pain (in muscles, bones, ligaments, tendons, or nerves) that persists for >6 months and is of moderate-to-severe intensity with a score of >5 on specific items on the Brief Pain Inventory
- Fully vaccinated against COVID-19 prior to study participation

Exclusion criteria

- Contraindications to intermittent theta burst stimulation/transcranial magnetic stimulation (eg, epilepsy, history of anoxic brain injury, or heart disease)
- Contraindications to magnetic resonance imaging (eg, claustrophobia, ferromagnetic metal implants)
- Pain believed to be associated with cardiac or ischemic conditions
- History of moderate-to-severe TBI
- Active seizure disorder or if they are taking psychostimulants (eg, amphetamines), anticholinergics, or other medications that may increase their risk of having seizures
- History of or current psychosis not due to an external cause (eg, due to illicit drug use)
- Are pregnant or nursing
- Within 12 weeks of a major surgery/operation
- Have questionably valid test profiles

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Recruitment

We will recruit veterans from a large VA medical center located in the midwestern United States, which houses a TBI/Polytrauma program that admits approximately 250 veterans per year. TBI/Polytrauma program personnel will inform the program members about the study through routine staff meetings. TBI/Polytrauma program personnel will add research team members as co-signers in the electronic medical record (EMR) of TBI/Polytrauma program patients recommended for screening for this study. We will then perform an EMR review for study eligibility criteria and send eligible veterans an informational letter about the study. We will make follow-up phone calls to perform initial eligibility screens. We will also mail informational letters to veterans who have completed our past studies and permitted us to contact them about future studies through a TBI Data Repository created for recruitment purposes (coprincipal investigators: AAH and TLBP, IRB#14-003).

Data Collection and Measures

MRI Data Acquisition, Neuronavigation, and Motor Thresholding

All participants will undergo a brain MRI. A high-resolution, 3D, T1-weighted, multigradient-echo sagittal anatomical scan (voxel size=0.8 mm isotropic resolution) will be collected in order to allow for iTBS treatment site neuronavigation for each participant. The images will be reviewed by a neuroradiologist. In order to ensure the MRI procedure will be safe, the participant will be asked to fill out a standardized MRI safety screening form before starting the study. Examples of potentially exclusionary issues include (1) metal fragments in the eyes or face, (2) implantation of any electronic devices such as (but not limited to) cardiac pacemakers, cardiac defibrillators, cochlea implants, or nerve stimulators, (3) surgery on the blood vessels of the brain or the valves of the heart, (4) claustrophobia, and (5) body piercing or tattoos.

Each participant's T1 MRI will be loaded into a Localite TMS Neural Navigator system to identify his or her motor threshold. A MagVenture C-B60 coil will be used to deliver single-pulse TMS to the nondominant motor cortex to identify the abductor pollicis brevis muscle brain coordinates. Stimulation intensity that will be used in iTBS will be determined by collecting each participant's motor threshold using the finger representations of the motor cortex. The consensus in the literature is that iTBS can be safely provided at 80% of active motor threshold (AMT) [49-53]. Since there is more within- and between-subject variability with AMT (eg, different gripping strengths) relative to resting motor threshold (RMT), scientifically, the RMT is preferred. There is also recent evidence that motor threshold estimates using RMT and AMT are equivalent [54]. This means that treatment intensity based on these 2 motor threshold estimation procedures would be equivalent. We will use RMT to estimate motor threshold and compute treatment intensity. RMT will be defined as the lowest stimulus intensity necessary to produce motor-evoked potentials ≥50 μV in 5/10 trials. Thus, the standard iTBS parameters will be used in this trial to maximize safety. iTBS will be provided at 80% of RMT.

Quantitative Data Collection

Information that will be collected via pre-enrollment telephone screening to assess for eligibility includes (1) probable mTBI, using the Ohio State University TBI Identification Method [55], (2) MRI safety, using a standardized hospital-wide MRI safety form, (3) self-reported age (to be verified in the EMR) and ability to read and speak English, and (4) a list of prescribed and over-the-counter medications and the length of time the participant has been on each medication (Table 2).

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Table 2. Quantitative study assessments.

Assessment name	Assessment purpose
Eligibility phone screen	
Ohio State University TBI[a] Identification Method	Identification of likelihood of mTBI event
Hines Veterans Affairs magnetic resonance imaging safety form and transcranial magnetic stimulation safety form	Magnetic resonance imaging and transcranial magnetic stimulation safety compatibility
Initial screening	
Structured Diagnostic Interview [47] with the Neurobehavioral Symptom Inventory [56]	mTBI eligibility
California Verbal Learning Test-II [57]	Memory and performance effort validity
Minnesota Multiphasic Personality Inventory-2-Restructured Form [58]	Symptom reporting validity
Demographics	Sample characterization
Baseline and endpoint	
TBI-quality of life (TBI-common data elements)	Preliminary quality of life data
Mayo-Portland Adaptability Index (TBI-common data elements)	Preliminary function and participation data
Brief Pain Inventory [8,48]	Preliminary pain data and eligibility
Therapy Activity Data Collection	Preliminary Therapeutic Activity Data
Session completion rates	Feasibility (endpoint only)
Structured qualitative interviews	Acceptability (endpoint only)
Satisfaction ratings	Acceptability (endpoint only)
Home and community yoga and meditation diaries	Covariate (each weekly session)

[a]TBI: traumatic brain injury.

Prior to study enrollment, we will conduct in-person screening with each potential participant, during which veterans will complete a finite set of assessments from the mTBI SACA [47]. The Structured Diagnostic Interview, included in the SACA, will be used to establish the mTBI history, including duration of loss of consciousness, alteration of consciousness, and posttraumatic amnesia [47]. The interview ends with the Neurobehavioral Symptom Inventory [56]. The California Verbal Learning Test-II (CVLT-II) [57] will be used to assess verbal memory, a cognitive domain affected by mTBI. To determine the validity of the test profiles, a cutoff score of 15 on the CVLT-II forced choice component will serve as a measure of effort performance [59]. To determine the validity of symptom reporting, the Minnesota Multiphasic Personality Inventory-2-Restructured Form [58] will be used to identify abnormal symptom reporting via this criteria: F, T score≥107; F(p), T score≥85; True Response Inconsistency, T score≥80; and Variable Response Inconsistency, T score≥80 [47].

Baseline and endpoint assessments, which will be collected at the participant's third and tenth visits include TBI common data elements (ie, TBI-related QoL, Mayo-Portland Adaptability Index) and the Brief Pain Inventory. The TBI-QoL is a self-report instrument developed by TBI Model System centers and VA Brain Injury Centers that assesses domains of TBI-specific functioning and health-related QoL [60]. The Mayo-Portland Adaptability Index is an outcome of abilities, adjustment, and participation that is validated for use in veterans with TBI [61]. The Brief Pain Inventory is a self-reported measure assessing the extent to which pain interferes with domains of functioning such as mood, work, sleep, and enjoyment of life [48].

At the endpoint visit, participants will also complete a 2-question satisfaction rating scale [28], which serves as a quantitative assessment of intervention acceptability. The questions include (1) "would you recommend this program to a friend?" and (2) "on a scale of 1 (poor) to10 (excellent), how would you rate the quality of this program?"

Feasibility will be defined by enrollment and the number of sessions completed by each participant. Participants will be instructed to complete weekly diaries throughout the intervention phase of the study detailing pain medication usage, other pain management strategies utilized, and the time they spent at home or in the community engaging in meditation or yoga practices. These factors will be used as a potential covariate in analyses.

Qualitative Data Collection

The acceptability of the intervention will be qualitatively assessed via semistructured interviews with a subsample of veterans who participate in the study (n=10). Interviews will elicit feedback about veteran experiences with intervention participation, barriers and facilitators to participation, perceptions of the intervention, how participation impacted key pain-related outcomes and QoL, and suggestions for improvement.

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Safety and Adverse Event Monitoring

Participants will participate in safety monitoring using the Data Safety Monitoring Scale before and after each iTBS session. This scale assesses vital signs (temperature, blood pressure, heart rate, oxygen saturation levels), fatigue, tinnitus (ringing in the ears), hours of sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, and substance use and directs how staff should respond if any of the values deviate significantly from the individual's baseline values.

An adverse event is any undesirable experience associated with iTBS measured as a deleterious change from baseline on the Data Safety Monitoring Scale. A serious adverse event is when the changes are disabling, life threatening, require hospitalization, or require intervention to prevent impairment. We will measure deleterious changes in (1) neurologic status, including cognitive symptoms, (2) somatic and vestibular symptoms, (3) and depression. Adverse events will be tracked using an adverse event log.

All iTBS sessions will be videotaped to allow for review in case of an adverse event. Acknowledgement for picture and video will be completed as part of Health Insurance Portability and Accountability Act (HIPAA) authorization documentation.

All serious, unanticipated adverse events that are related to this research study will be reported to the institutional review board within 5 days. If any unanticipated problem occurs, such as deviation from this protocol that involves risks or has the potential to recur, this information will be reported by the investigator to the institutional review board as well within 2 business days but no longer than 5 business days of the investigator or staff becoming aware of the event.

Any concern for seizure or seizure-like activity will result in stopping treatment and, if indicated, the participant will be withdrawn from the study. The on-site rapid response team will be paged to provide emergent medical care to the participant, including administration of seizure-abating medications and airway protection, if necessary. If emergent medical care is required, we will transport the patient to the hospital emergency room for further monitoring. All research team members have been educated on how to safely lower patient to the floor prior to the rapid response team arriving. If the participant ultimately does not require emergent care, they will be advised to follow up with their established health care provider. If concerning new conditions emerge or existing conditions worsen, we will withdraw the participant from the proposed study.

Experimental Interventions

iTBS Intervention

We will use a T1 MRI to localize the stimulation site, which will be each participant's dominant trunk representation area of the motor cortex. The 3-minute iTBS protocol will be delivered utilizing the MagVenture Mag-Pro X100 with the MagOption stimulator that includes active and placebo coils (C-B60 Butterfly coils) and equivalent active only Cool-B65 Butterfly treatment coil. Only the active setting will be used. iTBS parameters include 3 pulses of stimulation given at 50 Hz, repeated every 200 ms at 80% of the RMT. The interpulse interval is 20 ms. A 2-second train of TBS is repeated every 10 seconds for a total of 190 seconds, which equates to a total of 600 pulses [62].

LoveYourBrain Yoga

The LoveYourBrain yoga curriculum includes 6 weekly 90-minute sessions comprised of 10 minutes of breathing exercises, 45 minutes of gentle yoga, 15 minutes of guided meditation, and 20 minutes of facilitated discussion with psychoeducation. The program is detailed in a manual to ensure standardization of program content across time and instructors [28]. We adapted the existing psychoeducation component to include pain-related topics. We engaged key stakeholders to assist in the psychoeducation tailoring process, including the LoveYourBrain faculty and developers, TBI/Polytrauma and pain clinic teams at the study site, veterans, and the individuals from the pain management center at a nearby large rehabilitation hospital. Day et al's [63] conceptual model of the mechanisms for improvements after mindfulness-based interventions for chronic pain management informed our tailoring of the existing psychoeducation program to optimally engage those with pain (Figure 2). The LoveYourBrain yoga psychoeducation is already focused on resilience, which Day et al's model [63] identifies as a mechanism of improvement in pain after an intervention. Based on Day et al's [63] conceptual model, we also integrated pain beliefs, acceptance, and self-efficacy into the existing psychoeducation program.

Each LoveYourBrain yoga session will be led by 2-3 instructors. Each instructor will complete the 20-hour LoveYourBrain yoga Teacher Training certification course to learn how to deliver the LoveYourBrain yoga and adapt yoga, breathing exercises, meditation, and group discussion for TBI. The asana portion of the program will be led by certified yoga teachers. To support fidelity of intervention delivery, instructors will be required to submit recordings of mock teaching the LoveYourBrain yoga curriculum to LoveYourBrain faculty and receive detailed feedback. Instructors will also utilize LoveYourBrain's session flow sheets to ensure intervention consistency and fidelity.

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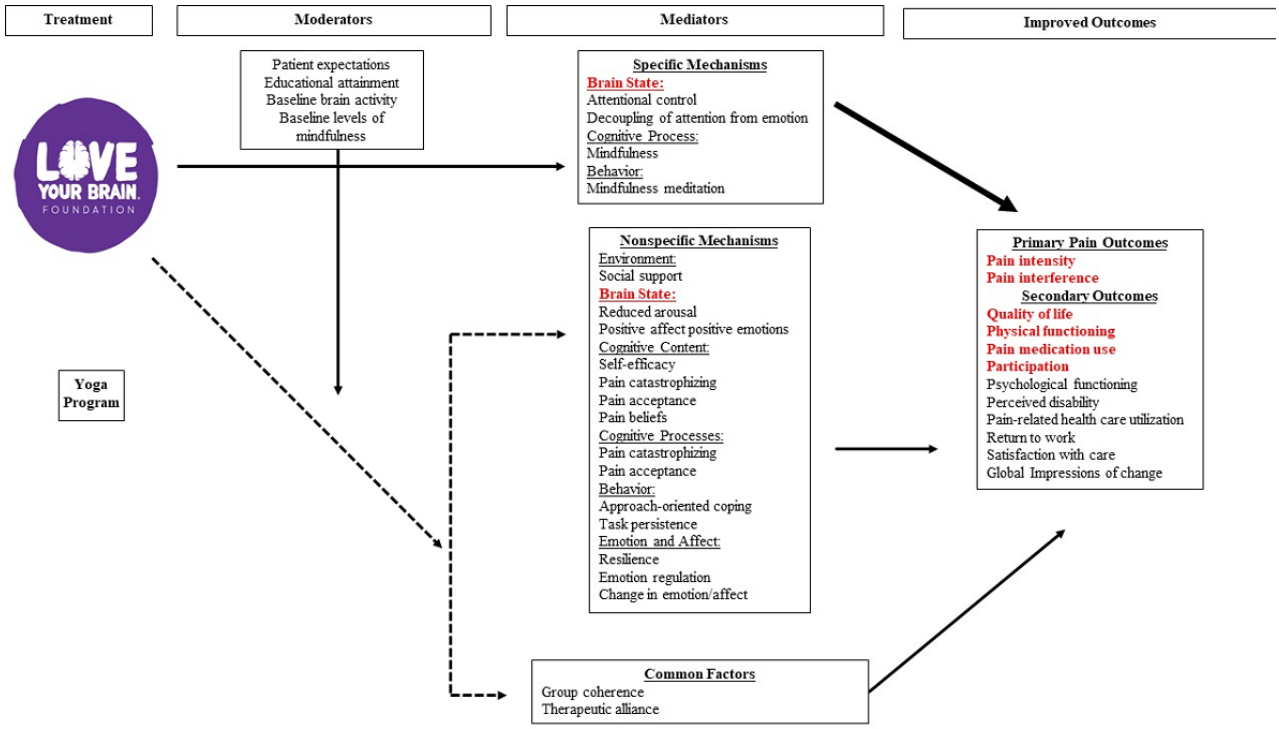
Figure 2. Adapted conceptual model of the mechanisms of mindfulness-based interventions for chronic pain management [63]. The mediators in bold red font represent those which we are targeting with intermittent theta burst stimulation paired with the LoveYour Brain yoga program. The outcomes in bold red font are those which we will formally assess at baseline and endpoint.



Study Procedures

A partial HIPAA waiver and waiver of informed consent for screening purposes will provide regulatory approval to screen candidates to determine study eligibility prior to obtaining informed consent. After the eligibility phone screening, we will cross-reference current medications with study eligibility criteria and the EMR to identify any antiepileptics and medications known to lower seizure threshold. If findings indicate possible contraindications to rTMS or MRI related to a metal implant, we will obtain the model and manufacturer of the implant to determine whether it is safe to expose the implant to a strong magnet. We will follow manufacturer recommendations regarding safety. If we do not identify any exclusionary factors in the eligibility phone screening, we will invite the participant to complete an in-person screening.

Several outcomes will be completed at the initial in-person screening (Table 2). After the screening, a study physician will evaluate the veteran's ability to engage in gentle exercise and their pain management strategy, including over-the-counter analgesics that they might take during the intervention. Participants will still be able to receive other potential treatments or medications to assist with the management of chronic pain. These pain management strategies must remain stable during study participation. Upon the initial evaluation and at each study visit, medication dosages and frequencies will be documented.

Intervention sessions will occur once a week for 6 weeks, with approximately 2-4 individuals participating simultaneously as a cohort. Prior to the interventions, participants will provide a urine sample for the detection of alcohol and certain drugs that lower seizure threshold. This includes pain medications such as morphine and Vicodin; benzodiazepines such as Valium, Librium, Xanax, and Ativan that are usually used to treat anxiety or alcohol withdrawal; and substances such as cocaine, marijuana, heroin, amphetamine or speed, and barbiturates. These screening results are only used to determine if participants are eligible to continue in this research study and will not be entered into the participant's medical record or reported to legal authorities.

Each intervention will start with individual iTBS for each of the approximately 2-4 participants per cohort. The order of receipt of iTBS will be counterbalanced so that each individual receives iTBS first, second, third, or fourth as close to the same number of times as possible. While not receiving iTBS, the participants will be instructed to rest quietly in another research space or waiting area. Each iTBS session will take about 15 minutes with setup and takedown.

Ear plugs will be placed in participants' ears for protection since the magnetic stimulator makes a loud clicking noise. Because of the known potential for pain associated with iTBS, we will recommend that participants bring an over-the-counter pain reliever of their choice to take prior to each iTBS session. We will ask participants when they took the medication and the amount.

Within 60 minutes of the first individual's receipt of iTBS, a 90-minute teacher-guided 2-4 person group LoveYourBrain yoga session will be initiated. If a participant misses a session, they will be contacted within 24 hours to determine reasons for missed sessions, which will also be tracked in an activity log. The participant will then be encouraged to make up for their missed session, which will be offered as an optional group makeup session at the end of the 6-week program. If participants miss less than 50% of the sessions (3/6), they will have the opportunity to make up the missed sessions. If the participants

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miss 3 or more sessions, they will have the opportunity to join the next cohort.

Analytic Plan

Quantitative Analysis

For each outcome, we will perform a paired, 2-sided *t* test between baseline and endpoint scores (α=.05). To measure the pairwise association between 2 outcomes, we will compute Pearson correlations and test for significance by using the Fisher Z-transformation. We will also examine the relationship between number of completed sessions and change score (endpoint – baseline) of each outcome with a linear regression model. We will extract information from this pilot study and compute effect sizes used for sample size determination in future studies based on the change score for each outcome and compute the sample size for 80% power with a 5% type 1 error rate.

Qualitative Analysis

Semistructured interviews will be audio recorded, transcribed verbatim, and analyzed by 2 qualitative experts by using thematic coding and constant comparison techniques. Our qualitative analysis will be supported by a codebook, the initial content of which will be guided by the elements of our conceptual model. Each interview transcript will be independently coded by 2 members of the research team; these individuals will then meet to discuss codes and resolve discrepancies as needed.

Results

As of March 2022, we have enrolled 6 individuals. We will collect data until November 2022. We expect the results of the study to be available by October 2024.

Discussion

Hypotheses

Our central hypothesis is that our combined iTBS+yoga intervention will be feasible and acceptable for veterans with mTBI+chronic pain. This hypothesis is based on existing literature and our preliminary data demonstrating that iTBS [38] and the LoveYourBrain yoga program [28], provided separately, are each feasible and acceptable among people with TBI. Further, we hypothesize that the relationship between iTBS+yoga and all outcomes will be positive, for example, more sessions will provide better change scores.

It is expected that veterans with mTBI+chronic pain will be able to attend the weekly sessions for 6 weeks. The quantitative satisfaction ratings will improve by the completion of the treatment. The semistructured interviews and feedback will allow for modifications to be made as warranted. Although we expect that the 3 outcome domains of QoL, function, and pain will improve, even if a single domain improves, we consider this positive. By exploring the associations between the above outcomes, we will better be able to interpret which outcome domain may be driving improvements.

Pending the results of this pilot trial, larger scale randomized controlled trials may be warranted to determine the efficacy of iTBS+yoga on improving QoL, function, and pain among veterans with mTBI+chronic pain.

Strengths of This Study

The strengths of this study are as follows. First, this study utilizes an established program already vetted for feasibility and acceptability for the population with mTBI. Second, both iTBS and yoga are readily available within the VA health care systems throughout the United States.

Limitations of This Study

The limitations of this study could be as follows:

1. The small sample size reduces the study power, which can limit the ability to interpret the significance of any differences found in outcomes but is reflective of the pilot nature of the study and the funding mechanism.
2. The open-label nature of this study could bias results but is also an important first step for developing this novel intervention.
3. Variability in the baseline characteristics of the patient population that are not being studied in detail in this project may negatively impact some measures of QoL and pain. Thus, we may explore treatment responsiveness by baseline characteristics.
4. Pain is a truly subjective measure; therefore, we will explore calibrating self-report pain outcomes on the basis of function and QoL outcomes.

Acknowledgments

This study is funded by the Veterans Affairs Rehabilitation Research and Development Small Projects in Rehabilitation Research grant, which began on December 1, 2020 (I21RX003611). The authors gratefully acknowledge the LoveYourBrain foundation, Hines Veterans Affairs traumatic brain injury/polytrauma and pain clinics, the Veterans Engagement Panel, and the Shirley Ryan AbilityLab Pain Management Center.

Authors' Contributions

KAK and AAH led the writing of this manuscript. AAH conceived the study design and obtained funding to support the project. All the remaining authors contributed to the study design and reviewed the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer-review report by the Rehabilitation Research and Development Small Projects in Rehabilitation Research (SPiRE) Program - Rehabilitation Research and Development Parent IRG, Office of Research & Development (RRDS) - United States Department of Veterans Affairs.
[PDF File (Adobe PDF File), 230 KB - resprot_v11i6e37836_app1.pdf]

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Abbreviations

AMT: active motor threshold
CVLT-II: California Verbal Learning Test-II
EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act
iTBS: intermittent theta burst stimulation
iTBS+yoga: intermittent theta burst stimulation paired with the LoveYourBrain yoga program
MRI: magnetic resonance imaging
mTBI: mild traumatic brain injury
mTBI+chronic pain: co-occurring mild traumatic brain injury and chronic pain
QoL: quality of life
RMT: resting motor threshold
SACA: symptom attribution and classification algorithm
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TMS: transcranial magnetic stimulation
VA: Veterans Affairs

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Protocol

Uneven Treadmill Training for Rehabilitation of Lateral Ankle Sprains and Chronic Ankle Instability: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Lateral ankle sprains (LASs) are common injuries among military service members. Approximately 40% of individuals with an LAS progress to develop chronic ankle instability (CAI), a condition that results in substantial mechanical and neurophysiological impairment and activity limitation. Since proprioceptive and balance training improve functional outcomes and prevent secondary injury following LAS, they are recommended in clinical practice. Uneven treadmills are an innovative modality that challenge the sensorimotor system while performing an ecologically valid task simulating environments frequently encountered by service members with LAS and CAI.

Objective: The aim of this study is to evaluate whether the inclusion of uneven treadmill training in standard rehabilitation can improve clinical, functional, biomechanical, and patient-reported outcomes compared with the standard of care alone in service members with LAS and CAI. The prophylactic effects of treatment on secondary injury and identification of any contributing or mediating factors that influence outcomes following treatment will also be evaluated. We hypothesize that service members receiving uneven treadmill training will demonstrate greater improvements in clinical and instrumented measures of impairment, patient-reported function, and lower risk of injury recurrence than the control group immediately post and 18 months following treatment.

Methods: A multisite, parallel randomized clinical trial will be performed among service members aged 18-49 years being treated for LAS and CAI in military treatment facilities in the United States. Participants randomly assigned and allocated to receive the experimental intervention will be provided up to 12 sessions of training on an uneven terrain treadmill over a 6-week

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treatment course to supplement standard rehabilitation care. Treatment intensity of the rehabilitation exercises and treadmill training will be progressed on the basis of patient-perceived intensity and treatment responses. Outcome measures will include patient-reported outcomes, functional assessments, performance measures, and biomechanical measures. Investigators collecting outcome measures will be blinded to treatment allocation. Reinjury rates and patient-reported outcomes of function will be tracked over 18 months following treatment.

Results: The project was funded in September 2020. Patient recruitment began in November 2021, with 3 participants enrolled as of February 2022. Dissemination of the main study findings is anticipated in 2024.

Conclusions: This study will assess the impact of an innovative uneven-terrain treadmill on treatment outcomes in the rehabilitation of service members with LAS and CAI. The results of this study will be used to inform rehabilitation practices and to potentially improve functional outcomes and secondary prevention in this patient population.

Trial Registration: ClinicalTrials.gov NCT04999904; https://clinicaltrials.gov/ct2/show/NCT04999904?term=NCT04999904

International Registered Report Identifier (IRRID): DERR1-10.2196/38442

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KEYWORDS

military personnel; ankle injuries; rehabilitation; recovery of function; secondary prevention; ankle sprain; treadmill

Introduction

Lateral ankle sprains (LAS) are one of the most common injuries in the United States [1]. The burden of these injuries is even higher in the military, where the incidence is substantially greater in enlisted service members (21.3 to 33.4 per 1000 person-years) than in their civilian counterparts (19.0 to 26.6 per 1000 person-years) [1,2]. LAS substantially degrade the ability of the military to meet operational objectives, with an average of 14 days of lost duty time per injury [3] and more than 92,000 medical visits for the care of these injuries incurred per year [4]. While the burden of LAS determined by historical medical encounters is high, the true burden is likely much higher. Perceptions of LAS as a benign and self-limiting condition preclude care-seeking by service members [5]. Moreover, injury recurrence is common during the first 12 months following injury [6,7] and beyond [8]. Approximately 40% of individuals with LAS are projected to progress to develop chronic ankle instability (CAI) [8,9]—a complex clinical entity characterized by mechanical and sensorimotor impairments that result in long-term disability and degraded health-related quality of life [10].

Peripheral and central sensorimotor impairments are common in LAS and CAI. These neurophysiological deficits are the result of deafferentation from connective tissue and muscle injury, peripheral nerve injury, spinal- and cortical-level inhibition, changes in the cortical motor map, and central sensory reorganization [11]. For example, individuals with CAI demonstrate increased reliance on visual afference during dynamic tasks [12], which is a compensatory strategy to counter diminished plantar sensation [12-14]. Altered walking mechanics are also common in individuals with CAI, specifically a wider base of support, increased shank external rotation, a more plantarflexed and supinated foot, and a more laterally displaced path of center of pressure (COP) progression compared with uninjured individuals [15]. These adaptations are due, in part, to deleterious neuromotor changes in function, which affect the response time to lateral perturbations and reduce the ability to counter ankle inversion to prevent reinjury [11,15].

Based on the burden and morbidity associated with LAS and CAI, proper management of these injuries is especially salient in service members. This population has high physical demands and esoteric occupational and environmental exposures that increase injury risk [2]. Clinical practice guidelines for the treatment of LAS recommend inclusion of early progressive weight bearing, manual therapy, and functional exercises that include proprioceptive balance training [16]. These updated guidelines further recommend these exercises for secondary prevention of subsequent injury and outline the necessity for graded exposure to occupational-related tasks [16]. Proprioceptive training has been shown to improve some of the postural control deficits and COP excursions in patients with LAS and CAI [11] and to decrease the risk of reinjury [7,16]. Provision of therapeutic exercises, including proprioceptive training, early in the rehabilitation course has been shown to be prophylactic during the first 12 months following LAS [7].

Despite the demonstrated benefits of proprioceptive training and early rehabilitation following LAS, there is no evidence to suggest that the burden of CAI is decreasing. Currently, most proprioceptive training encompasses the use of static balance exercises performed on solid and compliant surfaces [17]. While static exercises are indeed important as part of a comprehensive rehabilitation course, they have limited ecological validity and may not provide the specificity needed to prepare service members for environmental hazards frequently encountered in the performance of occupational duties. Treatment modalities that provide graded exposure to perturbations during functional activity may better help to facilitate sensorimotor plasticity and integration in preparation for return to duty [11]. The purpose of this pragmatic randomized controlled trial is to determine if incorporation of graded exposure on an uneven-terrain treadmill during standard rehabilitation care will lead to greater improvement in function and secondary preventive effects than standard rehabilitation care alone in military service members with LAS and CAI up to 18 months following treatment. The secondary aim of this is to identify the factors that predict and mediate treatment outcomes in this population.

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Methods

Study Design

This study will use a multisite, parallel randomized clinical trial, with Group (control and experimental) and Time as the independent variables. Methodological development was informed using the PRagmatic Explanatory Continuum Indicator Summary (PRECIS-2) tool [18]. The CONSORT (Consolidated Standards of Reporting Trials) statement for randomized trials of nonpharmacologic treatments [19] and the Template for Intervention Description and Replication (TIDieR) checklists [20] were used to guide reporting in this protocol.

Recruitment

A total of 312 participants (LAS: n=156; CAI: n=156) will be recruited across 3 sites in the Military Health System (MHS), including the Naval Medical Center San Diego, California, the Naval Hospital Camp Pendleton, and the San Antonio Military Medical Center from November 2021 to approximately March 2023. Individuals who incurred a recent LAS and were assessed in the MHS will be identified using the electronic medical records and be contacted to discuss their interest in participation. Patients referred by primary care and specialty care clinics will be provided information on the study and an opportunity to participate. All treatments will be delivered in an outpatient physical therapy clinical setting.

Inclusion and Exclusion Criteria

Individuals aged 18-49 years will be recruited to participate. Inclusion in the LAS stratum will require the occurrence of a substantial first-time sprain up to 2-6 weeks prior to obtaining consent, which limits functional activity for at least 1 day. Participants must be able to walk community distances without an assistive device and with a score of ≤4 out of 10 reported on the numeric pain rating scale (NPRS). Inclusion in the CAI stratum requires a history of at least one significant sprain greater than 12 months prior to consent, continued perceived or episodic “giving way” of the ankle, and reported decreased function on the Foot and Ankle Ability Measure (FAAM) activities of daily living (ADL) subscale (score≤90), FAAM Sports subscale (score≤80), and Cumberland Ankle Instability Tool (CAIT; score<24) [21]. Individuals will be excluded if they have previously undergone ankle surgery, had joint realignment owing to fracture, had recent (within the last 3 months) injury to other lower-limb joints, have a diagnosed connective tissue disorder (eg, Marfan syndrome or Ehlers-Danlos syndrome), have a neuromuscular disease or balance impairment (eg, visual or vestibular disorder) that precludes standing or walking, are pregnant, have nonremovable casting, or are unable to walk at enrollment.

Ethical Considerations

The study protocol was approved by the institutional review boards at the Naval Medical Center San Diego, the Naval Health Research Center, and the US Army Regional Health Command-Central in compliance with all applicable Federal regulations governing the protection of human subjects. Research data were derived from an institutional review board–approved Naval Medical Center San Diego protocol (NMCSD.2020.0028). All participants will be required to provide informed consent prior to study enrollment. Recruitment of military service members will occur in the absence of supervisory staff to avoid any perceived coercion. Participants will also be free to withdraw at any time during the study. Because this study is being conducted within the MHS, all participants who decline to participate in this research will still be provided standard rehabilitation care.

Intervention

Overview

Once consented and enrolled, participants will be randomly assigned to either the experimental or control arm at each site using a concealed, random blocked sequence. Stratified randomization will be used to ensure an equal number of men and women are assigned to both the control and experimental groups in the LAS and CAI strata. Group allocation information will be concealed using a password-protected electronic form that will be opened by an uninvolved research staff member and communicated to the treating clinician. Both experimental and control groups will be provided standard rehabilitation care—treatment that is guided by the recent revision of the clinical practice guideline promulgated by the Academy of Orthopaedic Physical Therapy [16] on the basis of clinician experience and patient values.

Participants allocated to the experimental group will also be provided a complementary progressive treatment under the supervision of a licensed physical therapist, consisting of walking on a custom uneven-terrain treadmill (Woodway, Inc) (Figure 1) that simulates negotiation of rocky terrain (Multimedia Appendix 1) [22] for approximately 30 minutes, twice weekly, for a maximum of 12 treatments until discharge from rehabilitation. Treatment will be advanced through 3 phases of activities based on observed performance and the participant’s perceived difficulty and symptom response. Each phase will contain activities that are broadly grouped by the intensity of the proprioceptive stimulus and will be completed on the uneven treadmill. All treating physical therapists will adhere to a single training protocol to ensure standardized delivery of the uneven treadmill training across all the participating sites.

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Figure 1. The custom uneven-terrain treadmill. Participants allocated to the experimental treatment will be provided a progressive gait retraining program in addition to standard rehabilitation care.

Experimental Treatment Progression

Phase 0: Familiarization

Participants will begin a familiarization trial during which they will walk on the treadmill at a low velocity (≤1.34 m/s) set at a level grade for at least 5 minutes while wearing an ankle brace. Continued use of the handrails for balance and offloading the injured limb will be allowed during this phase. Criteria for progression will depend on the symptom response, patient confidence, and the observed ability to walk unassisted.

Phase 1: Unloaded Treadmill Walking

Walking velocity will be progressively increased, and the ankle brace will be weaned on the basis of the pain response and perceived instability. As the participant acclimates to the activity, task difficulty will be incrementally progressed by manipulating the walking velocity, grade, and duration in accordance with patients' perceived difficulty and performance observed by the treating clinician.

Phase 2: Unloaded Treadmill Walking With Head Movement and Visual Manipulation

Building on phase 1, the purpose of this phase is to encompass the integration of head movement, visual occlusion, and distraction. The following conditions will be integrated to increase task difficulty, as appropriate:

1. Low light condition: dark sunglasses (Sunglass Couture, Inc) will be used to reduce the amount of ambient light.
2. Foot obscurement: foot placement will be obscured with dribble glasses (Liberty Imports) that obstruct participants' view of the ground while carrying an inert training rifle (Ring's Manufacturing Inc).
3. Head turning: during the head turning activity, participants will be instructed to walk while turning their head right, left, upward, and downward.
4. Distracted walking: during the distracted walking activity, participants will walk while playing a handheld electronic game (Classic 5 In 1 Poker, John N. Hansen Co, Inc).

Phase 3: Return to Duty and Recreational Running Tasks

The criteria for progression to this phase are met when the participant begins the transition from walking to running activities and has a FAAM ADL subscale score of >90 and FAAM Sports subscale score of >80.

1. Load carriage: the integration of a 12-kg load carried in a backpack (SOG Specialty Knives & Tools) will be included in phase-1 and -2 activities.
2. Uneven trail running: integration of jogging (<2.78 m/s) and running (≥2.78 m/s) may be optionally performed in preparation for return to duty or recreational running.

Outcome Measures

A series of clinical, instrumented, and patient-reported outcome measures will be collected to characterize ankle-foot impairment, activity limitation, and participation restriction at baseline, during treatment, and longitudinally following treatment. Figure 2 shows the CONSORT flow diagram that details the study time points. The primary outcome of interest is improvement in patient-reported function on the FAAM. To help elucidate clinical improvement in function, we will assess if the intervention has shifted COP progression more medially during walking and if recurrence of subsequent ankle injuries has been reduced. Reinjury count data will be collected and assessed in both groups.

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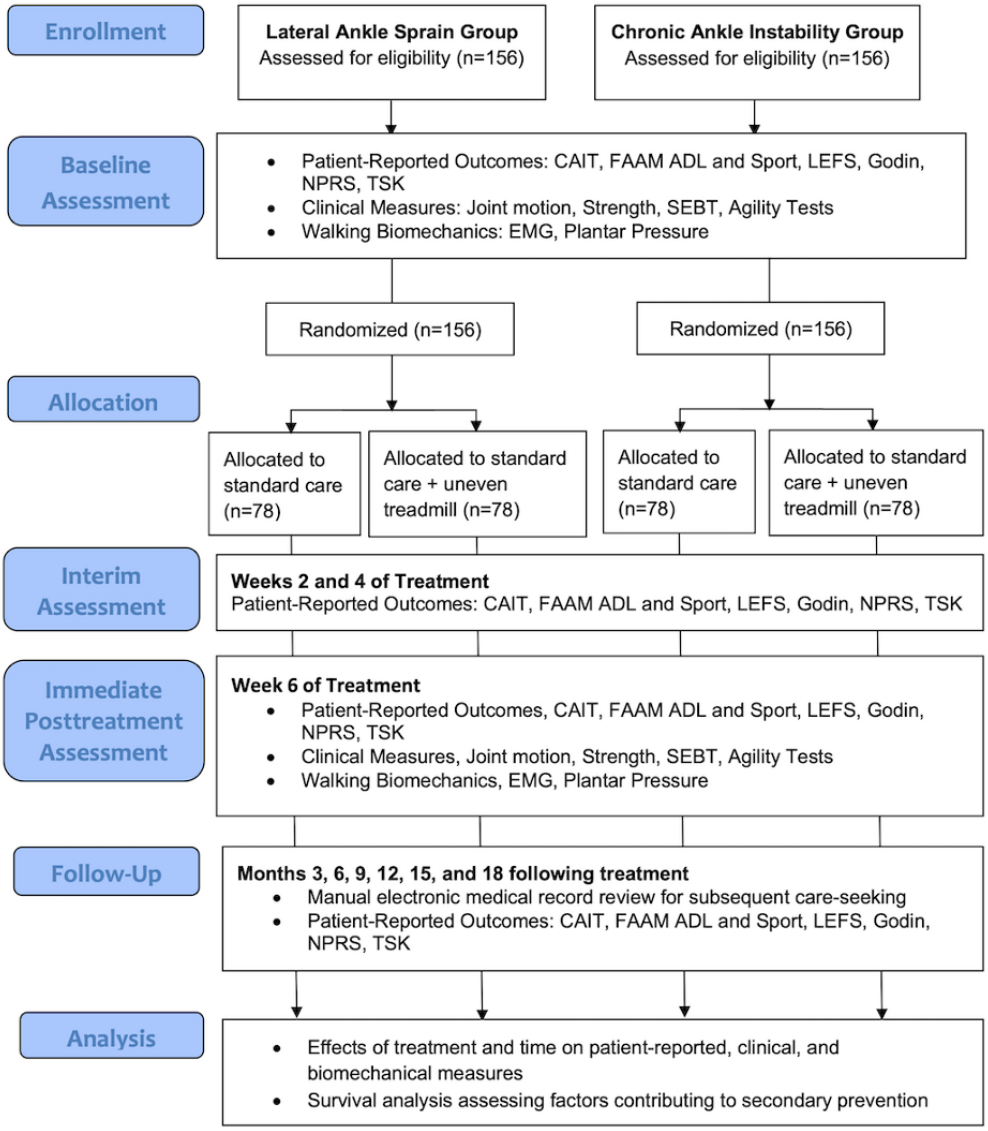
Figure 2. The CONSORT (Consolidated Standards of Reporting Trials) flow diagram. ADL: activities of daily living subscale, CAIT: Cumberland Ankle Instability Tool, EMG: electromyography, FAAM: Foot and Ankle Ability Measure, Godin: Godin-Shepard Leisure-Time Physical Activity Questionnaire, LEFS: Lower Extremity Functional Scale, NPRS: numeric pain rating scale, SEBT: Star Excursion Balance Test, TSK: Tampa Scale of Kinesiophobia.



Patient-Reported Outcomes

The CAIT [23] is a 9-question instrument examining ankle pain and feelings of instability. The FAAM ADL and Sports subscales [24,25] and the Lower Extremity Functional Scale [26] assess difficulties in performing a variety of tasks. The NPRS [27] and Tampa Scale of Kinesiophobia [28] will be used to assess the participants' pain and fear of movement due to the injury. Physical activity will be classified using the Godin-Shepard Leisure-Time Physical Activity Questionnaire [29] modified to record activity over the previous week rather than a typical week. These patient-reported outcomes will be recorded at all data collections (baseline, 2 interim sessions, discharge, and 6 postintervention follow-up assessments). Unstructured feedback requesting perceptions on participation in the uneven treadmill rehabilitation protocol will also be collected.

Clinical Measures

Clinical measures of ankle dorsiflexion (unloaded and loaded), plantarflexion, inversion, and eversion; forefoot on rearfoot inversion and eversion; and strength measures of dorsiflexion, plantarflexion, inversion, eversion, and hallux and lesser toe flexion will be performed, as described by Fraser et al [30]. The Star Excursion Balance Test evaluates dynamic balance and control by asking the patient to reach as far as possible along a measuring tape affixed to the floor in anterior, posteromedial, and posterolateral directions while maintaining balance on the supporting foot [31,32]. Failure to maintain balance, hands on the hips, or weight shift onto the reach limb will constitute a mistrial and will be repeated. Agility, speed, and power will be assessed using the side hop test [33], Edgren Side Step Test [34], and the T-test [34]. The side hop test records how many times a patient can hop back and forth on one limb over a distance of 30 cm in 30 seconds [33]. The Edgren Side Step Test has participants side-step back and forth over a 4-m course for 10 seconds [34]. The T-test measures the time to run 40 m

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multidirectionally over a T-shaped course [34]. Participants will be provided familiarization of the tests and practice trials prior to collection. Verbal encouragement will be provided during assessments.

Biomechanical Measures of Walking

Electromyography (EMG) and plantar pressures will be collected while walking on a standard treadmill at a self-selected velocity. Plantar pressure data will be recorded at 50 Hz using a Pedar-X shoe insole (Novel Electronics, Inc). EMG data (Trigno Avanti, Delsys Inc, and Noraxon DTS) will be recorded at 1500 Hz or greater bilaterally using Ag/AgCl electrodes affixed to 6 muscles (tibialis anterior, fibularis longus, lateral gastrocnemius, rectus femoris, biceps femoris, and the gluteus medius). Electrode placement will be performed as described by Weiss et al [35]. Visual inspection of the waveform during resisted contraction of each muscle will ensure cross talk is minimized. EMG data collected during walking will be processed by (1) using a fourth-order Butterworth filter for band-pass filtering between 20 Hz and 400 Hz, (2) rectifying the data, and (3) smoothing using a fourth-order Butterworth low-pass filter at 10 Hz and normalized to quiet standing. To compare walking EMG data between sessions, the amplitude will be normalized to the mean root mean square of processed EMG data collected during quiet standing for each muscle [36,37]. Gait cycles will be identified using a force-sensitive resistor located under the heel to detect heel strike. Data from at least 15 consecutive strides will be collected during steady-state walking.

Longitudinal Tracking of Reinjury

Injury count data derived following completion of the intervention will be employed to assess secondary preventive effects of the control and experimental treatments in the LAS and CAI strata. These follow-up data will be collected for 18 months. Both in-network and out-of-network medical care provided to service members will be captured by the MHS. Each recruiting site will conduct a chart review of the electronic medical record at the 6 posttreatment time points to assess for any additional medical care provided for ankle injuries in order to include physical therapy or surgical care. Participants will also be contacted directly to establish any secondary injury outcomes that were self-managed.

Blinding

Any research staff collecting data at any time point will be blinded to group assignment. Owing to the nature of the intervention, blinding of the participants or the clinicians providing the uneven-terrain treadmill rehabilitation intervention will not be feasible. Data analysis will be performed by researchers and statisticians blinded to group assignments.

Statistical Analysis

To assess whether the addition of the rocky treadmill intervention to standard-of-care physical therapy improves rehabilitation, 4 repeated measurements of several outcomes (eg, CAIT and FAAM) will be measured over the active intervention period of the study. The data will be analyzed using an analysis of covariance–type linear mixed-effects model with Group, Time, and Group×Time variables as fixed effects and subject-specific variables {intercepts, slopes} as random effects. The null hypotheses for both LAS and CAI populations are that the slopes of the control groups equal those of the treatment groups.

To identify predictors and mediators of successful or unsuccessful rehabilitation outcomes, a 2-level (hierarchical) Bayesian model will be used to connect participant-specific responses to 6 explanatory variables: {X1, . . . , X6} = {age, sex, body mass index, pain intensity, weight-bearing status, and initial injury severity} to the subject-specific variables {intercepts, slopes}. A directed acyclic graph detailing the results of the Bayesian linear model will be developed (Figure 3). The regression parameters from the hierarchical Bayesian model will be estimated using Bayesian inference with Gibbs Sampling software, which creates a Markov chain Monte Carlo simulation of all regression parameters.

To analyze the effect of the treatment on long-term reinjury rates between the 2 arms of the study, we will fit both logistic regression–type generalized linear mixed-effects (GLME) models to the data as well as Cox regression time-to-event models. The data that will be used in the analysis will be those obtained at baseline and during the postintervention period. In the GLME analysis, the response data will be (1) the self-reported survey instrument measure from the Patient-Reported Outcomes Measurement Information System and (2) the binary reinjury report (1/0). The GLME model will have Group, Time, and Group×Time as fixed effects and will use subject-specific variables {intercepts, slopes} as random effects. The null hypothesis of the GLME model is that the regression parameters associated with the Group and Group×Time effects are zero. In the Cox regression analysis, the response will be the time of suspension or the event along with a binary indicator of reinjury status, and the covariate will be Group. The null hypothesis of the Cox regression analysis is that the regression parameter associated with Group is equal to zero. In all analyses, a Bonferroni-type correction to the hypothesis test's P values or α levels will be used to account for multiple testing.

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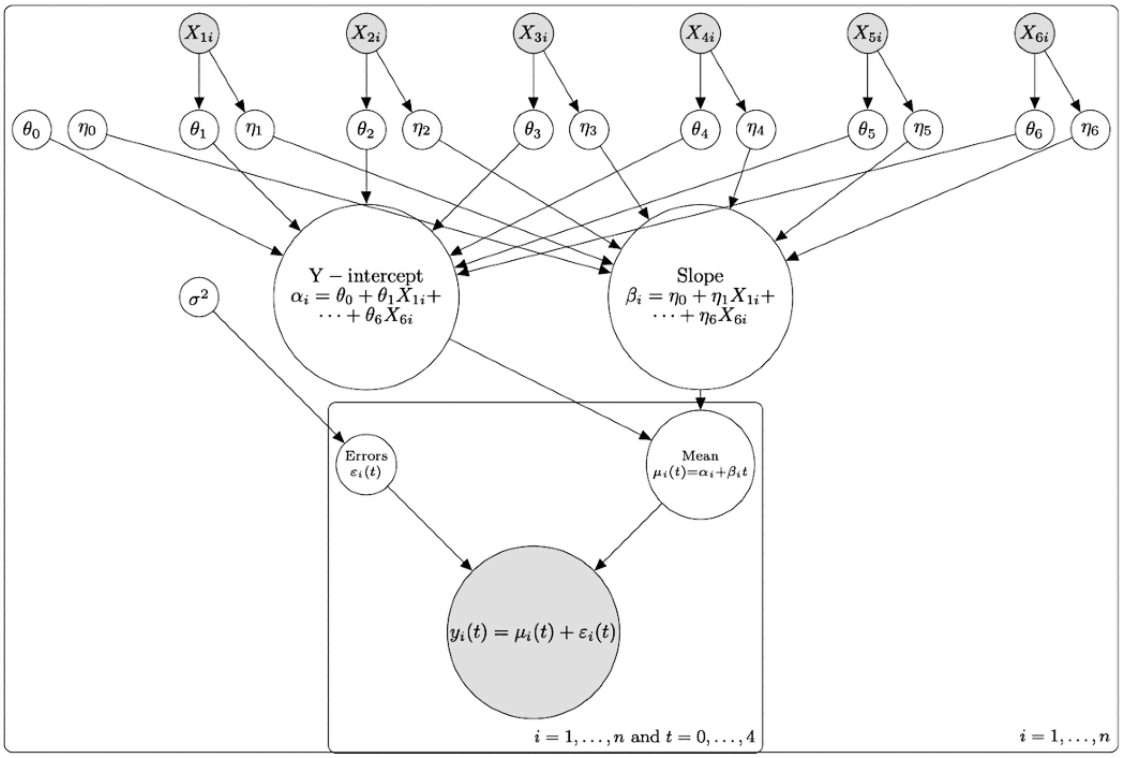
Figure 3. The direct acyclic graph of the Bayesian model acts like a causal diagram. In the model, the explanatory variables {X1, . . . , X6}: age, sex, BMI, pain intensity, weight-bearing status, and initial injury severity. These variables causally affect the subject-specific slopes and the y-intercepts. However, the slopes and y-intercepts of the responses are not directly observed, so they are considered latent variables. In the diagram, the shaded circles are directly observed variables, and the unshaded circles are latent variables. The Bayesian model has 2 levels of hierarchy: the first one establishes the best fit line that goes through the observed subject responses; the second one establishes how the explanatory variables {X1, . . . , X6} affect the slopes and y-intercepts. The regression parameters $\{\eta_0, \ldots, \eta_6\}$ are those that affect the slope of the subject responses and, as such, are particularly important because they affect the healing rate. Variables that significantly affect the healing rate will be retained in the model if the credible intervals for the regression parameters $\{\eta_0, \ldots, \eta_6\}$ do not include 0.



Power and Sample Size

The estimated sample to identify a minimum difference of 1 point in the FAAM between treatment groups across 4 time points in the intervention period was 17 participants per group for an estimated power of 90% and an α value of .05. To measure the effect of the long-term binary reinjury rates with 6 time points in a GLME model, a sample of 62 participants per group provided 80% power, assuming a 10% difference in the proportion between the treatment groups and similar trends between groups. Assuming a 20% rate of dropout throughout long-term follow-up, the required sample size is 78 participants per group. Between the 2 injury types (LAS and CAI), a total of 312 participants will be recruited for this study across the multiple sites.

Results

Data collection began in fall 2021. Dissemination of the main study findings is targeted for 2024.

Discussion

This pragmatic randomized controlled trial will assess the clinical effects of an innovative uneven-terrain treadmill in the rehabilitation of patients with LAS and CAI. We hypothesize that service members receiving uneven treadmill training will demonstrate greater improvements in clinical and instrumented measures of impairment, patient-reported function, and lower risk of injury recurrence than the control group immediately post and 18 months following treatment.

Integration of an ecologically valid activity that replicates negotiation of uneven, rocky ground commonly encountered by the military population may facilitate adaptive improvements in sensorimotor function and a return to occupation and recreational activities and may help prevent secondary injuries. Uneven-terrain treadmills present the opportunity to progressively increase the rehabilitation stimuli by incorporating tasks essential to military performance, including walking with a weapon (which obstructs the downward view of foot placement) and load carriage (which has been shown to reduce dynamic stability) [38]. Uneven-terrain treadmills also offer a relatively low-cost platform for progressive proprioceptive training, simulating real-world terrain that challenges ankle stability. The pragmatic nature of this study ensures that standard-of-care treatment is based on the specific needs of the individual patient and is consistent with the principles of evidence-based practice. This also allows for patients assigned to the intervention group to progress to more challenging rehabilitation activities on the uneven treadmill based on incremental improvements in observed findings and patient response to treatment. While a limitation to this approach is the potential for differential bias in treatment dosage, a variable that will be considered and controlled for during analysis, we view this approach to be especially salient in the evaluation of

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clinical effectiveness of the experimental intervention that will improve the external validity of our findings.

This clinical trial will help determine if incorporation of graded exposure on an uneven treadmill during standard rehabilitation care will lead to greater improvement in function and secondary preventive effects compared with standard rehabilitation care alone in service members with LAS or CAI up to 18 months following treatment. The incorporated patient-reported pain, kinesiophobia, physical activity, and ankle function, along with clinical and biomechanical measures, will help elucidate the clinical effectiveness of incorporation of uneven treadmill training on near- and long-term function, reinjury rates, and factors that may drive treatment outcomes. Findings from this work have the potential to directly impact the care of service members, veterans, and the broader civilian community with LAS and CAI. The findings of this study will be used to generate knowledge products that will include reports, clinician and patient education materials, and presentations that will be provided to MHS clinicians, leaders, and policy makers. In addition, the findings of this study will be promulgated as peer-reviewed conference abstracts and journal manuscript submissions.

Acknowledgments

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Data Availability

The data sets generated during and analyzed in this study are available from the corresponding author (JJF) on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental video [22]. Reused under CC0 license.
[MOV File , 103590 KB - resprot_v11i6e38442_app1.mov]

Multimedia Appendix 2
Peer-review report by the U.S. Army Medical Research and Development Command - Congressionally Directed Medical Research Programs - Fiscal Year 2019 Peer Reviewed Orthopaedic Research Program - Clinical Trial Award - Funding Level 1 - Office of the Assistant Secretary of Defense for Health Affairs.
[PDF File (Adobe PDF File), 806 KB - resprot_v11i6e38442_app2.pdf]

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Abbreviations

ADL: activities of daily living
CAI: chronic ankle instability
CAIT: Cumberland Ankle Instability Tool
CONSORT: Consolidated Standards of Reporting Trials
COP: center of pressure
EMG: electromyography
FAAM: Foot and Ankle Ability Measure
GLME: generalized linear mixed-effects
LAS: lateral ankle sprain
MHS: Military Health System
NPRS: numeric pain rating scale
PRECIS-2: PRagmatic Explanatory Continuum Indicator Summary
SEBT: Star Excursion Balance Test
TIDieR: Template for Intervention Description and Replication

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Protocol

A Telehealth Diabetes Intervention for Rural Populations: Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetes self-management education and support (DSMES) is a crucial component of diabetes care associated with improved clinical, psychosocial, and behavioral outcomes. The American Association of Diabetes Care and Education Specialists, the American Diabetes Association, and the American Academy of Family Physicians all recommend DSMES yet accessing linguistically and culturally appropriate DSMES is challenging in rural areas. The Diabetes One-Day (D1D) program is an established DSMES group intervention that has not been adapted or evaluated in rural communities.

Objective: The specific aims of this paper are (1) to adapt the existing D1D program for use in rural communities, called rural D1D (R-D1D); and (2) to conduct a patient-level randomized controlled trial to examine the effects of R-D1D and standard patient education, guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework.

Methods: This is a protocol for a pilot type II hybrid implementation-effectiveness trial of a culturally adapted virtual DSMES program for rural populations, R-D1D. We will use Boot Camp Translation, a process grounded in the principles of community-based participatory research, to adapt an existing DSMES program for rural populations, in both English and Spanish. Participants at 2 rural primary care clinics (4 cohorts of N=16 plus care partners, 2 in English and 2 in Spanish) will be randomized to the intervention or standard education control. The evaluation is guided by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework. Patient-level effectiveness outcomes (hemoglobin A_{1c}, diabetes distress, and diabetes self-care behaviors) will be assessed using patient-reported outcomes measures and a home A_{1c} test kit. Practice-level and patient-level acceptability and feasibility will be assessed using surveys and interviews.

Results: This study is supported by the National Institute of Nursing. The study procedures were approved, and the adaptation processes have been completed. Recruitment and enrollment started in July 2021.

Conclusions: To our knowledge, this will be the first study to evaluate both effectiveness and implementation outcomes for virtually delivered DSMES, culturally adapted for rural populations. This research has implications for delivery to other rural locations where access to specialty diabetes care is limited.

Trial Registration: ClinicalTrials.gov NCT04600622; https://clinicaltrials.gov/ct2/show/NCT04600622

International Registered Report Identifier (IRRID): DERR1-10.2196/34255

(JMIR Res Protoc 2022;11(6):e34255) doi:10.2196/34255

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KEYWORDS

diabetes; rural; telehealth; implementation science; community-based participatory research; Spanish; implementation; community; participatory; protocol; randomized controlled trial; intervention; adapt; framework

Introduction

Diabetes and Rural Populations

Diabetes mellitus is a chronic, progressive disease affecting 30.3 million people in the United States [1]. In addition to being the 7th leading cause of death in the United States, diabetes contributes to serious microvascular and macrovascular complications [1]. Diabetes self-management is the cornerstone to avoiding or delaying diabetes complications, and ongoing self-management is necessary. Self-management behaviors involve an often-challenging daily diet, medication, exercise, and glucose monitoring regimen, among others, and is complicated by social determinants of health (eg, transportation and access to high-quality care). Diabetes self-management education and support (DSMES) is a crucial component of diabetes care that provides the foundation necessary to self-manage diabetes. The American Association of Diabetes Care and Education Specialists, the American Diabetes Association, and the American Academy of Family Physicians all recommend DSMES [2]. DSMES can improve outcomes in both type 1 (T1D) and type 2 diabetes (T2D), including improving hemoglobin A_{1c}, quality of life, diabetes distress, and healthy coping [3-6]. However, there is variation in how DSMES interventions are structured, in terms of both content and delivery, and as such, some DSMES programs may be more acceptable, feasible, and effective than others [7].

Approximately 50% of adults with T1D [8] and 90% of adults with T2D in the United States are managed in primary care settings and not in endocrinology specialty practice offices [9], and therefore often lack access to services such as DSMES. Strikingly, 75% of counties in the United States have no endocrinologists at all, while primary care can be found in 96% of US counties [10]. Especially in rural areas, many people with diabetes receive their diabetes care at primary care practices and may have to travel long distances to access DSMES when not available in their medical home. When DSMES is available, there can be a lack of fit between the curriculum, materials, or mode of delivery and the resources of rural primary care practices and communities, including a lack of staff and lack of information tailored to the resources and culture in rural communities. There is a clear need for DSMES interventions, feasible for delivery in rural settings, that can address the unique social determinants of health and cultural adaptations appropriate for people with diabetes living in rural communities.

The 2017 National Standards for DSMES recommend a multidisciplinary team delivering DSMES, a curriculum reflecting current evidence and practice guidelines, individualized plans, and sources for ongoing support [11]. Personalizing care via DSMES is critical because it allows individuals to identify how to incorporate self-management into their own daily life [12,13]. While individual DSMES may be better suited for personalized approaches to care, group sessions can be more cost-effective than individual sessions [14] and offer opportunities for peer support. However, when sessions are held over several weeks, it can be challenging for individuals to complete leading to attrition [15]. A systematic review of 118 unique DSMES interventions found that patients who receive group and individual DSMES sessions, from multidisciplinary teams, are the most effective at reducing A_{1c} [15]. Interventions that address the need for group and personalized care can reduce disparities in rural populations. This study will address current gaps in rural diabetes care research and a widely recognized need to enhance access to DSMES among rural populations.

National data indicate that diabetes prevalence is higher in rural areas. Rural-dwelling adults are 17% more likely to have diabetes than their urban counterparts nationally [16]. For instance, the rates of diabetes in rural eastern Colorado average 12.3% compared to the state average of 7.3% [17]. Rural populations have limited access to DSMES, and health care access is more limited in rural areas, impeded with long travel distances, as well as higher rates of poverty than those individuals in urban settings [14]. These challenges contribute to a greater risk of suboptimal diabetes management and higher rates of diabetes-related complications [18]. The Diabetes One-Day (D1D) intervention is a condensed, one-day group DSMES session delivered via telehealth by a multidisciplinary team at a diabetes and endocrinology center. Patients are encouraged to invite a care partner (family member or friend) to attend D1D given that diabetes is managed in a social context. D1D was designed to address DSMES access challenges seen with multiple-day DSMES interventions. Evidence suggests that the D1D intervention is effective for improving diabetes self-management outcomes [19,20] and is a promising intervention to address specialty care access challenges seen in rural communities. Further consideration of cultural and social adaptations to D1D (ie, a Rural D1D [R-D1D] program) is needed to ensure fit for rural communities, especially those where English and Spanish are the primary languages spoken. We describe our protocol for adapting D1D for rural primary care and implementing, evaluating, and refining the resulting R-D1D intervention.

Intervention Logic Model

The logic model for this project (Figure 1) depicts the process by which the D1D intervention (Box A) is adapted, implemented, and refined for rural settings (R-D1D, Box B), to promote the successful adoption and implementation by rural practices and reach to patients in the target audience (Box C). Once adopted and implemented, a future study will assess effectiveness for patient-reported and clinical outcomes at the patient level and maintenance at the practice level (Box D). That is, to achieve impact on patient-level outcomes and to be sustainable for practices, the intervention must be acceptable, appropriate, and feasible for delivery in rural primary care, be implemented well, and reach target populations. The intermediate outcomes and impact outcomes align with the

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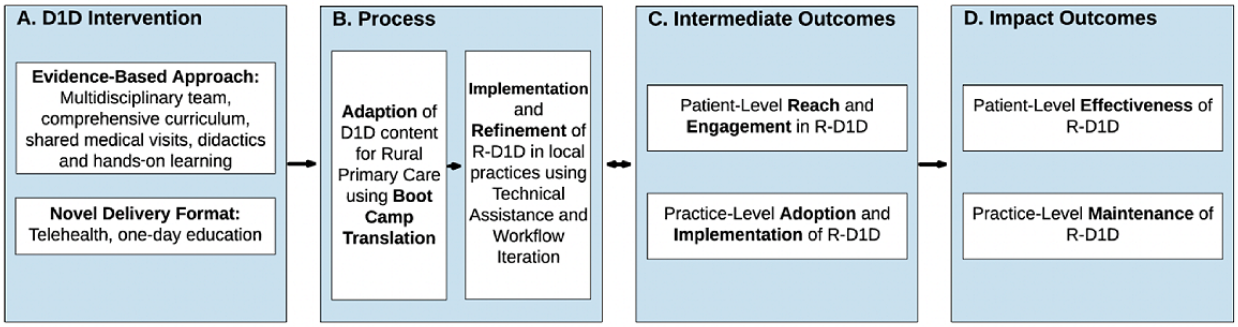
Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, a well-established framework for program planning and evaluation [21].

Figure 1. Intervention logic model. D1D: Diabetes One-Day; R-D1D: Rural Diabetes One-Day.



Aims and Hypothesis

The coprimary aim of this study is to adapt the existing D1D program for use in rural communities (R-D1D). Boot Camp Translation (BCT) [22,23] will be used to partner with diverse community members, including members from Spanish-speaking communities, to adapt diabetes self-management language and tools and delivery of D1D into a culturally relevant R-D1D for rural primary care practices, patients, and care partners.

The secondary coprimary aim is to conduct a patient-level pilot randomized controlled trial (RCT) to examine the effects of R-D1D (intervention group) vs standard patient education (attention control group), guided by the RE-AIM framework. We will implement and refine the R-D1D intervention, evaluate implementation at the practice level, and evaluate reach and effectiveness at the patient level.

Methods

Design

This study will use the BCT method to adapt the medical information, guidelines, and materials in the current D1D intervention for use with English-speaking and Spanish-speaking people living in rural eastern Colorado (R-D1D). Then, using a 1:1 type 2 hybrid trial, we will conduct a pilot test in 64 total patients from 2 practices to compare R-D1D to a standard education control. Acceptability and feasibility of R-D1D will be assessed at the patient and practice levels.

Setting

This project will take place in the High Plains Research Network, a practice-based research network of 53 primary care practices, hospitals, and communities in a 16-county region of rural eastern Colorado. Two High Plains Research Network primary care clinics will be included. To participate, clinical practices must be willing to identify and refer potential English-speaking and Spanish-speaking participants with T1D or T2D to the research team at the University of Colorado for eligibility screening and informed consent.

Sample and Recruitment

Provider and Staff

Practice providers and staff participants will be individuals (N=3 per clinic) who work at 1 of the 2 rural clinics where R-D1D will take place. A sample of providers and staff will be asked in person, by phone, or by email to participate in key informant interviews.

Patient and Care Partner

English-speaking and Spanish-speaking adults with T1D and T2D living in the proposed study region (N=64) and care partners in the intervention group (up to N=16) will be eligible for participation. We will use both community recruitment in venues identified during the BCT, as well as work with each of the 2 participating practices to help identify patients with diabetes who will then be randomized to either the intervention or attention control arm. They will be recruited using strategies recommended by the BCT participants, building upon successful recruitment strategies used in past projects. For instance, practices will distribute recruitment materials with messages created by the community-academic partnership through BCT and design elements selected by the community. This sample size is appropriate for iterating the intervention.

Eligibility Criteria

Provider and Staff

Participants will be eligible if they work at the rural clinic where R-D1D will take place and if they were involved with the planning or coordination of R-D1D or were a provider who had a patient participate in the R-D1D intervention. Possible participants could include physician, nurse, medical assistant, front desk support, and clinic administrator. There are no exclusion criteria for providers and staff.

Patient Participant

Participants will be eligible for inclusion if they (1) have a known diagnosis of T1D or T2D with any A_{1c} level; (2) are ≥18 years old; (3) live in a rural eastern Colorado; (4) speak and understand English or Spanish; and (5) are willing to participate in a telehealth intervention at home through Health Insurance Portability and Accountability Act (HIPAA)-compliant Zoom. Participants will be excluded if they (1) are participating in

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another diabetes study; (2) have significant cognitive impairment; (3) are pregnant or planning to become pregnant in the next year (as diabetes management recommendations are different in pregnancy); (4) have life expectancy of <6 months; or (5) plan to move during the time of the study.

Care Partner

Care partner participants will be eligible if they are (1) identified by the patient participant who randomized to the R-D1D intervention group; (2) are 18 years or older; (3) speak and understand English or Spanish; and (4) are willing to participate in a telehealth intervention with the patient participant. Care partners will not be directly recruited.

Group Randomization

R-D1D will be delivered to patients who receive diabetes care at 2 practices, once in English and once in Spanish at each practice. Thus, each site will have a total of N=32 persons with disability split into 4 groups (8 English control, 8 English R-D1D, 8 Spanish control, and 8 Spanish R-D1D). For each site and language, the participants will be randomized using alternating blocks of 2 and 4.

Existing D1D Intervention

The intervention is the adapted R-D1D from the existing D1D program. D1D was designed for adults with T1D and T2D and is delivered using a hybrid model that includes in-person small-group and individual DSMES sessions. D1D is delivered by an interdisciplinary faculty specializing in diabetes care, including a nurse practitioner, certified diabetes care and education specialist, pharmacist, exercise specialist, ophthalmology technician, chef, licensed clinical social worker, endocrinologist, and obesity medicine physician. The topics included pathophysiology, complications, screenings, laboratories, medication options, weight management, the importance of exercise, healthy eating, troubleshooting glucose levels, diabetes technology, and healthy coping with diabetes. A healthy breakfast, interactive lunch with a chef demonstration, and snacks were also provided (Multimedia Appendix 1). An emphasis on participants providing education and support to others in the group sessions was encouraged. The participants received written and digital educational materials, recipes, a copy of the Calorie King Book, and resistance bands.

We anticipate R-D1D adaptations may focus on healthy eating based on food available in rural communities, stigma surrounding mental health in rural communities as it relates to diabetes management, and program structure and timing.

Adapted R-D1D Intervention

R-D1D will be delivered by an interdisciplinary team of health care professionals specifically trained in the D1D program, including a nurse practitioner, physician, registered dietitian, certified diabetes care and education specialist, pharmacist, and a licensed clinical social worker. The R-D1D program will be delivered by telehealth by members of the original D1D team. An overview of the D1D curriculum that will be adapted is detailed in Multimedia Appendix 1.

Intervention group participants will meet with study staff to assess the participant's technology literacy, test the participant's internet connection and chosen electronic device, and provide instruction and demonstration for connecting to the videoconference platform. More than 1 meeting may be required. These meetings will be held via the same platform used for R-D1D intervention to allow the opportunity to troubleshoot directly with the participant.

Control Group

The control group will receive a standard patient education handout that covers the ADCES7 self-care behaviors (healthy coping, healthy eating, being active, monitoring, taking medication, problem solving, and reducing risks) [24].

Implementation Strategies

Implementation strategies refer to "methods or techniques used to enhance the adoption, implementation, and sustainability of a clinical program or practice" [25]. For this study, we will use several implementation strategies [26], including the following: (1) BCT to adapt and tailor D1D for the rural setting; and (2) technical assistance and workflow design. Grounded in the principles of community-based participatory research, BCT is a process used by partnerships of community members and academic researchers to translate medical information and guidelines into concepts and messages that partnerships believe will be relevant and actionable to local communities [27-30]. Partnerships develop materials and dissemination strategies that use and reflect local culture and assets to effectively move messages and materials to the desired audience. In the traditional BCT, community-academic partnerships are guided by the questions, "What is the message to our community?" and "How do we effectively share these messages with the community?" [31]. The process relies on the community members' and researchers' unique expertise, experiences, and perspectives. For this study, a modified BCT process will be used to adapt the existing D1D program for use in rural communities and primary care practices. Telehealth technical assistance will be provided by the community research liaisons or practice facilitators as needed.

Outcomes and Measures

The outcomes for this study are informed by the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework [32]. We will use multiple methods (qualitative and quantitative) to assess select RE-AIM domains. Reach and Effectiveness are both patient-level outcomes. Reach refers to the number and percent of eligible patients who participate in the intervention, characteristics of those who participate and complete the measures, and reasons for not participating. Effectiveness refers to clinical and behavioral patient-level outcomes. Adoption, Implementation, and Maintenance are practice-level outcomes (maintenance can also refer to patient-level maintenance of health outcomes over time). Adoption refers to the number, percent, and characteristics of clinical practices who were invited to offer the intervention to their patients who participate in the study. Implementation refers to consistency of delivery of the intervention as intended (ie, fidelity), as well as practice perceptions of the acceptability, appropriateness, and feasibility of delivering the intervention in their clinical practice setting [33]. Maintenance refers to

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sustained effects on patient outcomes over time and to continued intervention delivery within the clinical setting beyond the study period, which will be explored in a future study.

Practice-Level Adoption, Implementation, and Maintenance

We will conduct baseline practice characteristics surveys, practice culture surveys, and individual semistructured interviews with 3 providers or staff at each practice (N=6) to assess practice characteristics and context, perceived value and fit with practice goals and priorities, feasibility (including resources required and perceived burden), and sustainability (including factors influencing interest in continuing to offer R-D1D when available). We will also administer valid, reliable surveys on perceived R-D1D intervention acceptability, feasibility, and appropriateness using the scales developed by Weiner et al [33]. Interviews and surveys will be conducted after each cohort is delivered.

Patient-Level Reach

We will capture data on R-D1D attendance, percent of R-D1D sessions attended, R-D1D program satisfaction, and patient reasons for participating and not participating.

Patient-Level Effectiveness

For both intervention and control patients, patient-reported outcome measures will include psychosocial (diabetes distress measured via Problem Areas in Diabetes scale [34,35] and Family and Friend Involvement in Adults' Diabetes [36]), and behavioral (measured via Self-Care Inventory Revised [37]). Patient-level clinical outcome measures will include A_{1c}, blood pressure, and BMI. A_{1c} will be obtained by home kit. These data will be collected at baseline and 3-month follow-up.

Plans to Promote Participant Retention and Complete Follow-up

R-D1D is designed to be completed in 1 day. Study staff will encourage patient participants to participate in the study activities (intervention, follow-up surveys, and interviews) through phone calls, text messages, and email reminders.

Data Management and Ethics Approval

Data use agreements among participating organizations have been established. The study procedures were approved by the University of Utah Multiple Institutional Review Board on October 28, 2020 (IRB_00133179).

Statistical Methods and Analyses

Quantitative Analysis for RCT

Evaluating Reach will include description of the characteristics of those enrolled and screened ineligible and provide preliminary data on recruitment and retention capabilities for future studies. Quantitative metrics for recruitment and retention rates will inform population point estimates and 95% confidence intervals. For example, a 70% retention of 64 participants leads to a point estimate and CI of 70% (SD 6).

Descriptive statistics will be used to summarize R-D1D reach, adoption, and implementation at the participant and practice level. Special attention will be used to stratify outcome measures based on diabetes type, gender, and clinic site. For quantitative measures on feasibility, appropriateness, and acceptability, we will use the validated scales by Weiner et al [33]. Each of the 3 domains is composed of 4 Likert-scale questions (Completely Disagree 1 to Completely Agree 5). Our benchmarks for success will be to obtain domain means of 4 or greater.

Patient Level Effectiveness Analysis

Descriptive statistics will be used for intervention and control groups at baseline and 3 months stratified by language including outcomes from (1) surveys assessing diabetes distress as measured by the Problem Areas in Diabetes (PAID) scale and behavioral diabetes self-care as measured by the Self Care Inventory-Revised Version (SCI-R); and (2) clinical measures including A_{1c}, blood pressure, and BMI. We will estimate population standard deviations so as to determine the sample size needed for a fully powered study to test for clinically meaningful improvements in outcomes [38,39]. Exploratory mixed-effects models using maximum likelihood estimation will be used to examine change between baseline and 3 months comparing intervention and control groups. This analysis is in keeping with an intent-to-treat standard and allows the use of all available data for analyses regardless of missing data. Combined, the results from this study will provide an initial indication of patient-level effectiveness as a clinically meaningful treatment effect in preparation for a larger effectiveness trial.

Missing Data

Missing Values Analysis tools will be used to describe if there are patterns to missing data. However, for the mixed models with random effects and maximum likelihood, it is not necessary to eliminate observations from participants who subsequently drop out, nor is it necessary to impute individual observations. To minimize loss of scale scores due to missing items in a computed scale such as PAID and SCI-R, we will prorate the respondents' score based on their answered items. If a respondent is missing more than 30% of the items in a computed score, we will code the scale score as missing, thereby ensuring psychometric validity.

Qualitative Analysis

Qualitative descriptive analysis will be used to evaluate practice provider and staff interviews. Audio-recorded interviews with participants and practice providers or staff will be transcribed. Using standard qualitative content analysis, all investigators will review data, codes, and categories. Matrices will be used to organize codes by demographic variables (diabetes type, gender, and clinic site), patient reach, and practice-level adoption and implementation. Overarching themes will then be developed. Qualitative and quantitative data will then be triangulated to assess the R-D1D intervention.

Data Monitoring

The study team has developed data collection protocols to ensure maximum compliance and protection of informed consent documents, surveys, personal health information, and audio-recorded sessions (for interviews). The participants will

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complete electronic surveys via a weblink to REDCap (Research Electronic Data Capture), a HIPAA-compliant web-based application hosted at the University of Utah Center for Clinical and Translational Science, which will securely store and protect data. No names will appear on the surveys; however, the survey data will be linked to a practice location using an identification number. Survey data will be confidential and will only be used by the study team.

Interviews with practice staff will be conducted by the research team and will be recorded and transcribed with the respondent's permission. No protected health information will be collected from the interviews, and all data will be de-identified. All audio files from the interviews will be stored on a secure server maintained by the University of Utah College of Nursing information technology team, and only the study team will have access to the data.

Data collected from the medical chart (ie, A_{1c}, blood pressure, and BMI) or by phone (if participants are unable to complete electronic surveys) will be hand-entered by trained practice facilitators. Audio recordings of the participant interviews will be stored securely in a shared file system that only the study team will have access to. This file system will be backed up continuously and protected by the University of Utah firewalls.

A_{1c} data will be collected using home A_{1c} kits, which require 4 drops of blood (similar to checking a glucose level). The participants will mail the A_{1c} kits directly to the laboratory and will be tracked with a tracking number to ensure privacy and will allow the study team to link the data to the participant once the A_{1c} has been processed.

Harms

Risk of harm to participants (patient, practice, and staff) is minimal. Should any harm occur, it will be reported to all involved institutional review boards and the data safety monitoring team in accordance with institutional and federal policies.

Results

We completed BCT [40] and have begun recruiting participants for the RCT component of the study. This study is expected to conclude in July 2022.

Discussion

R-D1D will be developed in collaboration with patients with diabetes and other community members living in rural communities, providers and staff from participating practices, and academic clinician-researchers and their research teams.

While rural residents are burdened by higher rates of diabetes compared to their urban counterparts, it is difficult to access diabetes specialty care in rural areas. There is a critical need to test interventions to address diabetes health disparities in rural areas, in partnership with primary care practices, where the majority of people with diabetes receive their diabetes care in these areas. This study will adapt the D1D program, an effective, time-efficient diabetes self-management education and support program for adults with diabetes at University of Utah, for delivery in English and Spanish to rural residents of Eastern Colorado. Feasibility and acceptance will be evaluated. If successful, this project has potential for improving diabetes care nationally, not just for the residents of Colorado.

This project can provide valuable information on a program of research that is innovative and timely and has the potential to impact the delivery of diabetes specialty care in Spanish and English for rural regions beyond Colorado.

Acknowledgments

We would like to acknowledge the High Plains Research Network Community Advisory Council.

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Authors' Contributions

MLL and TKO conceptualized the study; LZ established the Boot Camp Translation processes; BMK and EI established Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) analytic processes; GL established technology processes; JS supported processes related to Spanish-speaking populations; and KC and JN supported program management at 2 sites. All authors reviewed, edited, and approved the final manuscript.

Conflicts of Interest

MLL received investigator-initiated trial funding from Abbott Diabetes Care and is on the DiabetesWise Professional Advisory Committee unrelated to this study. TKO serves as a consultant to Dexcom, Cecilia Health, and DiabetesWise Professional Advisory Committee unrelated to this study.

Multimedia Appendix 1
Comparison of the existing D1D (Diabetes One-Day) intervention and the adapted R-D1D (Rural Diabetes One-Day) intervention.
[PNG File , 218 KB - resprot_v11i6e34255_app1.png]

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Abbreviations

BCT: Boot Camp Translation
D1D: Diabetes One-Day
DSMES: diabetes self-management education and support
HIPAA: Health Insurance Portability and Accountability Act
PAID: Problem Areas in Diabetes
R-D1D: Rural Diabetes One-Day

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RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SCI-R: Self-Care Inventory-Revised Version
T1D: type 1 diabetes
T2D: type 2 diabetes

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Protocol

A Multiprofessional and Intersectoral Working Model to Detect and Support Preschool Children With Neurodevelopmental Difficulties (PLUSS Model): Protocol for an Evaluation Study

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Abstract

Background: Neurodevelopmental difficulties with various emotional and behavioral symptoms increase the risk of mental health problems later in life. Although we know that early detection and interventions are effective, there is a lack of intersectoral, integrative, and evidence-based working models to provide these services for preschool children and their parents. PLUSS (*Psykisk hälsa Lärande Utveckling Samverkan kring Små barn*; English translation: mental health, learning, development, collaboration around preschool children) is a collaborative "one way in" model involving parents, health care providers, preschools, social services, and researchers. PLUSS provides coordinated services to screen, evaluate, and support toddlers with neurodevelopmental problems. It also offers parental interventions and education for preschool teachers.

Objective: The model will be studied in a research project that aims to investigate (1) using a quasi-experimental study on longitudinal trajectories of neurodevelopmental difficulties and ability to function among participating preschoolers, (2) user satisfaction, and (3) implementation of the model and its effectiveness. The long-term goal is to provide evidence-based, coordinated services to reduce problems related to neurodevelopmental difficulties among preschool children and promote well-being and functioning in everyday life.

Methods: The population of interest is children aged 1.5-5 years, whom the child health care nurse refers for further assessment due to suspected neurodevelopmental problems. Data are collected using questionnaires and semistructured interviews. Measures include sociodemographic data, longitudinal data on neurodevelopmental problems, parental well-being and satisfaction, the effectiveness of parental and preschool teacher training and implementation of the model, and fostered multisectoral collaborations. Data will be analyzed with qualitative and quantitative methods.

Results: The PLUSS model has been approved by the National Ethics Review Board (2019–04839). This study was supported by FUTURUM grants 910161 and 910441. Data collection started in April 2019, with the data collection period planned to end in May 2024.

Conclusions: PLUSS is an integrative working model with multiprofessional competence and intersectoral collaboration capacity to help preschool children with neurodevelopmental problems and their parents. It will be studied using quasi-experimental cross-sectional and longitudinal study designs. Data will be collected from parents, health care providers, and preschool teachers, and will be analyzed using quantitative and qualitative methods. The study will run in one Swedish county, and generalizability needs to be studied separately. Loss of follow-up could impact the longitudinal analysis.

Trial Registration: ClinicalTrials.gov NCT04815889; https://clinicaltrials.gov/ct2/show/NCT04815889

International Registered Report Identifier (IRRID): DERR1-10.2196/34969

(JMIR Res Protoc 2022;11(6):e34969) doi:10.2196/34969

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KEYWORDS

early detection; early intervention; preschool children; multiprofessional; neurodevelopmental difficulties; parental support; preschool support; mental health; neurological; behavioural; emotional; paediatrics; pediatrics; parenting; children; neurodevelopmental; developmental

Introduction

Background

Neurodevelopmental problems among preschool children are common, with an estimated 7%-10% prevalence [1]. Early-onset externalizing or internalizing problems predict the later development of mental health problems, corresponding to or overlapping with the initial symptoms [1,2]. The earlier behavioral problems occur in a child's life, the greater the risk [3,4].

Early identification of children with neurodevelopmental problems is crucial for providing adequate support [1,5]. Despite this knowledge, several Swedish reports have highlighted a dire need for research into the mental health of children of preschool age [6-8]. For example, data on the current prevalence of significant neurodevelopmental problems among Swedish children aged 0-5 years are missing. Inherent to this is how many of these children have been offered and are receiving any kind of intervention. In addition, studies on longitudinal trajectories of problems and provided services are scarce.

In Sweden, child health care is responsible for the early detection and follow-up of developmental problems among preschool children [9]. Swedish child health care has a well-established screening program that reaches 95% of all preschool children [10]. In addition, preschools serve as an environment where children's problems can be identified, promoting good mental health [11]. Collaboration between child health care and preschools provides a significant opportunity to identify children and families needing support and treatment [12,13]. Standardized assessment methods, such as questionnaires, scales, and observations, with proven reliability are one way to further facilitate the early detection of emotional and behavioral problems related to neurodevelopment [14].

Despite the established health monitoring system, there is no homogeneous system of mental health services for children below school age in Sweden. Regional differences exist, and both public and private service providers are involved. Some children are referred to Child and Adolescent Psychiatry clinics, while others are assessed and followed up on by child habilitation or municipal counseling units [15]. There are also well-known shortcomings in collaborations between health actors and other multisectoral partners such as social welfare services [4]. Coordination of efforts is difficult to establish, and queues of several years for assessment and treatment are frequent.

Efforts to strengthen overall mental health in preschool children appear to have a positive effect later in life [1,16]. A preschool with adequate resources is suitable for health promotion and prevention, with learning opportunities that increase children's social, cognitive, and adaptive skills [17]. In addition, several studies have shown that group-based parent support programs can improve emotional and behavioral problems among preschool children. However, the long-term efficacy of these programs is uncertain, as are their primary prevention effects [18].

Theoretical Background of the Study

Theoretically, this project is based on Bronfenbrenner's socioecological model. According to this model, a child's development is, apart from genes, influenced by various microsystems (family, preschool teachers, peers, etc), the ecosystem's support of the family, and preschool structure, as well as by macrosystem-level laws, culture, and policies [19]. Here, concepts such as "person-process-context-time" are highlighted in the proximal process where the person (preschool child) in their approach (play) in his context (preschool/family) develops and learns, for example, interaction over time [20]. Early support to the child, parents, and preschool teachers is expected to promote positive development and increased everyday functioning over time.

A child's behavior undergoes age-related developmental changes, including progress in motor skills, language, self-esteem, and how to handle emotional regulation. One fundamental skill is self-regulation. It is a multilevel construct that describes the ability of an individual to optimally manage physiological arousal, emotions, attention, behavior, and cognition. Self-regulation helps the child acquire the behavioral, emotional, and cognitive self-control essential for competent functioning and autonomy, both in childhood and life [21]. Acquired developmental skills also support a child's functioning in everyday life, independent of age. There is an interplay between genes and environmental factors throughout life, including parental support, attachment to caregivers, and the child's emotional experiences [21]. Furthermore, interactions among preschool children are essential for developing cognitive regulation and coping skills and play a part in equipping children to handle demanding experiences in life [22,23]. Theories of risk and protective factors have determined that it is essential to increase dynamic/impactful health factors as early as possible and reduce the number of risk factors in the child's context [2].

The overall aim of this study is to study the PLUSS (*Psykisk hälsa Lärande Utveckling Samverkan kring Små barn*; English translation: mental health, learning, development, collaboration around preschool children) model that provides coordinated services to screen, evaluate, and support children (aged 1.5-5 years) with neurodevelopmental problems. The project has the following specific aims:

1. To study neurodevelopmental issues and the ability to function among preschool children longitudinally.
2. To study parental well-being and satisfaction with provided and used services.
3. To study the implementation of the model and its effectiveness, including parental and preschool teacher training and multisectoral collaborations.

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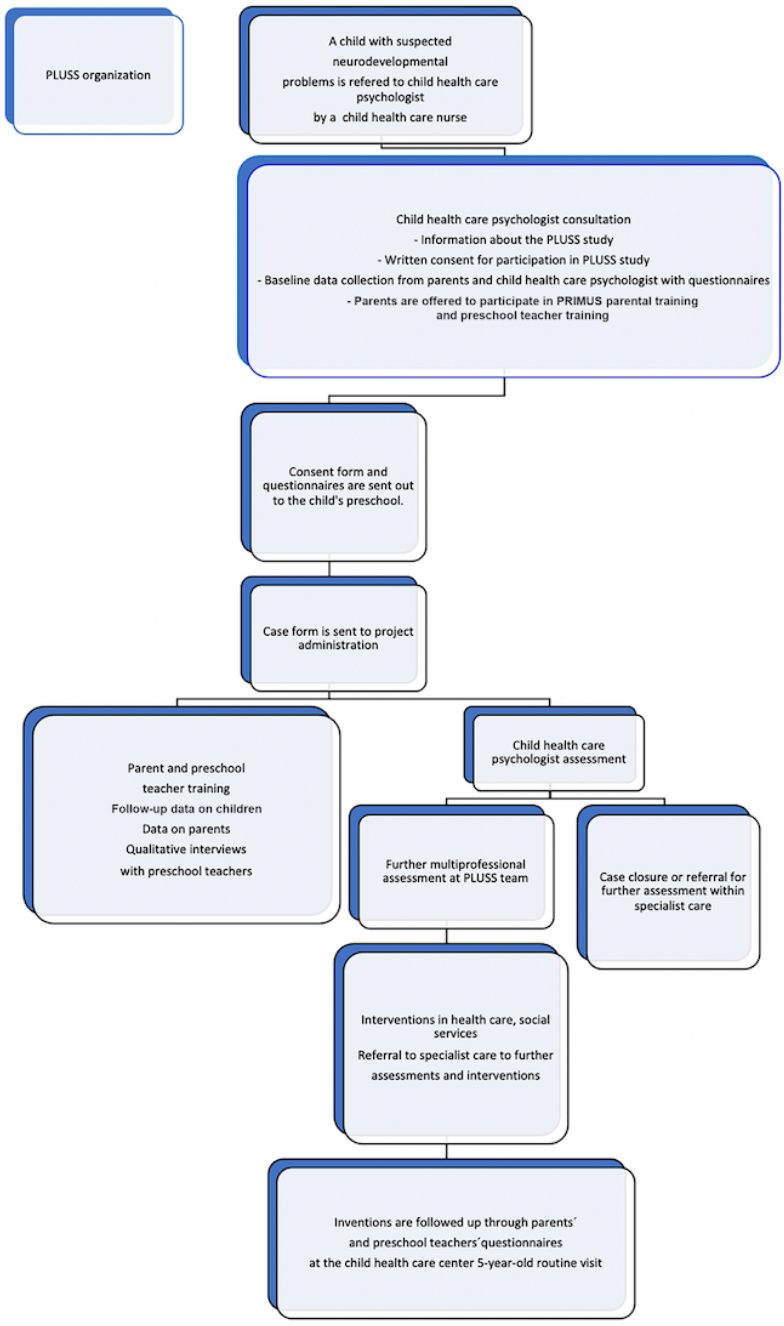
We hypothesize that a coordinated working model with multiprofessional and intersectoral collaborations will promote early detection and support of preschool children with neurodevelopmental problems. We expect that this will also positively impact mental health and well-being in the long run. In addition, we hope that this working model enhances user satisfaction and the effectiveness of processes to provide services.

Methods

Setting and Data Collection

The study is based in Jönköping County, in the south of Sweden, and runs within the PLUSS project. The PLUSS model is built upon existing processes for patient flow, from early detection to assessment and interventions. Figure 1 shows the PLUSS flow. Parents of children referred to child health care psychologists due to neurodevelopmental problems are informed about the study by child health care nurses. Parents sign a consent form for participation and fill out questionnaires before the child's health care psychologist consultation. Subsequently, parents are offered the possibility to participate in a parental training program (PRIMUS). Data are also collected from preschools and preschool teachers who are offered a separate training program. Following the child health care psychologist assessment, and initial parental and preschool teacher training, the child health care psychologist consults the multiprofessional PLUSS to plan and coordinate further evaluations and interventions.

Figure 1. The PLUSS procedure. PLUSS: *Psykisk hälsa Lärande Utveckling Samverkan kring Små barn* (English translation: mental health, learning, development, collaboration around preschool children).



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Study Design and Populations

Inclusion criteria include the following: a child referred to a child health care psychologist, aged 1.5-5 years, with ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) problems such as developmental delay, interaction, contact difficulties, language and communication difficulties, difficulties in everyday function, concentration/hyperactivity, self-regulation, acting/boundaries, and anxiety [1]. Exclusion criteria include the following: the family only needs parental support and/or there is a risk that participation in PLUSS would delay assessments or referrals to specialized services.

Detailed information about the study is given below. Research within PLUSS focuses on children, parents, and preschool teachers, and professionals working with the PLUSS are included in some substudies. Both cross-sectional and longitudinal quasi-experimental study designs are used. One substudy uses focus group interviews.

Sample Size

The aim is to collect data on 700 children. This sample size allows proposed analyses of primary outcomes related to the Strengths and Difficulties (SDQ) instrument as well as subgroup analysis and person-based analysis (cluster analysis and path analysis) with statistical strength of 0.80 and $\alpha<.05$. Power estimation is based on previous studies by Rothenberger et al [24]. The estimated number of children in the PLUSS pilot project during the first year is 160 children, and for Jönköping County, approximately 860 children per year. Studies on parental training and the user study have estimated sample sizes of n=160 and n=100, respectively. For qualitative studies, a sample size of n=20 is used [25]. Finally, the implementation study will collect data from n=80 professionals and n=100 parents involved in the PLUSS.

The control group (n=160) will be recruited from the parts of the county that have not yet been included in the PLUSS. This means that children/families belonging to the control group receive treatment as usual.

Instruments

Child health care nurses, psychologists, and preschool teachers serve as informants. Behavioral problems are measured with the SDQ (25 items and a supplement with 8 items). SDQ is validated, and proposed cutoffs are available for Swedish conditions [14,26,27]. The Children's Engagement Questionnaire (CEQ; 29 items) measures preschool children's targeted engagement and social interaction in everyday life [28,29]. The Joint Attention Observation tool (JA-OBS; 5 items) screens for the autism spectrum [30]. Psychosocial problems in the family are measured with LAPS (*lapsen psykososiaalisen terveyden arviointimenetelmä*; English translation: child mental health assessment form) [31]. A self-constructed questionnaire collects sociodemographic and background questions, including questions on mother tongue, possible diagnosis, education, professional activities, and parental ability. The health care process, for example, the number of investigations, waiting time for assessment, visits, and satisfaction, is also compiled with a separate questionnaire. Collaboration between professionals in different organizations is assessed using the "Spider" measurement, which has 10 questions [32].

Data Analysis

Table 1 summarizes the primary outcomes, confounders, and analysis that will be conducted. Quantitative multivariate analyses will be done in SPSS (version 28; IBM Corp), and longitudinal data will be analyzed using person- and group-centered analytic methods, cluster analysis, and path analysis. A comparison study with the control group and children referred to habilitation centers will occur. The focus group and semistructured interviews will be analyzed qualitatively with content analysis.

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Table 1. Summary of substudies included in the PLUSS.[a]

Study (design and time frame)	Study population	Informants (instruments)	Main outcomes
User study (qualitative focus group interview study, conducted 2019-2020)	Parents of a 1.5- to 5-year-old child with neurodevelopmental problems (n=13)	Parents (data collected with semistructured focus group interviews)	• Satisfaction with health care system
Pilot study on children with neurodevelopmental problems (quasi-experimental quantitative study, conducted 2020-2021)	1.5- to 5-year-old children with neurodevelopmental problems (n=80)	Parents, child health care psychologists, preschool teachers (data collected with SDQ, LAPS, CEQ, JA-OBS, background questions, medical records)	• Neurodevelopmental and mental health–related problems: development delay, interaction, contact difficulties, language and communication difficulties, motor difficulties, concentration/hyperactive, self-regulation, acting/boundaries, anxiety • Difficulties in everyday function • Psychosocial stress factors • Socioeconomic status, family constellation, mother tongue, possible diagnosis, education, professional activities • The health care process indicators (eg, number of assessments, visits, interventions)
Full-scale study on children with neurodevelopmental problems (quasi-experimental quantitative study with longitudinal follow-up, conducted 2022-2024)	1.5- to 5-year-old children with neurodevelopmental problems (n=160), compared to treatment as usual (n=160)	Parents, child health care psychologists, preschool teachers (data collected with SDQ, LAPS, CEQ, JA-OBS, background questions)	• As above
PRIMUS parental training program (cross-sectional quantitative study, conducted 2022-2024)	Parents to a 1.5-5-year-old child with neurodevelopmental problems (n=160)	Parents (data collected with PRIMUS evaluation questionnaire, SDQ, CEQ, LAPS)	• Self-rated parental ability • Neurodevelopmental and mental health–related problems: development delay, interaction, contact difficulties, language and communication difficulties, motor difficulties, concentration/hyperactive, self-regulation, acting/boundaries, anxiety • Difficulties in everyday function • Psychosocial stress factors

[a]CEQ: Children's Engagement Questionnaire; JA-OBS: Joint Attention Observation tool; LAPS:*lapsen psykososiaalisen terveyden arviointimenetelmä* (child mental health assessment form); PLUSS: *Psykisk hälsa Lärande Utveckling Samverkan kring Små barn* (mental health, learning, development, collaboration around preschool children); SDQ: Strengths and Difficulties Questionnaire.

Ethics Approval

Ethics approval has been granted by the National Ethics Board (2019-04839). Informed consent is obtained from all actors: parents, managers, preschool educators, child health care psychologists, and child health care nurses. All data are registered with a participant number and encoded directly at the time of collection, considering privacy protection. The code template for translation between participant number and the test subject can be found in a logbook inaccessible to unauthorized persons. The results are reported only at the group level, where no personal data will be recognizable. All data processing follows the Swedish data law. The parents have been informed that their children will receive the standard care even if they do not participate in the study. Upon parents' informed consent, the preschool manager and preschool teacher may consent to participate in the research, and the preschool teacher answers questionnaires.

Results

All research included in the PLUSS model has been approved by the National Ethics Review Board (2019–04839). Informed consent will be obtained from all study participants and legal guardians if the participant is younger than 15 years. Results will be available to caregivers, professionals working with preschool children, researchers, and funders.

This study was supported by FUTURUM grants 910161 and 910441. The funders had no role in designing the study, writing the report, or deciding to submit the paper for publication.

The study has been registered at ClinicalTrials.gov (NCT04815889). The data collection for the pilot study started in April 2019, with the prior data collection period finished by April 2021. Data collection for the full-scale investigation began during May 2021 and is planned to be completed in May 2024.

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Discussion

Principal Findings

Expected results from this study include estimates of the prevalence of neurodevelopmental problems in preschoolers, their impact on functional ability, and parental well-being. In addition, the effectiveness of the PLUSS working model is elucidated. Qualitative studies are expected to give us information about parents' and preschool teachers' experiences related to children with neurodevelopmental problems and how the system can support these children.

A research project conducted within ongoing clinical work provides an excellent opportunity to improve health care but is also affected by everyday obstacles. Not all activities and departments are accustomed to participating in clinical research work, and additional assignments for staff might cause skepticism to arise. The longitudinal study design will allow an analysis of changes over time in the same study participant, providing more substantial evidence for causality than could be obtained from a cross-sectional design. However, loss to follow-up may occur. Combining quantitative and qualitative approaches provides an excellent opportunity to understand the actual change in a child's behavior with satisfaction and well-being. Another strength is that collaboration and organizational measures are studied in PLUSS.

The project is based at Jönköping County's health care, collaborating with preschools and social services and researchers from Linköping University. Children and parents are not directly involved in the study design, recruitment, or conduct of the research. Parents are, however, engaged in focus groups that give, for example, input on how the parent educating group should be designed and what it should contain. The focus groups will involve parents of children with neurodevelopmental problems and obtain support from child health care and specialist health care. This study will be made available to the participants, the funders, professionals, researchers, and policy makers.

An important aim for future research in the PLUSS model is to follow the included children long term regarding symptom development, set diagnoses, and evaluate given interventions. Parental stress and perceived competence of parents of children with neurodevelopmental difficulties will also be considered in future research.

To improve children's mental health in Sweden, 5 suggested, evidence-based interventions were recently published, one of them being early detection and early interventions for young people at risk for future mental health problems [33]. Current knowledge of early detection and early interventions for children suggests they have been beneficial long term and economically justifiable [5,34]. The PLUSS model has been constructed to better meet the demands of health care today with early interventions for parents and children exhibiting neurodevelopmental difficulties.

Information about the ongoing study and obtained results will be communicated via the PLUSS project's steering group and working group within and outside the Jönköping County Region. The scientific results will be disseminated to the caregivers, professionals working with preschool children, researchers, and funders. Community policy makers and stakeholders will be targeted separately using Jönköping County's existing information channels and conferences.

Conclusions

PLUSS is an integrative working model with multiprofessional competence and intersectoral collaboration capacity to help preschool children with neurodevelopmental problems and their parents. The study has a quasi-experimental cross-sectional and longitudinal design. Data are collected from parents, health care providers, and preschool teachers and analyzed using quantitative and qualitative methods. The study is run in one Swedish county, and generalizability needs to be studied separately.

Acknowledgments

The authors want to thank all involved partners and the families participating in the PLUSS project.

Data Availability

Data collection is ongoing. The results from this project will be published in open access journals. The data sets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

BMG and LK conceived the idea for the study protocol article, designed the study, and drafted the manuscript. Both approved the final submitted version.

Conflicts of Interest

None declared.

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Abbreviations

CEQ: Children's Engagement Questionnaire
ESSENCE: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
JA-OBS: Joint Attention Observation tool
LAPS: *lapsen psykososiaalisen terveyden arviointimenetelmä* (child mental health assessment form)
PLUSS: *Psykisk hälsa Lärande Utveckling Samverkan kring Små barn* (mental health, learning, development, collaboration around preschool children)
SDQ: Strengths and Difficulties Questionnaire

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Protocol

Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies in Community Mobility Rehabilitation: Protocol for Evaluation and Rehabilitation of Mobility Across Continuums of Care

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Abstract

Background: Rapid advances in technologies over the past 10 years have enabled large-scale biomedical and psychosocial rehabilitation research to improve the function and social integration of persons with physical impairments across the lifespan. The Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies (BRILLIANT) in community mobility rehabilitation aims to generate evidence-based research to improve rehabilitation for individuals with acquired brain injury (ABI).

Objective: This study aims to (1) identify the factors limiting or enhancing mobility in real-world community environments (public spaces, including the mall, home, and outdoors) and understand their complex interplay in individuals of all ages with ABI and (2) customize community environment mobility training by identifying, on a continuous basis, the specific rehabilitation strategies and interventions that patient subgroups benefit from most. Here, we present the research and technology plan for the BRILLIANT initiative.

Methods: A cohort of individuals, adults and children, with ABI (N=1500) will be recruited. Patients will be recruited from the acute care and rehabilitation partner centers within 4 health regions (living labs) and followed throughout the continuum of rehabilitation. Participants will also be recruited from the community. Biomedical, clinician-reported, patient-reported, and brain imaging data will be collected. Theme 1 will implement and evaluate the feasibility of collecting data across BRILLIANT living labs and conduct predictive analyses and artificial intelligence (AI) to identify mobility subgroups. Theme 2 will implement, evaluate, and identify community mobility interventions that optimize outcomes for mobility subgroups of patients with ABI.

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Results: The biomedical infrastructure and equipment have been established across the living labs, and development of the clinician- and patient-reported outcome digital solutions is underway. Recruitment is expected to begin in May 2022.

Conclusions: The program will develop and deploy a comprehensive clinical and community-based mobility-monitoring system to evaluate the factors that result in poor mobility, and develop personalized mobility interventions that are optimized for specific patient subgroups. Technology solutions will be designed to support clinicians and patients to deliver cost-effective care and the right intervention to the right person at the right time to optimize long-term functional potential and meaningful participation in the community.

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KEYWORDS

health informatics; digital health; individualized care; acquired brain injury; community mobility; participation; physical rehabilitation; virtual reality; artificial intelligence; predictive analytics; biomedical; learning health system

Introduction

Acquired brain injury (ABI), including traumatic brain injury (TBI), cerebral palsy (CP)-fetal/perinatal brain injury, and stroke, are the leading causes of disability worldwide [1-3]. According to the World Health Organization, the global incidence of all-severity TBI is estimated at 69 million people, while 15 million people suffer a stroke worldwide each year [4-6]. Statistics Canada indicates that 100,000 Canadians will experience a stroke (59%) or a TBI (71%) each year [6]. Many individuals with mild-to-moderate ABI subsequently return home, yet they continue to experience ongoing cognitive and physical impairments, including mobility limitations resulting in restricted participation in meaningful activities at school, leisure, or work. Worldwide, between 1990 and 2019, there has been an 89% and a 79% increase in individuals with stroke and TBI, respectively, that require rehabilitation services [7]. Individuals with ABI face challenges once discharged from acute care or rehabilitation and with uncertainty regarding their potential for recovery and regaining independence [8]; see also Ahasani et al (unpublished data, March 2021). Mobility limitations in the community are common and affect 30% of persons with TBI [9-11] and up to 50% of stroke survivors [12], even after extensive rehabilitation. Long-term follow-up of individuals with ABI shows that limitations in mobility appear to undergo little change, even 10 years after the initial injury [10,11].

Mobility is a multidimensional construct and consists of the ability to move oneself independently within a “life space,” expanding from one’s home to the neighborhood and beyond [13,14]. The Webber framework identifies 5 vital interrelated determinants that influence mobility (ie, physical, environmental, cognition, psychosocial, and financial) [14] that are also reflected in the International Classification of Functioning, Disability and Health (ICF) framework mobility core set [15]. The built environment also influences community mobility [16,17]. Guided by the Webber and ICF frameworks, studies have shown that diagnosis alone is not enough to predict mobility limitations and that clinical variables (eg, length of hospitalization, performance-based measures), intensity of care, patient-reported outcomes (PROs) of health, and social determinants are needed to accurately predict return-to-work potential, work performance, or social integration [16,17]. In addition, social and healthcare decision makers recognize the importance of modifying features of the social and physical environment to decrease the incidence and severity of disability and enhance mobility and participation [15].

Currently, no reliable measure exists to jointly evaluate the intrinsic and extrinsic factors that influence mobility for individuals with ABI. For the most part, to measure mobility in research, we rely on expensive laboratory technologies and performance-based tools that are burdensome in terms of setup, as well as the time needed from highly qualified professionals, clinicians, or research staff for administration and analysis. Importantly, these tools cannot be readily applied in real-life community contexts. Further, electronic platforms that can collect real-time patient- and clinician-reported data are in their infancy, particularly in rehabilitation.

Rapid advances in technologies over the past 10 years have enabled large-scale biomedical and psychosocial rehabilitation research to improve the function and social integration of persons with physical impairments across the lifespan. In 2017, our team, a network of researchers and clinical partners, established the Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies (BRILLIANT) in community mobility rehabilitation to provide evidenced-based research to improve rehabilitation for individuals with ABI. BRILLIANT builds on the success of the Rehabilitation Living Lab in the Mall (RehabMaLL) [18], a strategic development project and the first transdisciplinary and intersectoral research program to explore the principal (including physical and social) obstacles to and facilitators of participation in public environments for persons with disabilities.

The vision of BRILLIANT is to optimize mobility following ABI across the lifespan. The main objectives are to (1) identify the factors limiting or enhancing mobility in real-world community environments (public spaces, including the mall, home, and outdoors) and understand their complex interplay in individuals of all ages with ABI and (2) customize community environment mobility training by identifying, on a continuous basis, the specific rehabilitation strategies and interventions that patient subgroups benefit from most. Here, we present the research and technology plan for the BRILLIANT initiative.

Working toward the vision of BRILLIANT, the deliverables that emerge from the program will be made available to the

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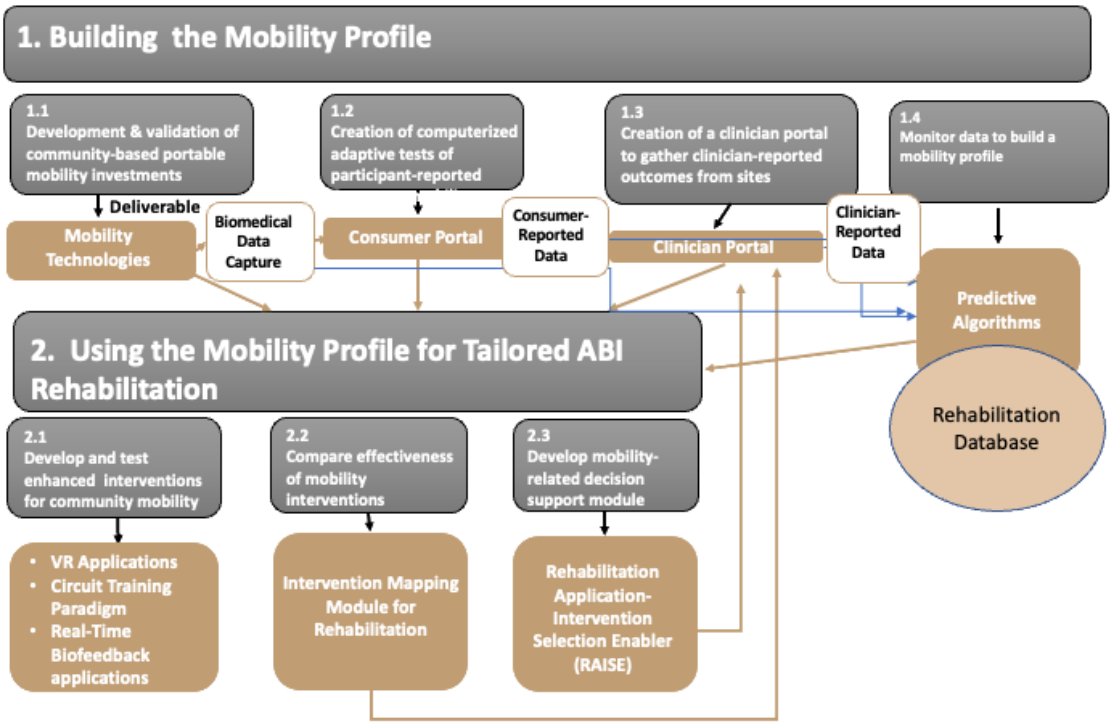
broader research and public community and health system partners. The continuously growing BRILLIANT database will provide the wider research community with data to conduct evaluative research, in particular comparative effectiveness research, to identify best practices. Community organizations will also be able to access the data to inform their strategic plans for addressing the needs of their members. The digital solutions will be created with health system partners to ensure they can be scaled up and sustained in the clinical programs. The goal is to create a learning rehabilitation system that allows for continuous garnering of data via technologies that can be shared back with clinicians, patients, and managers to inform clinical decisions.

Here, we present the subcomponents of the BRILLIANT program, referred to as activities that will allow for a multidimensional evaluation of mobility and the factors that influence mobility (Figure 1). Other subcomponents will utilize data generated from the BRILLIANT technologies to evaluate ABI-tailored rehabilitation interventions.

Figure 1. Subcomponents of the Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies (BRILLIANT) to support a learning rehabilitation system. ABI: acquired brain injury; VR: virtual reality. © BRILLIANT.



Methods

Clinical Sites and Community

A cohort of individuals, adults and children, with ABI (N=1500) will be identified and recruited. These will include patients from the acute care and rehabilitation partner centers within 4 health regions, and the patients will be followed throughout the continuum of rehabilitation services provided by the health care authorities (listed later). Within these 4 health regions, there are 16 clinical programs that provide intensive post-ABI rehabilitation following practice guidelines and in line with other provinces and countries [19-21]. All programs at each center are part of a defined continuum of care for ABI (stroke, TBI, CP). Each of the 4 health regions is responsible for a specific territory covered by the Centre intégré universitaire de santé et de services sociaux (CIUSSS) or the Centre intégré de santé et de services sociaux (CISSS), otherwise known as Quebec health authorities. The 4 sites include the CIUSSS du Centre-Ouest-de-l'Île-de-Montréal (CCOMTL), the CIUSSS Lanaudière, the CISSS de Laval, and the CIUSSS Centre-Sud-de-l'Île-de-Montréal (CCSMTL). Participants will also be recruited from the community to be able to address the BRILLIANT objectives among individuals living with ABI but no longer receiving active rehabilitation.

Study Population and Recruitment

For those recruited in the clinical settings, the sample will consist of patients and their caregivers, clinicians, coordinators, and managers. A consecutive sample of individuals admitted to acute or rehabilitation care that meet the inclusion criteria will be obtained from admission records. To be eligible to participate, patients or caregivers must be able to (1) provide informed consent to complete questionnaires and provide access to their provincial health data and (2) speak and read English or French.

Within each clinical site, the ABI rehabilitation sites' managers will obtain a list of emails from clinicians and coordinators interested in participating in the study. A research assistant will obtain consent electronically from clinicians, managers, and patients and caregivers.

Community participants will be recruited through social media and community partner (eg, Brain Injury Canada) organizations. Interested individuals will be invited to call the study coordinator or complete a form on the BRILLIANT website.

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BRILLIANT: Biomedical and Digital Health Technologies and Data Collection

Theme I: Building a Mobility Profile

The objective of Theme 1 is to aggregate data from different types of rehabilitation technologies to evaluate the complex interplay between biomedical, personal, and environmental factors that explain variability in mobility. This will be the first time this combination of technologies will be used to generate and validate mobility data that combines brain imaging (BrImagO), biomedical, and patient-reported and clinical measures. This will be accomplished by collecting data among the study population that will be followed through the continuum of care (starting in the hospital) and into the community (up to 2 years post-ABI), enabling us to integrate and analyze their synergistic relationships.

Activity 1.1: Development and Validation of Community-Based Portable Mobility Instruments

Moving in community environments is challenging for people with mobility restrictions, as they must adapt to constantly changing contextual/environmental demands (eg, avoid pedestrians/crowds, adapt to noise levels and changing terrains, carry loads). Current laboratory and clinically based evaluations of mobility do not sufficiently capture individuals' capacity (can do, controlled conditions) and performance (does in real life) as experienced in the community. We will measure complex visually guided mobility tasks (eg, walking and avoiding pedestrians) in community environments, in this case in a shopping mall (Alexis Nihon in Montreal). The mobile technologies we will develop and validate will capture the interaction of patients within the mall environment. Moreover, sensors integrated into assistive technology (eg, wheelchair seating, walkers and canes) will measure the movement, forces, and use of devices. Other sensors, installed in the mall environment, such as the mall floor, stairs, surfaces, and everyday objects, will measure individuals' movement and the use of key areas in the community environment.

We will also use portable electroencephalography (EEG) to develop metrics that characterize brain activation patterns in key regions of interest (eg, the premotor and motor cortices, posterior parietal cortex) while patients are performing mobility tasks in RehabMaLL. The data collected will provide unprecedented sensitivity that is needed to detect and measure biomedical parameters of mobility in the community. Standardized measurements of biomedical outcomes (BiomedO), taken at various stages of the individuals' recovery (acute, rehabilitation, and community reintegration phases), will be part of the data used to predict and then classify individuals with ABI into high, medium, or low levels of mobility based on the quality, precision, and coordination of their movement.

At the end of Activity 1.1, we will develop mobility technologies to evaluate personalized longitudinal BiomedO data in a timely manner, a kind of data currently unavailable for individuals with ABI who come to the clinic for follow-up evaluations.

Activity 1.2: Patient Outcome Reporting Research System—Creating Computerized Adaptive Tests of Patient-Reported Outcomes for Mobility-Related Domains

PRO data are crucial for understanding mobility as they enable researchers to measure factors influencing mobility that can only be provided by individual participants. The greatest challenge in collecting PROs in the laboratory, clinical, and community settings, however, is the length of time and repetitiveness of standardized paper-based measures, as well as their lack of precision and sensitivity to change [22]. Computerized adaptive tests (CATs) have emerged as a promising solution to capture PROs more efficiently, in less time, and without jeopardizing the validity and reliability of PRO scores [22]. The PRO, using built-in algorithms, adapts to the participant's ability level by selecting items or a set of items from a large item bank that are sorted from the easiest to the hardest items/questions based on metrics generated from item response theory analyses. The system starts by asking a question of mid-level difficulty (eg, "Are you able to walk 1 block?"), with response options ranging from 1 (unable to do) to 5 (without any difficulty). Depending on the individual's responses to the most recent items administered, the system selects the next item that will obtain more precise information (eg, if the answer to the mid-level item gets a high score, the next item selected has a higher level of difficulty, such as "Are you able to run to catch a bus?"). The CAT calculates a reliability estimate after each response (eg, typically 7-9 items from a larger item bank of up to 100 items) and stops asking questions when it reaches a predetermined (by the research group) reliability estimate. For this reason, it has also been called "tailored testing" that, rather than using a fixed-length questionnaire, only administers items that obtain new information. The testing software will include the text of each question as well as extensive information regarding test development and psychometric characteristics (calibration to place items on the same scale). The testing application will include item banks and computer adaptive algorithms developed and validated, providing a comprehensive PRO metric of mobility that classifies individuals with ABI across the lifespan and at all levels of mobility. Participants will be able to complete items using interactive voice recognition systems, smartphones, tablets, or desktop computers; this versatility will maximize user-centeredness and can be matched to the setting where the questionnaires are administered. The testing software will also enable researchers to compare the validity and sensitivity to detect change in mobility-related domains of CATs compared to traditional observed measures used in research and in clinical practice. Where possible and appropriate, Patient-Reported Outcomes Measurement Information System (PROMIS) CATs [23] will be used. CATs will be compared to gold standards, which include the Human Activity Profile, which focuses on low-level-to-complex mobility tasks (eg, turning in bed, walking, running), and the Assessment of Motor and Process Skills, which measures the motor and cognitive process skills of simple-to-complex community tasks (eg, retrieving a beverage from the refrigerator, shopping).

At the end of Activity 1.2, we will have developed, with our industry partner, the Participant Outcome Reporting Research

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System, a software application including CATs to measure low-to-high levels of mobility for persons with ABI.

Activity 1.3: Clinical Research System to Gather Clinician-Reported Outcomes From Clinical Research Sites

Data captured at the point of rehabilitation care (during episodes of care and as part of research trials) will provide information about the performance-based measures of mobility and rehabilitation interventions (physical, psychosocial, and cognitive). We will leverage this work to identify strategies to optimize implementation of the clinical research system (CRS), including the added value of mobility data for clinicians to identify which interventions are optimal for specific patient subgroups and to support clinical decision-making. Clinician-reported outcome (ClinRo) data obtained using performance-based evaluations of impairment, function, and mobility, as well as data on patient interventions (described in Activity 2.2), will be captured. Later, the system will be built step by step using separate modules for each type of data capture source (described in Activities 1.1-1.3) and intervention data source (eg, split-belt and conventional treadmills, virtual reality [VR], constraint, and biofeedback modules described in Activity 2.1) for patients enrolled in trials. Five years into the BRILLIANT research program, when predictive models are developed (after collecting a sufficient amount of data) and validated, the CRS will include a decision support module (see Activity 2.3) to provide recommendations for selection and implementation of appropriate mobility interventions, tailored to specific ABI characteristics (see Activity 2.2).

These ClinRo data will be captured using the CRS to be built using a commercial software package in partnership with an industry partner, allowing researchers and participants to enter data using tablets, smartphones, or computers.

Activity 1.4: Monitoring Data to Build a Mobility Profile

The BRILLIANT program will generate and pool biological biomedical data (BiomedO, ie, movement, forces, gaze, and neuromuscular data, portable imaging; Activity 1.1) and PRO data collected using the PRO research system (Activity 1.2) with ClinRo data using the CRS (Activity 1.3) and BrImagO data acquired using magnetic resonance imaging (MRI) during the acute, rehabilitation, and community reintegration phases. Many of the important underlying causes of aberrant motor performance have signatures that can be measured using MRI. Imaging modalities sensitive to changes in axonal structure, gray matter thickness, functional neurophysiology, neurochemical balance, and microvasculature hold the greatest promise in detecting and characterizing ABI. These imaging modalities have shown great utility for detecting and diagnosing brain damage. Ptito and coworkers [24] also successfully used MRI to evaluate brain function (blood oxygenation, flow and volume using functional magnetic resonance imaging [fMRI]) to characterize patients with mild TBI (mTBI) and also applied this to pediatric populations with Gagnon et al [24]. Importantly, the group is amongst the first to demonstrate the power of fMRI to detect and diagnose mTBI and document recovery. They also used repetitive transcranial magnetic stimulation (rTMS) to increase dorsolateral prefrontal activity and relieve symptom severity in patients with mTBI [24]. Imaging can thus be used to zoom in and resolve functional changes in frontal regions, including motor and premotor cortices.

Using individual-level data, predictive analytics will be performed to explain variability in mobility. This will enable estimation and validation of predictive models of mobility to assess the independent and joint contribution of explanatory variables, allowing us to identify mobility subgroups. Only with the data from the network of technologies, and experimentation in multiple longitudinal cohorts of persons with ABI of varying levels, and healthy controls of all ages as a comparison, will researchers be able to create such a mobility profile. The combination of the predictive models informed by expert researchers, collaborating industry and clinical partners, and end users will define the rules by which factors are encoded to develop a characteristic mobility profile.

Theme 2: Using the Mobility Profile for Tailored ABI Rehabilitation/Retraining

The objective of this theme is to develop cost-efficient community mobility interventions that optimize outcomes for mobility subgroups of patients with ABI. This will allow us to customize community environment mobility training by identifying, on a continuous basis, specific rehabilitation strategies and interventions that patient subgroups benefit from most.

Activity 2.1: Developing and Testing Enhanced Interventions for Community Mobility

Moving around in community environments requires the skills to cope with multiple simultaneous dimensions (eg, walking speed and distance, traffic level, sensory cues, postural transitions, cognitive demands). Such skills remain compromised in the majority of individuals with ABI due to nonspecific interventions [25,26]. Best-practice guidelines for all age groups recommend the use of task-specific interventions that are individually tailored, goal oriented, meaningful, engaging, progressively adapted, and of sufficient intensity and duration. As these principles are incorporated into contemporary practice, mobility interventions remain largely focused on training rhythmic/repetitive movements (eg, treadmill walking, robot-assisted movements) in clinical laboratory environments. Such practice underestimates the need for (1) movement adaptation in response to varied, meaningful real-life contexts; (2) coengagement of motor, sensory, perceptual, and cognitive systems and influence of fatigue; and (3) development of problem-solving skills/preplanned strategies [27] for community mobility. In the context of this activity, we will develop and test individually tailored interventions grounded in the best evidence in community ambulation, principles of motor learning and participatory action research with end/knowledge users.

Specifically, for patients who are in the intensive rehabilitation phase (ie, first 3 months of rehabilitation and predischarge to home/community), enhanced practice of community mobility skills (walking and wheeling) will be provided through VR applications comprising mobility tasks and environments of increasing complexity (eg, from unobstructed single-task walking a short distance to walking 100 m in a crowded mall while remembering shopping items). These VR applications

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will be developed collaboratively with knowledge users (patients of various ages and clinicians) as well as key industrial partners specialized in video game development and VR applications for the clinical setting. For patients with ABI in the community reintegration phase (postdischarge from intensive rehab), mobility interventions taking place within the community will be codeveloped and subsequently tested in collaboration with Cominar (owner of Alexis Nihon and partner in RehabMaLL) and other community partners (eg, ALTERGO [28]). We will implement circuit training for mobility within the rehabilitation setting to develop and test a circuit training paradigm involving complex community mobility skills in a community environment (eg, the mall). Using wearable sensor technology, we will further develop real-time biofeedback applications to provide online knowledge of performance on movement strategies (eg, lower-limb movement and weight-bearing symmetry), instantaneous walking, and propulsion speed and distance while patients move about in community environments.

Activity 2.2: Comparative Effectiveness of Mobility

Recent research suggests that accounting for the time spent in *specific* physical and occupational therapy activities (intervention-level data), above and beyond patients' characteristics (patient-level data), has the potential to enhance the predictive value of models explaining rehabilitation outcomes after ABI [29]. Capturing accurate and comprehensive intervention-level data (also a ClinRo) at different times within the continuum of care (eg, acute care and then transitioning to inpatient and outpatient rehabilitation and community reintegration) allows us to identify the mediating effects of specific rehabilitation interventions to the recovery of mobility in different patient subgroups. This electronic intervention data capture application will involve validation of intervention parameters within the Canadian context (and for children/youth) and follow the most recent international reporting guidelines for interventions (eg, the template for intervention description and replication [TIDieR] checklist) [30] to create an ABI-specific treatment classification in a research-based therapeutic coding system (with a focus on mobility). This mapping application will allow adding specific treatment variables and refining the predictive power of the models to guide decision support (Activity 2.3). We will compare how the intervention mapping applies to VR, gait retraining (eg, gait circuits in a gym, split-belt treadmill, treadmill propulsion) and community-based interventions for mobility and extend to persons with ABI.

We will build on this work to create the intervention mapping module for rehabilitation in the CRS (Activity 1.3) to capture intervention parameters mentioned before and strategies used by therapists when teaching indoor/outdoor community mobility skills.

Activity 2.3: Mobility Decision Support Development

In this activity, we will develop and evaluate the impact of a decision support module, Rehabilitation Application-Intervention Selection Enabler (RAISE), on clinician and patient clinical decision-making in terms of mobility and practices. Using the predictive models developed in Activity 1.3 and the analysis of intervention factors developed in Activity 2.2, we will build RAISE for clinicians and conduct the first-ever implementation studies and randomized trials on the acceptability and effectiveness of RAISE for referral and discharge across transitions in care and selection of mobility retraining strategies. Since length of stay in intensive rehabilitation is shortening, therapists have to assign optimal community-based rehabilitation strategies early on in the treatment plan.

A second challenge arises when transitioning from acute care to home, when families and patients need a clear understanding of the mobility prognosis to make decisions about discharge planning resources and alterations to their home environment. RAISE will also be able to identify the best responses to questions posed by clinicians using plain language. For example, clinicians will be able to enter a question regarding the mobility prognosis, such as "When will patient X be able to climb 12 steps independently based on their present profile?" or "Will patient X be able to walk in a shopping mall independently at 6 months?" or "Would protocol A or B work best for this patient?" RAISE and natural language applications will leverage the data collected in Theme 1 and the analysis from Activities 2.1 and 2.2 to inform the intervention plan and answer these types of questions.

RAISE, as an add-on within the CRS (Activity 1.3) will be designed to allow clinicians to produce personalized intervention plans for subgroups of patients based on their mobility profile using data-driven methods.

Ethics Approval

Ethics approval for each activity is ongoing.

Results

Current Status

The biomedical infrastructure and equipment have been established across the research labs and clinical sites. The participating reporting outcome system contains CAT PRO measurements (PROMs), including the Patient-Reported Outcomes Measurement Information System (PROMIS) [23] and the Assistive Technology Outcome Profile for Mobility (ATOP) [23,31], and development of other modules for feedback of PROM and mobility outcomes to participants is ongoing [32,33]; see also Alhasani et al (unpublished data, March 2021). The development of the clinical information system is also ongoing. Recruitment is expected to begin in May 2022.

Knowledge Mobilization Process With Partners and End Users

In addition to traditional knowledge dissemination (publications in scholarly journals and conferences), the BRILLIANT team will undertake yearly interactive knowledge mobilization sessions with health system and community partners and end users. These sessions will include, but will not be limited to, dedicated work sessions with informatics specialists, patient representatives from a range of subpopulations, clinicians, and the provincial health ministry (Ministère de la Santé et des Services sociaux [MSSS]).

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To ensure that experiential knowledge is effectively exchanged within the research community, the team will offer 1-day specialized training sessions. This intensive course will be directed at training clinicians, trainees, and highly qualified professionals on the use of the CRS, including the RAISE decision support system, and offered in person and virtually. Because such a commitment can be difficult for many clinicians, the BRILLIANT program will hold 4 half-day training sessions annually at clinical sites to be close to clinical programs and activities.

The mobility technologies and decision supports that identify optimal mobility interventions will have important repercussions for changes to clinical guidelines and practices. The BRILLIANT knowledge mobilization plan will also inform policies of the Quebec health care system and insurance compensation of victims of automotive accidents (eg, the Société d'Assurance Automobile du Québec [SAAQ]), workplace accidents, and violent crimes. We will further communicate our results to rehabilitation policy planners across the province and nationally to inform program planning for individuals with ABI, from rehabilitation-based interventions to community planning to support ongoing monitoring and mobility retraining support in the community. Linkages with the national and international brain injury, health professional, and accreditation associations will help to disseminate the results to persons with a vested interest in improving the lives of individuals with ABI.

Over time, through international collaborations, BRILLIANT will build partnerships to adapt and disseminate BRILLIANT innovations to other research networks and clinical settings. This work has started via the Virtual Health and Wellbeing Living Lab Infrastructure (VITALISE) initiative that brings together 3 European living labs and BRILLIANT to share resources and expertise in technology development for rehabilitation, transitions in care, and smart living environments [34-36].

Once tested and validated, we will explore commercialization opportunities with our industry partners. We will aim to make the participant reporting system, CRS, and RAISE readily available through an open source framework for other investigators to keep building and deploying RAISE, and health networks to deploy within their clinical programs.

Discussion

Summary

The BRILLIANT digital health and biomedical technologies will enable users to conduct research along the 2 main themes of BRILLIANT: to collect necessary data allowing the creation of a mobility profile for patients with ABI in community environments and to make use of the mobility profile for customized rehabilitation and retraining programs. The BRILLIANT research innovations will result in technology development with industry, evidence-based practices by clinical end users, and changes to clinical and governmental guidance, designed to positively impact ABI clinical outcomes.

The breakthroughs and outcomes of benefit to rehabilitation care from BRILLIANT include:

- Community-based tracking of mobility: Thousands of patients with ABI admitted annually to acute care and rehabilitation centers will see their lives improved by having a means to monitor limitations in mobility once they leave the care setting. Indeed, for children and adults who return home from acute rehabilitation, there has been limited measurement of their functioning in their own community. The community-based tracking deliverable will enable our practice teams, including physicians in the community who do not usually have access to information on functioning, to measure the mobility limitations that persons with ABI experience in their environments. Ultimately, the benefits are that patients will be able to return to their home environment sooner with greater mobility and function.
- ABI mobility limitations, interventions, and comparative effectiveness research: The patient research system to efficiently and precisely evaluate PRO domains that influence mobility, and the CRS will allow for data capture at the point of care. The CRS will include a much-needed taxonomy of rehabilitation interventions. As there is currently no rehabilitation electronic health record in the participating sites, there are no mechanisms to capture these data, limiting a clinician's ability to evaluate patient progress, and for researchers and health administrators, to identify the care patients receive in rehabilitation. The CRS will be 1 of the first-ever rehabilitation electronic records.
- A predictive model to explain variability in mobility: The BRILLIANT data collected will allow us to continuously develop and validate predictive algorithms to explain variability in mobility. This will further enable estimation and validation of predictive models of mobility to assess the independent and joint contribution of explanatory variables, allowing us to identify mobility subgroups. For clinicians, this provides a means to identify which factors to focus on in rehabilitation mobility retraining, using a personalized approach (tailored to context) rather than the current prescriptive or recipe approach.
- Customized rehabilitation/retraining programs: The decision support tool will utilize the predictive models to build a mobility decision support, RAISE. Currently, patients receive relatively the same rehabilitation mobility training interventions that often do not target the specific factors limiting a given individual's mobility. For patients, this means that receiving interventions that address their specific needs is likely to optimize their outcome following rehabilitation. This provides clinicians with a means to distinguish the mobility levels of patients and the interventions that are most likely to be effective.

Conclusion

BRILLIANT represents the first large-scale use of biomedical community–based technology and health informatics to support a person-centered (personalized) approach to measuring function over time and developing interventions to improve community-based mobility. We expect the innovations created to accelerate research and discovery in ABI research and deliver the information needed for clinicians to be able to deliver cost-effective care that includes *the right intervention to the right person at the right time*, while achieving long-term

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functional potential and meaningful participation in the community.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Canada Foundation for Innovation (Multidisciplinary Assessment Committee and Special Multidisciplinary Assessment Committee).
[PDF File (Adobe PDF File), 190 KB - resprot_v11i6e12506_app1.pdf]

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Abbreviations

ABI: acquired brain injury
ATOP: Assistive Technology Outcome Profile for Mobility

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BRILLIANT: Biomedical Research and Informatics Living Laboratory for Innovative Advances of New Technologies in Community Mobility Rehabilitation
BrImagO: brain imaging
CAT: computerized adaptive test
CISSS: Centre intégré de santé et de services sociaux
CIUSSS: Centre intégré universitaire de santé et de services sociaux
ClinRo: clinician-reported outcome
CP: cerebral palsy
CRS: clinical research system
fMRI: functional magnetic resonance imaging
MRI: magnetic resonance imaging
mTBI: mild traumatic brain injury
PRO: patient-reported outcome
RAISE: Rehabilitation Application-Intervention Selection Enabler
RehabMaLL: Rehabilitation Living Lab in the Mall
TBI: traumatic brain injury
VR: virtual reality

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Proposal

Primary Prevention of Stroke in Children With Sickle Cell Anemia in Nigeria: Protocol for a Mixed Methods Implementation Study in a Community Hospital

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Abstract

Background: In Nigeria, approximately 150,000 children with sickle cell anemia (SCA) are born annually, accounting for more than half of all SCA births worldwide. Without intervention, about 11% of children with SCA will develop a stroke before their 20th birthday. Evidence-based practices for primary stroke prevention include screening for abnormal transcranial Doppler (TCD) measurements coupled with regular blood transfusion therapy for at least one year, followed by hydroxyurea (HU) therapy indefinitely. In high-resource countries, this strategy contributes to a 92% decrease in stroke incidence rates. In 2016, as part of a capacity building objective of the Stroke Prevention Trial in Nigeria (1R01NS094041: SPRING), TCD screening was adopted as standard care at Barau Dikko Teaching Hospital in Kaduna. However, with just 70 radiologists and only 3 certified in TCD screening in the state, just 5.49% (1101/20,040) of eligible children with SCA were screened. Thus, there is a need to explore alternate implementation strategies to ensure children with SCA receive standard care TCD screening to decrease stroke incidence.

Objective: This protocol describes a study to create a stroke prevention program in a community hospital in Kaduna through task shifting TCD screening to nurses and training medical officers to initiate and monitor HU utilization for stroke prevention.

Methods: This study will be conducted at 2 sites (teaching hospital and community hospital) over a period of 3 years (November 2020 to November 2023), in 3 phases using both quasi-experimental and effectiveness-implementation study designs. In the needs assessment phase, focus groups and structured interviews will be conducted with health care providers and hospital administrators to identify barriers and facilitators to evidence-based stroke prevention practices. Results from the needs assessment will inform intervention strategies and a process plan to fit the needs of the community hospital. In the capacity building phase, nurses and medical officers at the community hospital will be trained on TCD screening and HU initiation and monitoring. In the implementation phase, children with SCA aged 2-16 years will be recruited into a nonrandomized single-arm prospective trial to determine the feasibility of initiating a task-shifted stroke prevention program by recording recruitment, retention, and adherence

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rates. The Reach and Effectiveness components of the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework will be used to evaluate implementation outcomes between the community and teaching hospitals.

Results: The needs assessment phase of the study was completed in February 2021. Manuscript on findings is currently in preparation. Capacity building is ongoing with TCD training and sickle cell disease and stroke education sessions for nurses and doctors in the community hospital. Recruitment for the implementation trial is expected to commence in July 2022.

Conclusions: This study proposes a structured, theory-driven approach to create a stroke prevention program in a community hospital in Kaduna, Nigeria, to decrease stroke incidence among children with SCA. Results will provide preliminary data for a definitive randomized clinical trial in implementation science.

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KEYWORDS

sickle cell anemia; stroke prevention; transcranial Doppler ultrasonography

Introduction

Background

Sickle cell anemia (SCA) is the leading cause of stroke in children globally. Without any intervention for primary stroke prevention, children with SCA have a 10% annual risk of developing a stroke [1]. In sub-Saharan Africa, about 11% of these children will develop a stroke before their 20th birthday [2]. In Nigeria, the country with the highest birth rate of newborns with SCA, over 150,000 births per year, there is a minimum estimate of 10,000 stroke episodes in children with SCA for the birth year cohort (assuming minimum mortality) [3]. In high-income countries, evidence-based practices for primary stroke prevention in children with SCA involve screening for abnormal transcranial Doppler (TCD) ultrasound velocity coupled with regular blood transfusion therapy for at least one year followed by hydroxyurea (HU) therapy indefinitely [4,5]. This strategy has decreased the risk of stroke by 92%, leading to a 10-fold drop in stroke incidence from 0.67 to 0.06 strokes per 100 patient-years [6,7]. Unfortunately, well-established evidence-based practices for SCA have not yet been transferred to low-resource settings such as Nigeria. There exists a gross paucity of TCD services in Nigeria, largely due to a lack of trained personnel certified in performing TCD and a shortage of TCD machines dedicated to primary stroke prevention [8,9]. In Nigeria, TCD ultrasonography training is primarily restricted to radiologists.

In 2012, a feasibility trial to determine the acceptability of HU therapy for primary stroke prevention in children with abnormal TCD measurements was conducted in Kano, Nigeria (SPIN [Stroke Prevention in Nigeria]: NCT01801423). The team demonstrated high participant recruitment, retention, and adherence rates for HU as primary stroke prevention in children with SCA living in northern Nigeria and established standard care for stroke prevention using HU at 20 mg/kg/day [9]. Further, a multicenter trial (SPRING [Primary Stroke Prevention in Nigeria]: NCT02560935) was completed in 3 centers in 2 states, Kano and Kaduna in northern Nigeria, to answer a critical question on the optimal dose of HU (20 mg/kg vs. 10 mg/kg) for primary stroke prevention. Results demonstrated that in low-income settings without access to indefinite regular blood transfusion therapy, fixed low-dose HU of at least 10 mg/kg/day is effective for primary stroke prevention [10]. More recently, the 2020 American Society of Hematology guidelines on central nervous system complications in sickle cell disease (SCD) recommend that children with SCD and abnormal TCD measurements living in low- and middle-income countries where regular blood transfusions are not readily available receive at least moderate dose (20 mg/kg/day) of HU [11].

The earlier trials (SPIN and SPRING) were all conducted in academic hospitals with the right combination of staff and facilities and, suffice to say, research and implementing findings into usual care may be more feasible in such resource-rich centers. To achieve equitable translation of "research to practice," there is a need to include community hospitals in the conduct of research. For us to rapidly translate the findings from our Stroke Prevention Trial, we propose transporting evidence-based practices for stroke prevention from our trial site, Barau Dikko Teaching Hospital (BDTH), a 300-bed academic hospital located in Kaduna North Local Government, to Yusuf Dantsoho Memorial Hospital (YDMH), a 100-bed community hospital located in Kaduna South Local Government run by the State's Ministry of Health. The premise of this feasibility trial is that improving access to TCD screening in a community hospital will dramatically increase the rate of TCD screening, thereby leading to a decrease in stroke occurrence among children with SCA.

Our prior findings indicate that physician-only TCD screening is insufficient to increase the reach of TCD screening for stroke prevention among children with SCA living in Kaduna or the rest of Nigeria. Of the approximately 20,040 children aged 0-14 years with SCD eligible for TCD screening in Kaduna metropolis, only 5.49% (n=1101) have ever had a TCD screening in their lives [12,13]. Prior to the Stroke Prevention Trial, no TCDs were performed in the state owing to a lack of trained personnel and absence of TCD machines. Currently, there are approximately 300 radiologists available in Nigeria serving a population of nearly 175.5 million, an estimate of 1 radiologist per 658,000 people [14,15]. Given the paucity of radiologists in the region, an alternate implementation strategy focused on training nurses in community hospitals to perform TCD screening will dramatically increase the number of eligible children who will have access to stroke prevention services. Similarly, training the medical officers already working in the

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community hospital on initiation and monitoring of HU administered to children with abnormal TCD measurements will be far more efficient and sustainable than full dependence on the insufficient numbers of specialists and subspecialists (pediatricians or hematologists). Additionally, significantly more people attend the community hospital (YDMH) because of its location in a more densely populated area of the metropolis and lower cost compared with the teaching hospital (9214 people/km^2 vs. 6835 people/km^2 and US $4.58/outpatient visit vs. US $6.77/outpatient visit, respectively) [16].

Rationale for Task Shifting

The World Health Organization (WHO) defines task shifting as "the rational redistribution of tasks among health workforce teams. Specific tasks are moved, where appropriate, from highly qualified health workers to health workers with shorter training and fewer qualifications in order to make more efficient use of available human resources for health" [17]. In Nigeria, as with many other resource-constrained countries, there is a shortage of well-trained health workers [18]. Currently, WHO estimates 4 doctors per 10,000 population in Nigeria compared with 26 doctors per 10,000 population in the United States [19,20]. Additionally, the available health workers are unevenly distributed, with a higher concentration in urban areas and private sectors [18,21]. Even if Nigeria embarks on an emergency training of doctors equipped to offer stroke prevention to children with SCA, it will take 6 years to certify generalists and another 4 years to train a specialist (radiologist or hematologist). Clearly, other alternatives are needed to address this shortage of qualified health personnel. Therefore, task shifting "presents a viable solution for improving health care coverage by making more efficient use of human resources already available and by quickly increasing capacity while training and retention programs are expanded" [17]. Task shifting can produce equivalent or superior outcomes for many diseases and health interventions [22].

Objectives

The overall goal of this protocol is to create a stroke prevention program in a community hospital (YDMH) through task shifting of TCD screening to nurses and initiation of HU to nonspecialist medical officers. This strategy will help in translating research to usual care by (1) reaching a larger number of children with SCA eligible for stroke screening and (2) identifying those with abnormal TCD values who will benefit from stroke prevention with HU, thereby decreasing stroke occurrence.

The specific objectives of this protocol are to

1. Identify barriers and facilitators that influence the adaptability of the transported evidence-based practice intervention, including the implementation process;
2. Build capacity for stroke detection and prevention in SCA at a community hospital; and
3. Conduct a feasibility trial comparing the effectiveness of a physician-based primary stroke prevention program at an academic site with a task-shifted primary stroke prevention program at a community site.

Methods

Study Design and Setting

This study will be conducted at 2 sites, BDTH academic hospital and YDMH community hospital, using both quasi-experimental (objectives 1 and 2) and effectiveness-implementation (objective 3) designs. Procedures will be conducted in 3 phases: (1) needs assessment, (2) capacity building, and (3) feasibility of the implementation trial.

Phase 1: Needs Assessment

Objective

The goal of this phase is to better understand the current knowledge and perception of health care providers and hospital administrators on stroke in SCA to inform future interventions in the community hospital using a prospective, qualitative study design.

Recruitment, Eligibility, and Stratification

Nonspecialist physicians and nurses working in the pediatric unit at the YDMH community hospital will be recruited to participate in a series of focus groups, after an advocacy visit and permission is received from the hospital management. These providers run a weekly SCD clinic with an average attendance of 50 patients per week. We will use a purposeful recruitment approach to maximize input from participants on the needs assessment [23]. Per best practices, multiple focus groups will be planned from different perspectives (samples) to triangulate issues and concerns. We will stratify within each sample and conduct several focus groups per stratum [24,25]. We anticipate a total of 4 focus groups per sample (comprising 4-6 participants each) among nurses and doctors. We anticipate that 2 focus groups per stratum will be adequate for saturation. If needed, we will conduct a third group in each stratum.

We will also conduct informant interviews for key hospital administrators, notably the Medical Director, Director of Administrator, Chief Matron, and Chief Accountant of the Community Hospital.

Focus Group and Interview Procedures

Following individuals' consent to participate and self-reported eligibility confirmation, the research coordinator will convene focus groups at times convenient for participants. Providers will receive a reminder phone call or SMS text message 48 hours before the scheduled focus group to maximize attendance. Focus groups will be led by a trained facilitator and will last about 45 minutes. During the focus group, the principal investigator (PI) will provide supplemental education on SCD, and participants will be provided with lunch. Focus groups will be audiotaped, transcribed, and deidentified. During the focus group, a research assistant will take field notes to supplement the transcript. Throughout the needs assessment phase, the PI and other senior key personnel will meet weekly to assess fidelity, focus group processes and progress, discuss emerging themes, and assess progress toward saturation. Interviews with hospital administrators will be scheduled at times convenient for the individual and last about 30 minutes.

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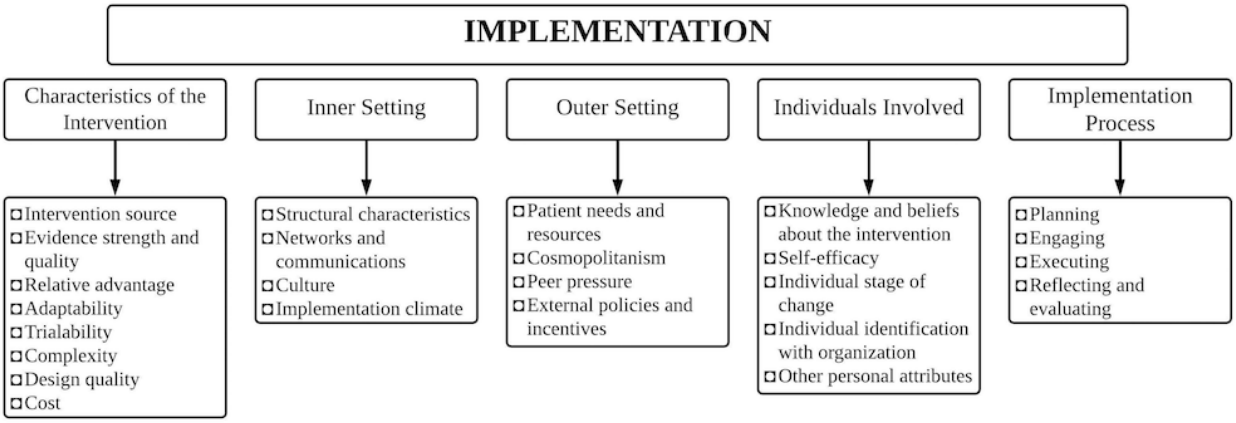
Facilitators of the focus groups and interviews will use a structured guide, including moderator instructions, key questions, and suggested probes, developed by the PI and mentors (see Multimedia Appendices 1 and 2). The focus group and interview guides, informed by the Consolidated Framework for Implementation Research (CFIR), will address 5 domains of implementation (Figure 1). Textbox 1 presents sample questions. Similar questions will be asked for each stratum with minor wording changes where appropriate. The semistructured interview conducted with hospital administrators will mainly address barriers and facilitators to the implementation process.

Figure 1. Consolidated framework for implementation research.



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Textbox 1. Consolidated Framework for Implementation Research domains to be addressed by focus groups and interviews.

Intervention Characteristics (Adaptability)

Health Care Providers

Do you think it is possible to task shift the conduct of transcranial Doppler (TCD) and stroke detection to nurses?

- What role do you think nonphysicians should play in stroke prevention in children with sickle cell disease (SCD)?
- Tell me how you feel about nonphysicians doing TCD screening and stroke detection
- Tell me how you feel about task shifting

Administrators

How do you feel about task shifting?

- How do you think task shifting should be done in your organization?
- Who do you think should be involved in task shifting?

Characteristics of the Individual (Knowledge and Belief About the Intervention and Self-efficacy)

Health Care Providers

What do you know about SCD and stroke?

- Tell me how you think a child with stroke will look like
- How do you think you can recognize a child with stroke?

Do you think you can help prevent stroke in children with SCD?

- In what ways do you think you can help?
- Tell me what will you do
- Tell me the skills you would like to have for you to help prevent children from having a stroke

Administrators

Do you know about SCD and stroke?

- How do you think stroke affects children?
- How do you think children can be prevented from having a stroke?
- Do you think children can have a stroke?
- Do you think children that had a stroke will recover completely?
- How do you think you can help them?

Outer Setting (Patient Needs and Resources)

Health Care Providers

Do you think you need more information on SCD and stroke?

- Tell me what you would like to know about SCD
- How would you like the information to be provided?

Administrators

Tell me the kind of information you would like to have on SCD

- How would you like the information to be provided?

Inner Setting (Implementation Climate)

Health Care Providers

How do you think task shifting will fit into your current schedule?

- How do you feel about task shifting?
- Tell me how you think you will adapt
- Tell me how you will help in making task shifting efficient

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Administrators

How will you implement task shifting?

- Tell me how you will introduce task shifting
- Tell me how you will ensure that task shifting is sustained

Implementation Process (Planning and Engaging)

Health Care Providers

How do you intend to inform parents about the stroke prevention program?

- Tell me the ways that you will ensure parents bring their children for TCD and stroke detection
- How will you follow children to ensure they have their TCD at the scheduled times?

How will you get the buy-in of parents/caregivers for the program?

- Tell me how you will engage parents/caregivers to advocate for TCD screening in the community
- Tell me how you will communicate with them

Administrators

How do you intend to start the stroke prevention program?

- Tell me how you will ensure your staff supports the program
- Tell me how you will ensure the program is continued

How will you get the buy-in of staff within your organization?

- Tell me how you will identify champions within the organization

Tell me how you intend to engage them

We will also administer a brief (<10 minutes) prediscussion survey before each focus group and interview (Multimedia Appendices 1 and 2). For nurse and doctor participants, we will query age, gender, ethnicity, job description/title, patient population, percentage of patients with SCD, and years of experience caring for individuals with SCD. For hospital administrator participants, we will query age, gender, job description, average cost of hospital admission, approximate number of individuals with SCD attending the hospital annually, role in redistribution of staff within the hospital, and about 5 questions on SCD complications and the approximate cost of care.

Data Analysis

Qualitative data will be analyzed based on principles from grounded theory using both inductive and emergent coding strategies and methods used in previous studies [26-28]. Coding will begin with open coding of the transcript to identify topics and codes to develop a codebook. This will be followed by thematic coding to identify common categories and meanings to reach thematic saturation (ie, no new themes will be captured with further analysis). Primary and secondary coders will develop a codebook of themes to complete analysis. Removing identifiers from transcripts will preserve participants' confidentiality. We will also remove any participants' reports of unusual circumstances that could make them identifiable.

Phase 2: Capacity Building

Objective

The goal of this phase is to address the barriers to stroke prevention identified in the needs assessment phase by providing education and training using a pre- and poststudy design. We will apply a previously established education program for stroke detection in children on nurses and medical officers at the community hospital [29]. We will also train nurses at the community hospital to conduct TCD screenings through a previously established TCD certification program. To guide the application of these already established educational and training materials [29], we will use our findings from the needs assessment phase, guided by the CFIR framework (Figure 1), and focus particularly on the "characteristics of the individuals" domain to address the "knowledge and beliefs about the intervention" construct.

Recruitment and Eligibility

We will use convenience sampling for the conduct of this phase, and participants will be selected based on availability and willingness to participate [23]. Four nurses working in the pediatric clinic at YDMH community hospital will be approached for training on stroke detection and TCD screening. Based on interest, 2 nurses will be selected for training. Reasons for interest and disinterest will be documented. All medical officers working in the pediatric clinic will be approached for participation. Two medical officers will be recruited based on interest. Children with SCD meeting the eligibility criteria for TCD screening will be recruited for training purposes via the

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weekly pediatric SCD clinic. The recruitment and training will be done over a period of 6 months.

Training Procedures and Outcome Measures

Following consent, nurses and medical officers will be enrolled in an educational course, which will emphasize detecting strokes and common clinical problems seen in children with SCA. A 20-minute video in Hausa (native language of most individuals that live in Kaduna, Nigeria), developed with members of our team, has already been created to reinforce the common causes of morbidity in children with SCD, including fever management, splenic sequestration, vaso-occlusive pain episodes, and stroke. This video will be used to support didactic lectures and will serve to augment the key learning objectives expected in the courses.

For stroke scale certification, nurses will be taught to perform the Pediatric National Institutes of Health Stroke Scale (PedNIHSS), a validated, standardized neurological examination used in previous trials [9,30]. Nurses will watch a set of 5 videos created by a certified neurologist, designed to instruct nonphysicians on how to conduct a pediatric neurological examination as per the PedNIHSS. Topics include (1) stroke in SCD, (2) pediatric neurology history and examination, (3) neurologic history and examination findings that suggest a child has had a stroke, (4) the PedNIHSS, and (5) supportive care immediately after a stroke has occurred. Similarly, educational materials describing SCD, mode of transmission, and some complications including symptoms of stroke, for example, FAST (Face drooping, Arm weakness, Speech difficulty, and Time to call for help), already being utilized at the teaching hospital (BDTH) will be shared with health providers at the YDMH community hospital for patient education during weekly health talks. A card describing the FAST acronym with pictograms and simple, concise language (both English and Hausa) will be provided and shared with patients to take home with them. We will administer a pre- and posttest after each health education session to assess for changes in knowledge among participating nurses.

The Stroke Prevention Trial protocol will be used to train nurses on TCD screening [7]. One of the 2 original Nigerian TCD-certified radiologists will implement the preexisting TCD screening training program, which covers didactic theory lectures and practical aspects of TCD measurements for a minimum of 60-90 hours for 2 weeks. All TCD training and examinations will be done on the same nonimaging TCD machine (Lucid M1 Systems; Neural Analytics Inc.). The research team will interview participating nurses during and at the end of the training to capture challenges, feasibility, and acceptability of the training program. Feedback from nurses will be used to adapt the training for future trials.

Data Analysis

To pass the stroke scale certification training, nurses will be required to pass the online NIH (National Institutes of Health) Stroke Scale Certification, which requires a total of 84 correct answers out of 90 in each of the 6 sections of training [31].

Nurses will obtain TCD certification based on Spearman rank correlation (r) between the trainer and nurse trainees. As per the protocol in our Fogarty-NINDS–funded R21 and R01 randomized controlled primary stroke prevention trials, each trainee and trainer will have at least 40 paired TCD measurements as part of their TCD certification examination, with at least four children that have prior documented abnormal TCD measurements. Passing the TCD certification will require a correlation between the trainee and trainer exceeding the lower bound of 0.76 (ie, 85% of the documented trainer's correlation as the minimum acceptable correlation threshold) [32]. The data will be analyzed using R Core (2016) [33].

Phase 3: Feasibility of the Implementation Trial

Objective

The goals of this phase are to (1) conduct a nonrandomized single-arm prospective trial to determine the feasibility of initiating a stroke prevention program for children with SCA in a community hospital (YDMH) through "task shifting" by recording recruitment, retention, and adherence rates; and (2) conduct an effectiveness-implementation study to test the hypothesis that a "task-shifted" approach for primary stroke prevention in a community hospital demonstrates noninferior effectiveness in identifying children with abnormal TCD and stroke compared with a physician-led primary stroke prevention at a teaching hospital.

Recruitment and Eligibility

We will use convenience sampling, and participants will be selected based on availability and willingness to participate [23]. Children meeting the following eligibility criteria will be recruited via pediatric SCD clinics at both BDTH (teaching hospital) and YDMH (community hospital): (1) diagnosis of SCA (hemoglobin [Hb] SS or Sβthal^0), and (2) between 2 and 16 years of age. Children will be excluded from participation if they meet any of the following criteria: (1) prior overt stroke (a focal neurological deficit of acute onset) by history, focal neurological deficit on standardized neurological examination, or concern for moderate or severe neurological deficit (which could be due to stroke); (2) already on HU therapy either for stroke prevention or for other indication; (3) prior participation on the therapy arm of the SPRING trial [34]; (4) have comorbid conditions such as asthma or epilepsy; and (5) have other exclusions for HU including significant cytopenia (Hb <6 g/dL, absolute neutrophil count $<1.5 \times 10^9$/L, platelets <150,000/µL, reticulocytes <80,000/µL [unless Hb is >9 g/dL], renal insufficiency [creatinine >0.8 mg/dL]). The study will be introduced to patients during the routine "health talk" given in the morning of every clinic, and informational leaflets and flyers will be provided. Informed consent will be obtained from a legal guardian for all participants. Assent will be obtained from participants aged 5-16 years. Enrolled participants will be followed for 12 months.

Feasibility Trial Procedures and Outcome Measures

Consenting participants will undergo TCD screening and neurological examination for stroke detection. Participants' medical history will be taken and physical examination conducted. Blood and other biological samples will be drawn for laboratory investigations.

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If the participant has elevated TCD levels (≥200 cm/second on 2 consecutive measurements or a single measurement ≥220 cm/second), they will be offered blood transfusion first as the default standard care in primary stroke prevention in SCA. If the participant and family elect not to receive blood transfusions, they will be invited to participate in the study. The participant will complete the consent and assent process for study screening and evaluations as outlined in Table 1. If the participant and family elect to participate, the participant must successfully swallow a pill (vitamin C tablets) in the presence of study personnel prior to being allocated to receive study therapy. If successful, study personnel will review the schedule of study procedures with the participant and family as shown in Table 2. For children with conditional TCD measurements (>180 and <200 cm/seconds), we recommend that follow-up TCD measurements be done as per routine clinical practice, but typically a child with a conditional TCD velocity would have a repeat TCD measurement within 3 months, and often sooner.

Both study sites will complete laboratory monitoring to identify potential adverse events or complications associated with SCD and being on HU therapy. A local monitor based at the site will review all laboratory values weekly. Based on the laboratory values of the SPIN Trial (NCT01801423), we have been able to select the 10th and 90th percentile for each laboratory value that will be assessed. We have also established decision rules for each laboratory value to guide health care providers on how to monitor for potential toxicities (Table 3). In circumstances where laboratory monitoring cannot be completed at the study site due to institution or local strike, it will be conducted at a back-up laboratory.

Table 1. Screening and initial evaluation.

Procedure	Visit 1
Initial review for study screening	
Informed consent and assent for study screening	✓
History and physical examination	✓
CBC/diff[a], reticulocytes	✓
Hb[b] F and S quantification	✓
Urinalysis	✓
Urea/electrolyte/creatinine	✓
Liver function test	✓
Confirm eligibility for study screening based on laboratory values	✓
Continued initial review for study screening for participants with Hb greater than 6 g/dL	
Baseline Stroke-Free Questionnaire	✓
Baseline PedNIHSS[c] neurological evaluation	✓
TCD[d]	✓
Capsule swallowing confirmation by research personnel	✓
Pregnancy test (same time as urinalysis when menses is reported)	✓
Confirm eligibility for study therapy	✓
Obtain informed consent and assent for study therapy	✓

[a]CBC/diff: complete blood count with differential.

[b]Hb: hemoglobin.

[c]PedNIHSS: Pediatric National Institutes of Health Stroke Scale.

[d]TCD: transcranial Doppler.

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Table 2. Schedule of study procedures.

Procedure	Interim visits for HU[a] therapy (months 1-12)	Month 12
Informed consent and assent for study therapy	Reconsent as needed	Reconsent as needed
History and physical examination	✓	✓
TCD[b]	Every 3 months	✓
Follow-up Stroke-Free Questionnaire	✓	✓
Study medication refill/pill counting	✓	✓
Adherence intervention	✓	✓
CBC/diff[c], reticulocytes	✓	✓
Urinalysis	✓	✓
Urea/electrolyte/creatinine	✓	✓
Liver function test	✓	✓
10 Questions neurological screening	✓	✓
Annual PedNIHSS[d] neurological evaluation	✓	✓

[a]HU: hydroxyurea.

[b]TCD: transcranial Doppler.

[c]CBC/diff: complete blood count with differential.

[d]PedNIHSS: Pediatric National Institutes of Health Stroke Scale.

Table 3. Laboratory monitoring of HU.

Laboratory parameters and when to stop therapy	Remarks
Hb[a]	
• Hb <6 g/dL • Give blood transfusion if Hb <5 g/dL • Resume HU[b] if Hb >6g/dL	• Evaluate for nutritional deficiency (Fe, B12, folate). If iron deficiency is suspected, give FeSO4 at 3 mg/kg • Investigate for other causes (bleeding, helminthiasis, malaria, renal diseases)
Platelet count	
• Platelet <80 × 109/L • Resume HU if platelets >80 × 109/L	• Repeat CBC[c] on the same day or within a week. Investigate for viral infections.
ANC[d]	
• ANC <1000 × 109/L • Resume HU if ANC >1000 × 109/L	• Stop HU and repeat CBC weekly until ANC >1000 × 109/L. If ANC <1000 × 109/L after 2 weeks, refer to the consultant pediatrician. Once ANC is >1000 × 109/L, restart HU at a dose decreased by 20%. Repeat CBC after 2 weeks of change in dose.
Reticulocyte count (not available routinely)	
• Reticulocyte count <1% and Hb <6 g/dL	• Repeat reticulocyte and Hb measurements in 1 week. Evaluate for other causes (bone marrow disorder, nutritional deficiencies [Fe, B12, folate]). Refer to a consultant to treat underlying cause.

[a]Hb: hemoglobin.

[b]HU: hydroxyurea.

[c]CBC: complete blood count.

[d]ANC: absolute neutrophil count.

In an effort to maximize adherence to HU therapy, we have developed a *Parent Handbook* that is part of standard care for children on HU therapy and has been translated into Hausa. The Handbook emphasizes the following:

- The key to the success of retention and follow-up will be attention to detail; consistency of the research team; and trust among the parents, patients, and staff. The staff will contact parents immediately and reschedule patients' appointments when missed.
- Close monitoring of participants' visits and need for return appointments with follow-up telephone calls are key elements for monitoring patient attendance and prevention

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of study participants' being lost to follow-up. Every attempt will be made by the study team to contact patients prior to their scheduled visit based on the allocated schedule for participants on HU therapy.
- Identification of a stable contact person (such as a grandparent, neighbor, teacher, friend) who does not live with the participant's family, but always knows the family's whereabouts will assist in tracking patients and decrease the number lost to follow-up.
- Additionally, the site will log patients who are approached to participate in the study and document whether the patient and family elects or declines involvement with the study. The rationale for not participating in the trial will be inclusive of but not limited to time commitment for the study, therapy regimen, adherence to HU therapy, etc.

All participants will be followed for up to 12 months to assess rate of recruitment, retention, and adherence to the treatment protocol for primary stroke prevention for those with abnormal TCD measurements. *Recruitment rate* is defined as the proportion of participants who agreed to participate in the study out of the total number of persons approached. For this study, we anticipate a minimum recruitment rate of 80% based on our team's experience with the SPIN trial in Kano, Nigeria [9]. *Retention rate* is defined as the percentage of study participants who completed the study protocol at the end of 12 months. We expect a retention rate of greater than 80%. *Adherence rate* is defined as the proportion of children with laboratory evidence of sustained HU therapy (primary measure), measured by an increase in mean cell volume of at least 10 fL from baseline, and by the percentage of pills returned from the total amount administered to the pharmacy every 3 months (secondary measure). We expect a therapy adherence rate for both primary and secondary measures of at least 80% (eg, 80% of patients will have an increase of at least 10 fL in mean corpuscular volume from baseline [9]).

We will use the "Reach and Effectiveness" components of the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework to evaluate implementation outcomes between the community and teaching hospitals [35,36]. The number of eligible children with SCA that have TCD screening in both the teaching and community hospitals will measure the "Reach"; while "Effectiveness" will be measured by the proportion of children with abnormal TCD measurement started on HU (averting stroke) between the academic and community site (primary outcome). Secondary outcomes will include (1) incidence of other clinical events including pain crises, fever, acute chest syndrome, or severe anemia in children with abnormal TCD measurements receiving HU in both the academic and community sites, (2) incidence of clinical events among children with SCA not receiving HU, and (3) death.

Sample Size Determination

For the feasibility trial, our focus is whether or not this trial is feasible based on rates of recruitment, retention, and adherence to trial therapy. We will use a CI approach to ensure that we can achieve a minimal level of recruitment, retention, and adherence rates to trial medication (HU) that would be acceptable. If we do not achieve this minimum rate, we will examine other alternative approaches and barriers needing to be resolved before proceeding with a full-scale trial. In this case, we consider compliance is dichotomous (yes or no). Thus, we can assume a binomial distribution, and calculate corresponding 95% CIs. Because we are only focused on ensuring a floor level of compliance, where we define compliance as an increase in mean corpuscular volume ≥10 fL, we will use 1-sided CIs (ie, ensure lower bound is above our lowest acceptable rate of 75%). With a sample size of 100, and observed compliance rates of 83% and higher, using the Clopper-Pearson formula, we will obtain a lower bound of 75.6% or greater.

Data Analysis

We will use proportions and CIs to calculate the percentages of participants who have agreed to be part of the trial, adhere to the trial drug (HU), and complete the 1-year follow-up. Person times will be calculated to determine incidence rate ratio of stroke. We will use Cox regression and the Kaplan-Meier plot to calculate the hazard rate for stroke recurrence and probability of recurrence.

Quantitative data will be analyzed using descriptive, comparative, and correlational statistics to measure the implementation outcomes of Reach and Effectiveness before and 12 months after intervention.

Ethics Approval

The ethics committee of the Kaduna State Ministry of Health and BDTH/Kaduna State University approved this protocol on June 9, 2020, and June 22, 2020, respectively.

Results

Funding for the study is from the Fogarty International Center and National Institute of Neurological Disorders and Stroke (K43TW011583). The Institutional Review Board of BDTH and Kaduna State Ministry of Health approved the study. The needs assessment phase of the study was completed in February 2021. Manuscript on findings is currently in preparation. Capacity building is ongoing with TCD training and SCD and stroke education sessions for nurses and doctors in the community hospital. Recruitment for the implementation trial is expected to commence in July 2022.

Discussion

Principal Findings

This study proposes a structured, theory-driven approach to create a stroke prevention program in a community hospital in Kaduna, Nigeria, to decrease stroke incidence among children with SCA. Results will provide preliminary data for a definitive randomized clinical trial in implementation science.

We hypothesize that establishing a stroke prevention program in a community hospital by task shifting of TCD screening to nurses and administration of HU to children with abnormal TCD values to medical officers will increase the number of children with SCA identified with the risk of stroke, leading to a decrease in stroke incidence. Because of the lack of skilled personnel, stroke prevention programs are only available, prior

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to this study, at academic hospitals where there are many specialists that offer these services. Our task-shifting strategy will address the gap in the available human resources at the community level by building the capacity of nurses and medical officers.

Comparisons With Prior Work

We have previously established stroke prevention programs in academic hospitals following the successful completion of the SPIN (NCT01801423) and SPRING (NCT02560935) trials in Nigeria. Given the paucity of radiologists, nonspecialist medical officers were trained to conduct TCD screening in our previous trials. However, we figured this was not a very sustainable strategy because after sometime, these medical officers go on to start their specialist training. Therefore, to ensure sustainability, we chose to train nurses in the community hospital on the conduct of TCD. This way, children will be seen and have their TCD done on the same day and those that have abnormal TCD values can be started on HU.

Strengths and Limitations

The strength of our study lies in the mixed method design we are using. The qualitative aspect gives us an insight into the context of the community in which the intervention is being introduced. We will be able to identify the barriers and facilitators to the intervention and tailor them toward implementation and sustainability. Additionally, using quantitative methods will allow us to measure the actual impact of the stroke prevention program. A weakness we have identified is the cost associated with the multiple trainings that nurses and medical officers have to undergo and our inability to address some of the identified barriers, which may be out of our control.

Future Directions

This study will set the stage for further scaling-up stroke prevention services that will be accessible to eligible children with SCA living in low-middle income countries like Nigeria. Further, the approach of conducting TCD screening and initiation of HU on the same day can serve as a basis for "reverse innovation" in other resource-rich countries where the uptake of TCD screening is suboptimal.

Conclusion

This study proposes a structured, theory-driven approach to create a stroke prevention program in a community hospital in Kaduna, Nigeria, to decrease stroke incidence among children with SCA. Results will provide preliminary data for a definitive randomized clinical trial in implementation science.

Acknowledgments

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Authors' Contributions

AAK, HB-M, and MRD designed the study. HB-M, AAB, and AAK wrote the manuscript. HB-M, LH, AMT, BUF, ASK, GYB, AAK and ASM conducted the study activities. AAK, AAB, and MRD critically reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group discussion guide.
[DOCX File , 37 KB - resprot_v11i6e37927_app1.docx]

Multimedia Appendix 2
Key informant interview guide.
[DOCX File , 22 KB - resprot_v11i6e37927_app2.docx]

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Abbreviations

ANC: absolute neutrophil count
BDTH: Barau Dikko Teaching Hospital
CBC: complete blood count
CFIR: Consolidated Framework for Implementation Research
FAST: Face drooping, Arm weakness, Speech difficulty, and Time to call for help
Hb: hemoglobin
HU: hydroxyurea
NIH: National Institutes of Health
PedNIHSS: Pediatric National Institutes of Health Stroke Scale
PI: principal investigator
RE-AIM: Reach, Effectiveness, Adoption, Implementation and Maintenance
SCA: sickle cell anemia
SCD: sickle cell disease
SPIN: Stroke Prevention in Nigeria
SPRING trial: Primary Stroke Prevention in Nigeria
TCD: transcranial Doppler
WHO: World Health Organization
YDMH: Yusuf Dantsoho Memorial Hospital

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Proposal

HIV Digital Vaccine Strategy: Proposal for Applying Blockchain in Preventing the Spread of HIV

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Abstract

Background: The HIV epidemic imposes a heavy burden on societal development. Protection of susceptible populations is the most feasible method for eliminating the spread of HIV. In the absence of a biological vaccine, the definitive solution is enabling susceptible populations to recognize and avoid high-risk sexual behavior.

Objective: The objective of this study is to use specific technologies and strategies to establish a system by which high-HIV-risk individuals can determine the HIV infection status of one another anonymously, conveniently, and credibly.

Methods: This study proposes an HIV digital vaccine (HDV) strategy, a decentralized application (Dapp) based on blockchain for use by individuals with a high risk of HIV and accredited testing agencies (ATAs). Following testing, only the HIV-negative results (or linked information) are uploaded to the blockchain, which results in high-risk individuals being able to determine the HIV-negative status of each other anonymously, conveniently, and credibly.

Results: Future work includes the following: (1) a survey of the willingness to use Dapps among high-HIV-risk populations, (2) a larger framework containing both HDV and people living with HIV (PLH) and discussing the influence of HDV on PLH and its possible solutions, and (3) coordinating with the blockchain development team, ATAs, community-based organizations, and third-party organizations to raise funds, develop the Dapp, formulate detailed plans, and publicize and promote it. The exact timeline for achieving these objectives cannot be determined at present.

Conclusions: The HDV strategy may reduce the occurrence of high-risk sexual behavior and effectively protect susceptible populations; combined with current strategies, it is a promising solution to prevent the spread of HIV. The included concepts of decentralized surveillance and surveillance as intervention may spark a change in current infectious disease prevention and control modes to introduce beneficial innovations in public health systems globally.

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KEYWORDS

HIV; blockchain; digital vaccine; decentralized surveillance

Introduction

Background

The HIV epidemic is a major global public health problem. Between 2000 and 2015, the international community provided approximately US $109.8 billion worth of development assistance for HIV prevention and control [1]; however, the spread of HIV has not been effectively curtailed, with approximately 2 million new HIV infections occurring globally every year [2]. At the 20th International AIDS Conference in 2014, the Joint United Nations Program on HIV and AIDS adopted the 90-90-90 strategy to help end the HIV epidemic. By 2020, 90% of all people living with HIV (PLH) should know their HIV status, 90% of all people diagnosed with HIV infection should receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy should achieve viral suppression [3]. The core components of this strategy require substantial scaling up of HIV testing to identify sources of infection, subsequent scaling up of treatment, and assurance of

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effective treatment to control the sources of infection. However, this strategy requires a huge amount of resources [4], and researchers have expressed different opinions on its feasibility [5-7]. Although many countries and regions have made good progress, the United Nations AIDS report shows that in 2020, the global target of 90-90-90 has not been met, and a large gap remains in most countries and regions. At the same time, low- and middle-income countries are 30% short of the funding needed to meet the 90-90-90 targets, and this gap is widening [8]. It is apparent from the lack of cost considerations that the 90-90-90 strategy is the best attempt by the international community in the absence of a vaccine.

Main Problems Faced in Preventing the Spread of HIV

Considering the chain of infection (infection source, transmission route, and susceptible population), it is apparent that implementing preventive measures for all sources of infection is extremely difficult. In a previous study, based on a mathematical model, the estimated cost per new HIV case diagnosed in the United States was at least US $2528 and could be up to US $63,053 under specific circumstances [9]. Because of factors including incurability and the long asymptomatic stage of HIV as well as the protection of individual rights, even if most sources of infection are found, it is impossible to control them thoroughly and effectively. Furthermore, the management of HIV transmission routes, which are mainly sexual, cannot be realized because sexual activity is a basic human need. Therefore, currently, the most feasible method for preventing HIV spread is protecting susceptible populations. In the absence of a vaccine, the definitive solution is enabling susceptible populations to recognize and avoid high-risk sexual behavior. However, the key barrier to this method is the lack of a system by which individuals can determine the HIV infection status of one another conveniently, anonymously, and credibly. Therefore, the use of specific technologies and strategies to establish such a system has great significance for protecting susceptible populations against HIV infections.

Attempts at Solving the Problem

To solve this problem, the HIV infection status of individuals must first be known. Forced by circumstances [10], the Chinese government used its administrative power to launch a real-name system for universal HIV screening of former paid blood donors in 2004 [11]. Subsequently, comments regarding HIV testing and the issue of individual rights were raised in an article [12]; this approach had many disadvantages that outweighed the benefits of social balance. Therefore, in noncritical situations, the government may not be inclined to use such methods. More importantly, without effective control of the infection sources and transmission routes, HIV spread cannot be eliminated.

The advent of the internet has changed the strategies of disease prevention and control [13]. With the popularization and convenience of the internet, an increasing number of studies have used this medium for the testing, intervention, and management of specific diseases or for providing relevant services [14-16]. The feasibility, acceptability, and influence of novel internet technologies in HIV infection prevention have also been confirmed [17,18]. Current internet-based testing, management, intervention, and treatment methods aim to identify HIV-infected persons and provide treatment and behavioral intervention. Though it is helpful to approach 90-90-90 targets, this strategy is unable to address the need for a method that allows individuals to check the HIV infection status of one another conveniently, anonymously, and credibly.

Overview of Blockchain Technology and the Surrounding Concept

The advent of blockchain technology offers possibilities for solving the aforementioned problems. Blockchain technology is the underlying foundation of cryptocurrencies such as Bitcoin and was first described in the foundational article entitled “Bitcoin: A Peer-to-Peer Electronic Cash System” published in 2008 [19]. China’s Ministry of Industry and Information Technology defined blockchain technology as a novel application of computer technologies, including decentralized data storage, peer-to-peer transfers, consensus mechanisms, and encryption algorithms, in the internet era [20]. With blockchain technology, information is encrypted and anonymously recorded in a network. As the recorded information is indelible, open, and transparent, a highly effective and convenient decentralized network storage system can be established. These properties help society achieve lower costs of trust, enable wider collaboration, and provide the foundation for a form of self-organization independent of governments and markets [21,22]. With the industry changing constantly in recent years, application-based research in the fields of health and medicine is also increasing continuously [23-25].

Smart contracts add more value to the blockchain ecosystem. They are executable codes that run on top of the blockchain to facilitate, execute, and enforce an agreement between untrustworthy parties without the involvement of a trusted third party [26]. The decentralization, autoenforcing ability, and verifiability of smart contracts enable their encoded business rules to be executed in a peer-to-peer network, where each node is “equal,” and none has any special authority without the involvement of a trusted authority or a central server. Smart contracts are expected to revolutionize many traditional industries, such as finance, health care, and energy [27].

Smart contracts can be used as standalone applications. For instance, smart contracts are commonly used to create a tradeable digital token, which can represent a currency, an asset, a virtual share, or a proof of membership. A smart contract may define a token with a fixed supply or even act as a central bank that can issue tokens [28]. Tokens are created on top of existing blockchains, and cryptocurrency is native to its own blockchain. In practice, cryptocurrencies and tokens are frequently used interchangeably. Here, crypto asset is used as an umbrella term. Crypto assets represented by Bitcoin are an important element of blockchain applications. A token represents the typical crypto asset; its simple issuance, transparent distribution, efficient circulation, and programmable characteristics are all advantages over the existing banking and currency system [26]. The improvement and abundance of tokens make communication between various entities cheaper and collaboration more efficient, thus making the application of blockchain possible in more scenarios.

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Alternatively, a smart contract may be used as the back end of a multitiered application. Any application that relies on one or more smart contracts as its back end is known as a decentralized application (Dapp) [28]. In contrast to traditional applications in which the back-end code runs on centralized servers, Dapp is a novel form of the blockchain-empowered software system [29]. Its main properties include being open source, providing internal cryptocurrency support, ensuring decentralized consensus, and having no central point of failure [30]. In practice, an ideal Dapp should be completely hosted by a peer-to-peer blockchain system and will need no maintenance and governance from the original developers. The cost and profit are shared by all participants in the decentralized autonomous organization [31]. Currently, owing to the performance limitation of the current blockchain and smaller ecosystem, smart contracts still need to be run locally to complete the application [29]. Nevertheless, many Dapps have already been running stably and effectively on smartphones. The latest reports have shown 1 Dapp's daily user count reaching 1 million users [32]. Crypto assets are used to purchase services in Dapps. Information and assets of users are interacted with and exchanged via Dapps. As the number of users increases and the application mode expands, webs of trust with different scopes can be formed among people.

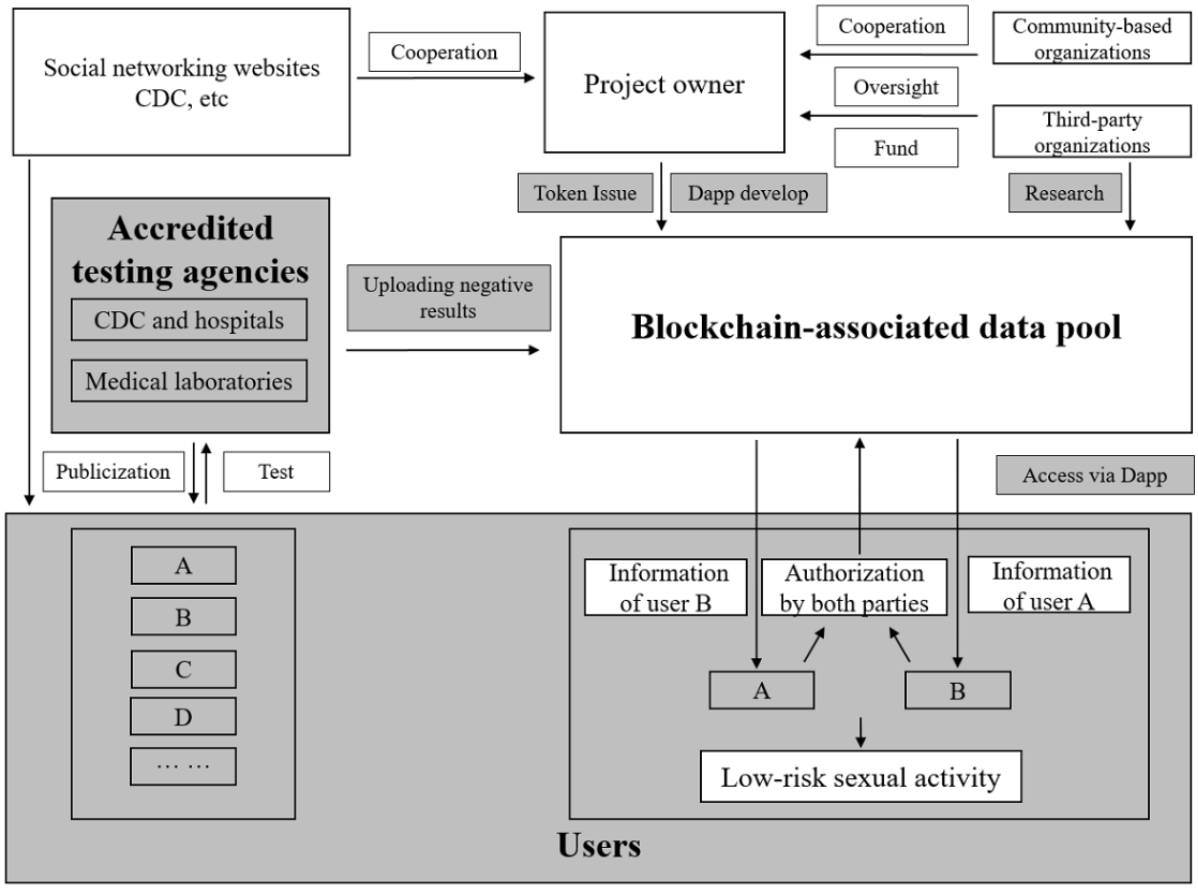
The objective of this study was to use blockchain and its ecosystem to establish a system by which high-HIV-risk individuals can determine the HIV infection status of one another conveniently, anonymously, and credibly.

Methods

HIV Digital Vaccine (HDV) Strategy and Decentralized Surveillance

Under the oversight of community-based organizations, the project owner develops a Dapp based on the public permissionless blockchain. Subsequently, the Dapp is publicized to facilitate the addition of individuals belonging to high-HIV-risk populations as users. After testing is completed at accredited testing agencies (ATAs), only the HIV-negative results (or linked information) are uploaded to the blockchain. Fingerprint recognition is used to ensure the reliability of the user's identity in the case of anonymity, and the parties involved in high-risk activities can access the blockchain via their smartphones to check the HIV-negative status of one another conveniently, anonymously, and credibly. Thus, high-risk populations can avoid high-risk sexual behavior and gain effective protection against HIV infections. As the number of users increases, prevention of HIV spread can be ultimately achieved. Figure 1 shows the technical flow chart of the strategy.

Figure 1. Technical flow chart of the HIV digital vaccine strategy. A, B, C, and D represent individuals belonging to high-HIV-risk populations. Tokens are exchanged when transactions occur among participants. Various transaction patterns can be used in different regions and they may vary when the situation changes. Behaviors in the gray frames are associated with blockchain. The participants in the gray frames are the major users of the Dapp. CDC: Centers for Disease Control and Prevention; Dapp: decentralized application.



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Segments of the HDV strategy

The main segments of the HDV strategy are as follows:

1. High-HIV-risk populations benefit the most from the prevention of HIV spread, and therefore have the motivation to promote this strategy. Men who have sex with men (MSM) constitute one of the key populations in the global HIV epidemic scenario [3]; more importantly, they have their own communities, especially internet-based communities such as Jack'd and Blued, which have the largest concentration of MSM in the United States and China, respectively [33,34]. For these reasons, MSM-specific social software operation teams (which often include MSM) are a natural fit for the project. Hospitals, as primary ATAs with closely related interests and the ability to provide more health services, are also suitable as joint project owners. It is ideal for the operation team and hospitals to jointly become project owners, which is more convenient for the collaboration between users and service providers. In view of the public interest characteristics of the strategy, the public permissionless blockchain platform is the best choice.
2. Dapp comprises two types of users: general users and ATAs. ATAs are genuine and authentic agencies (eg, Center for Disease Control and Prevention, hospitals, and medical laboratories) that can conduct actual tests and upload the test results of general users. ATAs post test results directly on the blockchain via Dapp or regular wallets (only with the time-stamped test result). General users will then have approved the addition of such data to the chain attached to their blockchain address. After the test results (or linked information) are uploaded to the blockchain, general users can authorize other users to access relevant test results. In some cases, to avoid using a Dapp, which is limited and not very user-friendly, a regular mobile app linked to an off-chain data repository that connects to the actual blockchain via smart contracts could be another option (private key management via fingerprint). Importantly, no general user registration is required, and no personal information is collected. Thus, the data on the server are totally anonymized.
3. Publicization of the Dapp is an important segment of this strategy. Maintaining complete anonymity for general users is the basis for publicization and promotion. Initial publicization efforts must be focused on populations with a strong demand through ATAs, community-based organizations, social networking websites, and HIV publicity activities; tokens could be used as incentives both for these entities and users. Further publicization can be performed among other high-risk populations after accumulation of experience and results.
4. A token used in the strategy mainly for information exchanges and value transfers, which can be the native cryptocurrency or the already-issued stable coin on the special public-permissioned blockchain, can meet the need. Furthermore, if extension of the strategy is considered, a larger ecosystem may lead the project owner to consider issuing a new token for crowdfunding and coordination of interests. These extensions may include addressing the negative externalities of the strategy (ie, compensating for the potential impact on PLH), other health services for high-HIV-risk populations, or prevention and control of other sexually transmitted diseases. Such a larger ecosystem cannot rule out the possibility of forming a new public chain.
5. Tokens can be issued by the project owner and used in transactions in the Dapp, which include the following: (1) A portion of the tokens is initially distributed to participating entities. (2) Project owners can promote the use of the Dapp by rewarding users with tokens. (3) Tokens are exchanged among users to allow for checking test results. (4) Users can use tokens to purchase additional Dapp services. (5) The government and industry can use data in the blockchain for monitoring, assessment, and research purposes. Following routine assessments, the government can purchase tokens in exchange for acquired social benefits. Various requirements ensure the circulation of tokens. Multiparty transactions of tokens ensure that the token economy system forms a closed loop for value realization, whereas listing and circulation provide a market safeguard for the token value.
6. When the segments described above are realized, the participating parties, which mainly comprise high-HIV-risk populations, jointly form a self-organizing community that can perform real-time information exchanges and value transfers.

The settings for the project owner, Dapp, and token are open and flexible. More possibilities exist as new models/infrastructures emerge. For example, the non-fungible token approach, which has recently gained much attention [35], is also worth considering. Users can grant access to each other's test reports by sending non-fungible tokens.

The voluntary checking of HIV status by individuals falls under virtual surveillance, which occurs before high-risk sexual behavior; both the implementers and recipients are HIV-negative individuals. This differs from the current mode of surveillance conducted by governments and industry, and this new mode of surveillance can be named decentralized surveillance.

In the decentralized surveillance network, which is jointly constructed by involving individuals, people can check the HIV-negative status of each other conveniently, anonymously, and credibly. Provided that 1 user is unable to confirm the HIV-negative status of his temporary sexual partners, he would refuse to have sex or take advantage of other interventions (such as condoms or pre-exposure prophylaxis) to protect himself, thereby providing the user with the ability to avoid high-risk sexual behavior and preventing HIV infections. As a matter of fact, during the process of surveillance, real-time intervention occurs automatically. The seamless conjunction mode of surveillance and intervention is indeed surveillance as intervention (SasI); the publicization and use of SasI in populations of an adequate scale can effectively curb new HIV infections. As this blockchain technology–based strategy is similar to the vaccination strategy and the effects of its application are identical to those of biological vaccines, this proposed strategy has been named the HDV strategy.

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Results

This study aims to propose and discuss the concept and framework of HDV, with a considerable amount of future work to be conducted:

1. A survey of the willingness to use Dapps among high-HIV-risk populations is needed to provide a basis for formulating the scheme to implement the HDV strategy. The survey is being prepared for use in Zhengzhou, China, and the survey protocol is currently being refined.
2. A larger framework containing both HDV and PLH is needed, accompanied by analysis of the influence of HDV on PLH and its possible solutions. Research on financial incentive frameworks for HIV treatment is being conducted; the payments made by high-HIV-risk populations in the HDV strategy can be used as financial incentives for HIV treatment populations, provided that the financial incentives for HIV treatment are reasonable, precise, and efficient. The HDV incentive for HIV treatment and HIV treatment back to HIV prevention (effective treatment suppresses viral load and prevents HIV transmission) forms a good ecology of HIV prevention and treatment, and it helps reduce the social costs of HIV containment.
3. Coordination with the blockchain development team, ATAs, community-based organizations, and third-party organizations (charities, investment institutions, research institutes, etc) is necessary to raise funds, develop the Dapp, formulate detailed plans, and publicize and promote the HDV strategy. The exact timeline for these objectives cannot be determined at this time.

Discussion

Significance of the Study

This study proposes the blockchain-based HDV strategy to enable individuals to avoid high-risk sexual behavior and thereby prevent new infections in the population level. The new public health concepts and models such as HDV, decentralized surveillance, and SasI were introduced for the first time. A significant amount of groundwork is required before HDV can be implemented, as mentioned in the Results section. As blockchain brings HIV prevention to a completely new field, the necessity, feasibility, and challenges merit further discussion.

Necessity of Decentralization and Advantages of Blockchain

We consider whether non-blockchain–based centralized methods can enable the verification of HIV infection status conveniently, anonymously, and credibly. The answer to this question can be derived from simple reasoning. The strategy in question is relatively simple and would have been previously considered or implemented by the government, industry, or even community-based organizations. However, the fact that this strategy never gained traction demonstrates the existence of certain unassailable barriers. These barriers involve multiple political, economic, social, and psychological concepts and may include, but are not limited to, the following interlinked problems:

1. Government direction (or entrusted to a third party) is the conventional approach under the current system. The HDV strategy may lead to the isolation of HIV-infected people, whereas government direction may result in a higher tendency for HIV-infected people to experience a strong sense of exclusion.
2. The HDV strategy involves multiple types of entities (such as governments, hospitals, medical laboratories, community-based organizations, and social networking websites), and it is difficult to coordinate their interests. The existing government/business direction approach is inefficient, thus resulting in a low cost-benefit ratio and making long-term implementation impossible.
3. In general, credibility and anonymity cannot be concurrently achieved with centralization, leading to low acceptability in high-risk populations.
4. Centralized servers and real-name systems are at risk of data breaches, with the risk increasing with the scale of publicization.
5. The high costs of collaboration between countries/regions restrict the entire strategy once a single problem becomes irresoluble and results in apprehension from governments, whereas low acceptability among users also poses a barrier to sustained publicization. Therefore, non-blockchain-based centralized methods cannot provide an effective means for checking HIV infection status among individuals conveniently, anonymously, and credibly.

In view of the aforementioned problems associated with centralized strategies, the following advantages of the blockchain are apparent:

1. The property of decentralization makes blockchain technology naturally suitable for approaches not requiring government direction. Individuals are free to choose whether to use Dapp, and the absence of government direction leads to a weaker sense of exclusion.
2. Blockchain brings new forms of self-organization. The issuance and distribution of tokens facilitates consensus among participating entities, allowing for efficient and effective collaboration. Moreover, trading and circulation of tokens facilitates the flow of information and value between participating entities and users, which is a unique advantage of blockchain.
3. Anonymity and credibility are the basic characteristics of blockchain. Dapp does not require the user's basic information.
4. Decentralized information storage will prevent large-scale data breaches, and information leakage in systems without real names does not have a significant effect on individuals.
5. The blockchain-enabled efficient approach reduces collaboration costs between countries/regions.

Certainly, in extreme cases (such as a high prevalence of HIV or where there is a trend in a certain region), the government may use a similar strategy without blockchain by expending significant amounts of resources to mandate screening and registration, but such coercion may be costly, disruptive to liberty, and eventually difficult to implement. Therefore, from a political economy viewpoint, the HDV is feasible simply because of the lower organizational and transaction costs and

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minimal interference with individual liberty enabled by the blockchain.

Feasibility

The HDV is a simple strategy. Testing facilities, community-based organizations, and social networking websites can establish a complete system and achieve effective system operation by integrating existing resources. The use of sexual and health needs as motivators for the acceptance of Dapp by high-risk populations is in line with human nature, and the concept that testing facilities and social networking websites are rewarded by the prospect of occupying the most advantageous position on the blockchain is in line with the long-term interests of such organizations. The acquired data can be used in public health services to benefit testing facilities and community-based organizations, ultimately contributing to the overall benefit of humankind. In addition, with tokens as a continuous reward system, this strategy falls in line with the principal benefits of the various participating entities; therefore, there is ample driving force to guarantee the feasibility of the strategy.

Blockchain technology can guarantee that the information in the network is immutable, but it cannot solve trust issues in the real world. With respect to the HDV, the main problems are ensuring that the results can only be used by their owners and preventing malicious use by other parties. Fingerprint recognition technology is widely used in smartphones. If Dapp is set to use only fingerprints as the unlocking method, then the entire process, including account generation, test and result uploading, result display, and transaction, would only use a unique and an unchangeable fingerprint. This would solve the malicious usage problem.

The cost-benefit ratio is an important factor that determines whether a strategy can be implemented. As this strategy is aimed at curbing HIV spread, its cost-benefit ratio should be compared with the total costs of HIV/AIDS prevention in the current society. Currently, government efforts in terms of publicity, testing, and services are ongoing; therefore, the integration of publicization and testing into the strategy does not incur additional costs, whereas the development and maintenance of Dapp only requires minimal human and financial resources. Part of the token value may have to be realized by the government through the purchase of acquired social benefits; however, such a move is relatively simple and cheap compared to launching a comprehensive HIV/AIDS prevention program. In addition, the huge social benefits arising from implementing this strategy are inestimable, thereby resulting in an extremely high cost-benefit ratio when combined with the relatively lower costs.

Innovations and Outlook

Taking the United States as an example, current HIV surveillance collects, analyzes, and disseminates information about new and existing cases of HIV infection through the National HIV Surveillance System. By meeting the surveillance goal, the Center for Disease Control and Prevention can direct HIV prevention funding to where it is needed most [36]. After allocating funds, the government uses numerous proven interventions to prevent new HIV transmissions [37]. The entire process from initiation of surveillance to implementation of interventions is complex, time-consuming, and costly, but this is indeed the status quo of HIV surveillance and intervention in most countries. Different from the current surveillance process, HIV infections are not considered in decentralized surveillance, and the data are no longer required by the government for collection, processing, and deciding how to implement interventions. Instead, the data are collected by users and immediately used for self-intervention, namely the SasI. Methods that ensure convenience and anonymity, data flows that are fast and secure, and a convenient and flexible token reward system enable the joint participation of individuals with relevant demands. Data on infectious diseases can be collected and shared, thus concurrently enabling self-protection and the prevention and control of infectious diseases. Hence, the SasI mode is more precise and efficient. With the development of blockchain, such a model may potentially spark the change of current government-funded infectious disease prevention and control modes and can bring about beneficial innovations in public health systems globally.

A vaccine is derived from Variolae vaccinae, which was first developed by Edward Jenner from cowpox. The term was created during the first industrial revolution by Louis Pasteur to honor Jenner and cover the new protective inoculations. It has since been expanded to denote a biological preparation that provides active acquired immunity to a particular disease. Benefiting from the information technical revolution, the concept of a vaccine has been further expanded in this paper. According to the discussion of the HDV, we can portray the concept of a digital vaccine. It is a strategy based on new digital information technology for establishing effective channels for information communication and value exchange among target populations so that individuals are capable of avoiding particular infection sources. With the wide application of blockchain in health care, the concept of a digital vaccine could be extended and improved, expanding the concept of a vaccine.

The HDV can provide a more efficient and thorough solution for the protection of susceptible populations; combining it with the present HIV prevention strategies directed by “90-90-90” could serve as a promising solution to prevent HIV spread.

Challenges and Responses

This strategy is for prevention and does not bring direct benefits to PLH. Because a mutual check of HIV infection status is needed before sexual behavior among high-HIV-risk individuals, who access protection from the HDV, it may be unpleasant to check for HIV infections even if they are not involved. Privacy should be fully protected and free of discrimination. Meanwhile, the rights of HIV-susceptible populations against uninformed infection should also be ensured. HIV- positive individuals are obliged to inform their infection status to sexual partners, but this cannot be fully ensured only through moral restraint. This strategy does not impose any restrictions on HIV-positive individuals and can be applied to protect susceptible populations from uninformed infection. It can balance the rights of various individuals. From a broader perspective, when the health of the entire population is guaranteed, humans have enough resources

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to cure diseases including AIDS, which will eventually benefit HIV-positive individuals. Preventing the transmission of HIV requires much more resources, which could indirectly slow the progress of studies on curing AIDS. Measures such as devoting a proportion of tokens paid by users to the research on treatment and cure of AIDS should be considered for practical implementation.

In particular, because there exists a window period and test results visible in the Dapp are uploaded 15 days ago, users with HIV-negative results may have been contaminated with HIV or become HIV positive later. The issue of the discordance between the actual status and test results still carries the risk of leading to HIV transmission, but it can be solved through the setting of the Dapp usage rules; the analysis and resolution are presented in Multimedia Appendix 1.

If the tokens of the HDV ecosystem are newly issued, the possibility of tracking wallet owners that own tokens to identify them as high-HIV-risk individuals exists, provided that users exchange real-world resources for the tokens. Solutions include the project owners/ATAs providing services that exchange the token to fiat currency or mainstream stable coin/cryptocurrency or a service for users with privacy needs for converting the token to other anonymous cryptocurrencies on exchanging. As long as the HDV ecosystem continues to evolve, users' needs will always be met gradually.

The emergence of blockchain technology and its applications in interdisciplinary fields are in the early stages. The transaction speed and volume of clinical data, privacy and security, patient engagement, and incentives are major barriers in the health care field [38]. Meanwhile, there is no prior similar study on the HDV strategy that can be used as a reference or a standard academic system that could provide scientific support; some arguments concerning the strategy have been deduced based on the development logics of human nature, and thus unpredictable issues may emerge during the actual application. Therefore, this study proposes the concept and framework of the HDV strategy, although not as a detailed practice program, which needs to be jointly explored and developed by practitioners in multiple industries.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Analysis and resolution of the discordance between user test results and actual status in HIV digital vaccine strategy.
[DOC File , 291 KB - resprot_v11i6e37133_app1.doc]

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Abbreviations

ATA: accredited testing agency
Dapp: decentralized application
HDV: HIV digital vaccine
MSM: men who have sex with men
PLH: people living with HIV
SasI: surveillance as intervention

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Protocol

The Need for Standards Unification in Forensic Laboratory Practices: Protocol for Setting Up the Arab Forensic Laboratories Accreditation Center

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Abstract

Background: Despite the recent trend toward developing and applying quality control measures in the forensic science disciplines, there is a heightened interest to efforts to ameliorate disparate quality among laboratories through the enforcement of standards and best practices.

Objective: This protocol aims to set up the Arab Forensic Laboratories Accreditation Center (AFLAC) to act as a key driving legal force for accreditation of the different forensic laboratories in the Arab region.

Methods: Upon its development, the Forensic Laboratory-Arabian Gate (FLAG) platform will serve as a preliminary stage for the AFLAC, and 2 preparatory steps will be achieved through the FLAG platform: the first one is a scoping study to analyze the international guidelines regarding the forensic laboratory practices in different specialties, and the second one is mapping surveys to explore how the international and national guidelines are translated into practice in Arab forensic laboratories. Development of the Arab forensic laboratories accreditation center will be initiated by building the AFLAC quality management system, which comprises formation of the forensic science committees to achieve the standards required for accreditation in each discipline. This will be followed by the attainment of regional accreditation recognition of the Arab Accreditation Cooperation (ARAC) and the International Laboratory Accreditation Cooperation. This recognition necessitates achieving International Organization for Standardization/International Electrotechnical Commission 17011 standard requirements prior to official application to the ARAC.

Results: The first phase of our work (the FLAG platform) began in February 2022 and is expected to end in December 2022. The FLAG platform was proposed to the Arab Society of Forensic Sciences and Forensic Medicine in March 2022, and we received approval to host this web development project. Subsequent phases are anticipated to begin in January 2023 and are expected to end in 2025.

Conclusions: This work describes our approach to provide a valuable tool for forensic laboratory accreditation services to promote the best practice and its consistency in the field of forensic sciences in the Arab region.

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KEYWORDS

forensic; practice; Arab countries; accreditation; standards; protocol; best practices; laboratories

Introduction

The term forensics has been linked to many different branches: economics, anthropology, engineering, dentistry, psychology, pathology, toxicology, entomology, accounting, and computer forensic science [1]. There are several disciplines of forensic science including, but not limited to, forensic biology; forensic chemistry, including seized drugs and postmortem toxicology, and forensic chemistry; trace evidence; digital or multimedia forensic science; forensic medicine; forensic physics or pattern interpretation; and forensic scene examination [1].

Forensic science is a highly specialized area that mandates the collaboration of the forensic community in Arab countries to utilize forensic technologies and techniques to solve crimes, investigate deaths, and protect the public [2,3].

Several challenges are faced by the forensic community, including assortment (standard operating procedures, methods, resources, and oversight); lack of mandatory standardization, certification, and accreditation; the extent and diversity of forensic science branches; the interpretation of forensic evidence (such as the validity of the various disciplines and the degree of scientific research); the need for measures of performance; and the use of forensic evidence in legal action [4,5].

These challenges definitely pose a continuing and serious threat to the quality and truthfulness of forensic science practice. it is evident that change and advancements, both systemic and scientific, are necessary to ensure reliability, exchange experiences, establish enforceable standards, and promote best practices and their consistency in the field of forensic sciences [6,7]. Establishing standards for the accreditation of forensic science laboratories and the certification of forensic scientists and medical examiners or forensic pathologists play a vital role in promoting the development of forensic science and achievement of best practices [8].

In the forensic arena, there are multiple organizations around the world that provide accreditation to the International Organization for Standardization (ISO), using the standards of 17020 and 17025, which together encompass the forensic investigation process from the scene to the court. Accreditation represents assurance given to the judicial system and the confidence given to the public that a quality standard has been followed and will be maintained throughout the process. It includes the policies, procedures, and practices with method validation and staff competence. Proper application of a quality system, which is mandatory to achieve the standards required for accreditation, will detect potential problems at the individual and systemic levels [9].

The Arab Accreditation Cooperation (ARAC) is the regional cooperation body, which aims at coordinating and developing the accreditation infrastructure in the regional Arab countries. The ARAC is officially incorporated as the regional accreditation cooperation body for the region with a developed quality management system including all procedures, guidelines, and forms following the International Laboratory Accreditation Cooperation (ILAC) and the International Accreditation Forum (IAF). The ILAC is the international organization for accreditation bodies operating in accordance with the ISO 17011:2004 conformity assessment and ILAC and IAF requirements [10,11].

Our aim is setting up the Arab Forensic Laboratories Accreditation Center (AFLAC) to act as key driving legal force for accreditation of different forensic laboratories in the Arab region. This will be proceeded by the development of the Forensic Laboratory-Arabian Gate (FLAG) platform.

Methods

Phase 1

Overview

Development of the FLAG platform will serve as a preliminary stage for the AFLAC. The aim of the FLAG platform is to represent the scientific, academic, and professional network of the Arab forensic community members by allowing discussing, sharing, and exchanging of ideas regarding scientific analytical methods, protocols, and guidelines related to forensic laboratory practices.

There are 2 preliminary steps to achieve through our FLAG platform: the first one is to analyze the international guidelines regarding the forensic laboratory practices in different specialties (a scoping study) and the second one is to explore how the international and national guidelines are translated to practice in Arab forensic laboratories (mapping surveys).

Participants

Membership to the FLAG platform is achieved through election and is open to all individuals who possess sufficient appropriate experience or qualifications relevant to, or those who can show a constructive interest in, the forensic sciences.

The identification of experts in different forensic medicine specialties in the Arab region will carried out using the following strategies: announcement and distribution of the FLAG platform and calls for membership, and direct communication with state or public institutes, university departments, authors of on-topic publications, and national professional associations. Different forensic sciences committees will be constituted and will be invited to the scoping study, mapping surveys, and developments of the standards and guidelines for best practices in their respective relevant specialties.

The scoping study aims to analyze the international and national guidelines on forensic science practices. It includes guidelines approved by international and national professional associations or national toxicologist working groups, in addition to documents published by national authorities or international

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organizations regarding scientific or expert recommendations [12]. For example, search strategies for relevant documents in the field of forensic toxicology have been developed between January and March 2022 using the following sources: PubMed, Web of Science, and Google with the search keys "forensic toxicology" (to derive guidelines or standards for forensic practice) and "drugs" OR "drugs of abuse" OR "illegal drugs" OR "drug-related deaths" OR "poisoning and forensic chemistry services"; a targeted document search on the websites of The International Association of Forensic Toxicologists, the Arab Scientific Working Group of Forensic Toxicology, the Arab Society for Forensic Sciences and Forensic Medicine, International Association of Forensic Toxicologists, the Scientific Working Group for Forensic Toxicology, the Nordic Association of Forensic Toxicologists, and the Society of Forensic Toxicologists [13-15].

Surveys of Practices: Mapping the Practices Implemented in Each Country

The objective of these expert surveys was to analyze how international and national guidelines regarding forensic investigations are translated into practice in forensic laboratories in Arab countries.

Data Collection

Forensic practitioners and experts representing different forensic specialties will be invited to complete a series of surveys (specific for each discipline generated by the relevant committee); for example, the forensic toxicology survey (see Multimedia Appendix 1). Experts on toxicological analysis based in laboratories undertaking postmortem analyses will be contacted and asked to participate in a survey on their laboratory performance in suspected drug-related deaths, guidelines and standards for laboratory practice and result reporting, analytical strategies, technical equipment, equipment validation, laboratory quality control principles, and potential hindrances or challenges to their daily work on drug-related deaths. Finally, based on these results, some general conclusions will be drawn and potential implications discussed with regard to how to interpret drug-induced deaths and prevalence data, taking into consideration the background of toxicology standards and capacities in different countries.

Results Analysis

Data collected from the mapping surveys will be analyzed in comparison to the recommended national and international guidelines to evaluate the actual practice and to strengthen areas of defects, if present.

Phase 2: Setting up of the AFLAC

Overview

For seeking international recognition, the AFLAC is required to develop their operating policies and procedures and ensure that its structure conforms to the requirements specified in the international standard ISO/International Electrotechnical Commission (IEC) 17011 standard, "Conformity assessment - General requirements for accreditation bodies accrediting conformity assessment bodies," and other IAF and ILAC criteria and for regional recognition by the ARAC.

A number of mandatory documents of the IAF and ILAC contain mandatory provisions for policies and procedures, and guidelines for the delivery of the accreditation services must be implemented. In general, the ISO/IEC 17011 standard specifies requirements with respect to impartiality, competence and experience of the staff, management systems, accreditation processes and assessment practices, on-site assessment, surveillance visits, complaints and appeals, and contractual requirements between the accreditation body and its accredited bodies [16].

Key Milestones of the FLAG/AFLC Project

The milestones will include announcement and distribution of the FLAG platform as a scientific platform for forensic scientists, medico-legal experts, and academics, allowing their memberships; mapping survey data collection, analysis, and result declaration; establishment of the AFLAC management system and committees for different forensic disciplines; regional accreditation recognition through regional cooperation with the ARAC; development of regional Arab guidelines and AFLAC standards for different forensic science disciplines; distribution and implementation of the AFLAC; and international recognition of the AFLAC by the ILAC and the IAF.

Results

The first phase of our work (the FLAG platform) began in February 2022 and is expected to end in December 2022. The FLAG/AFLAC platform was proposed to the Arab Society of Forensic Sciences and Forensic Medicine in March 2022, and we received approval to host web development projects on it. Subsequent phases are anticipated to begin in January 2023 and end in 2025.

Discussion

The vast majority of Arab forensic labs are lacking in the resources (money, staff, training, and equipment) necessary to promote and maintain strong forensic science laboratory systems [17,18].

The result, depth, reliability, and overall quality of standing information and the results arising from the forensic laboratories vary strongly across Arab countries. Operational principles and procedures for many forensic science disciplines in forensic laboratories are not standardized, which further compound such a fragmentation issue. There is no uniformity in the certification of forensic practitioners or in the accreditation of crime laboratories [19-21]. Often, there are no standard protocols governing forensic practice in a given discipline, and even when protocols are in place (eg, scientific working group standards), they often are vague and are not enforced in any meaningful way. In brief, there are several limitations that clearly generate a serious and continuing threat to the quality of forensic science practice, such as the lack of obligatory standardization, certification, and accreditation; the absence of proper training and continuing education; mandatory certification and accreditation programs; commitment to robust performance standards; and effective oversight [21].

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Accreditation and certification are both undertaken using third-party bodies, which are, in turn, accredited to perform this service. Many accreditation bodies are signatories to the ILAC. The ILAC is the international organization for accreditation bodies operating in accordance with the ISO/IEC 17011:2004 conformity assessment, which is a general requirement for bodies providing assessment and accreditation of conformity assessment bodies and documents regarding supplementary requirements [22-25].

The Arab region was the only region in the world lacking a regional structure for cooperation in the accreditation field till 2010. Arab countries had no access to support services and training. They have to approach the international accreditation bodies for seeking support, recognition, and training. This process was lengthy and costly and deprived a large number of countries from accessing these services [10]. Furthermore, Arab countries were neither well represented at the international level nor managed to achieve international recognition. Against this backdrop, the United Nations Industrial Development Organization supported a cooperation project for establishment of the ARAC in 2010 as a platform upon which Arab countries can build and develop their accreditation infrastructure. The ARAC has 4 multilateral recognition arrangement signatories: the Egyptian Accreditation Council (EGAC); the Jordanian Accreditation and Standardization System; the GCC (Gulf Cooperation Council) Accreditation Center; and the Emirates International Accreditation Centre [11,12].

Analysis of the accreditation services related to the field of forensic laboratories provided by ARAC members revealed that all of them provide accreditation services only for medical laboratories, while forensic science laboratory accreditation is only provided by the EGAC. The EGAC is the first accreditation body in Arab countries and in the Middle East to begin providing accreditation for forensic service providers, offering accreditation of forensic testing and inspection services in accordance with ISO/IEC 17025 and 17020 standards [10,18].

Areas currently accredited by the EGAC include DNA fingerprinting, autopsy, forensic histopathology, examination of people who have experienced crime, assailants of violence cases, crime scene examination, photography, and radiology. However, forensic toxicology analysis and other forensic services are not covered in the scope of EGAC accreditation. Our aim is to fill this gap by establishing AFLAC to act as key driving legal force for accreditation of the different forensic laboratories in the Arab region [26,27].

Laboratory accreditation and individual certification of forensic science professionals should be mandatory, and all forensic science professionals should have access to a certification process. In determining appropriate standards for accreditation and certification, the AFLAC will consider recognized and established international standards such as those developed by the ISO [28,29].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Mapping survey.
[PDF File (Adobe PDF File), 458 KB - resprot_v11i6e36778_app1.pdf]

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Abbreviations

AFLAC: Arab Forensic Laboratories Accreditation Center
ARAC: Arab Accreditation Cooperation
EGAC: Egyptian Accreditation Council
FLAG: Forensic Laboratory-Arabian Gate
GCC: Gulf Cooperation Council
IAF: International Accreditation Forum
IEC: International Electrotechnical Commission
ILAC: International Laboratory Accreditation Cooperation
ISO: International Organization for Standardization

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Protocol

Investigating the Potential for Clinical Decision Support in Sub-Saharan Africa With AFYA (Artificial Intelligence-Based Assessment of Health Symptoms in Tanzania): Protocol for a Prospective, Observational Pilot Study

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Abstract

Background: Low- and middle-income countries face difficulties in providing adequate health care. One of the reasons is a shortage of qualified health workers. Diagnostic decision support systems are designed to aid clinicians in their work and have the potential to mitigate pressure on health care systems.

Objective: The Artificial Intelligence–Based Assessment of Health Symptoms in Tanzania (AFYA) study will evaluate the potential of an English-language artificial intelligence–based prototype diagnostic decision support system for mid-level health care practitioners in a low- or middle-income setting.

Methods: This is an observational, prospective clinical study conducted in a busy Tanzanian district hospital. In addition to usual care visits, study participants will consult a mid-level health care practitioner, who will use a prototype diagnostic decision support system, and a study physician. The accuracy and comprehensiveness of the differential diagnosis provided by the diagnostic decision support system will be evaluated against a gold-standard differential diagnosis provided by an expert panel.

Results: Patient recruitment started in October 2021. Participants were recruited directly in the waiting room of the outpatient clinic at the hospital. Data collection will conclude in May 2022. Data analysis is planned to be finished by the end of June 2022. The results will be published in a peer-reviewed journal.

Conclusions: Most diagnostic decision support systems have been developed and evaluated in high-income countries, but there is great potential for these systems to improve the delivery of health care in low- and middle-income countries. The findings of this real-patient study will provide insights based on the performance and usability of a prototype diagnostic decision support system in low- or middle-income countries.

Trial Registration: ClinicalTrials.gov NCT04958577; http://clinicaltrials.gov/ct2/show/NCT04958577

International Registered Report Identifier (IRRID): DERR1-10.2196/34298

(JMIR Res Protoc 2022;11(6):e34298) doi:10.2196/34298

KEYWORDS

differential diagnosis; artificial intelligence; clinical decision support systems; decision support; diagnostic decision support systems; diagnosis; Africa; low income; middle income; user centred design; user centered design; symptom assessment; chatbot; health app; prototype

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Introduction

Background

Basic health care is insufficient for an estimated 4 billion people worldwide due to a global shortage of up to 7.2 million health care workers, which is expected to increase to a shortage of 12.9 million workers by 2035 [1]. The shortages in sub-Saharan Africa will be among the most profound because of a scarcity of medical schools in the region and an overall lack of training [1]. Additionally, poor clinical knowledge is a concern in regards to the level of care given worldwide [2]. A World Bank report found that 50% of rural health care workers were unable to diagnose 5 common conditions affecting patients in Tanzania [3]. Clinical deficiencies lead to a high number of excess deaths in low- and middle-income countries (LMICs) that would be prevented by the provision of higher-quality health care [4]. Clinical decision support systems (CDSSs), such as diagnostic decision support systems (DDSSs) can help to mitigate these problems. A few studies have investigated whether mobile phone–based CDSSs have enabled health care workers to provide better treatment, but thus far evidence is inconclusive [5]. It is therefore important to undertake further research on this topic in order to assess the potential role of mobile device–based CDSSs.

CDSSs are often implemented in real clinical settings and used by health care providers (HCPs) to aid decision-making at the point of care or for a specific care situation. The usefulness of CDSSs can be measured according to many different types of outcomes, such as clinical and health care processes or user workload and efficiency [6]. There is a great opportunity for CDSSs to improve patient outcomes with proper adherence; an example of these improved outcomes can be seen in one study, in which the final process composite score and patient satisfaction were higher in the patient group that used the CDSS compared to the group that did not [7]. One great challenge to CDSS and DDSS adoption and their clinical benefits is system usability. These systems must be practical and useful in a manner that supports their ongoing use by HCPs; this is a consistent challenge with almost all CDSSs [8,9].

DDSS Evidence Base

A number of studies have explored the use of DDSSs in high-income countries (HIC) [10], where the rate of diagnostic error in clinical medicine is estimated to be as high as 15% to 50% [11]. A published systematic review of available DDSSs showed that they can provide accurate diagnostic suggestions [10], with a pooled accurate diagnosis retrieval rate of 70%. That review also presented preliminary evidence that small but significant improvements in physician diagnostic accuracy accompanied DDSS use. It has also been recognized, however, that many DDSSs provide long lists of suggested conditions, which might increase clinician uncertainty. Another barrier to DDSS uptake is the additional time required for their use. A systematic review by Riches et al [10] suggested that junior members of clinical teams, or those with less medical experience, input more data and were therefore more likely to benefit from the use of DDSSs. This is indicative of the potential of DDSSs in LMICs, where diagnoses are often made by HCPs with less formal medical training than medical doctors [3]. Overall, the review concluded that differential diagnosis generators have the potential to improve diagnostic practice among clinicians; however, the literature that they reviewed also revealed many caveats that must be considered in the application of these systems and their further development. For example, it was reported that accurate diagnosis retrieval alone does not predict the uptake or effectiveness of differential diagnosis generators in clinical settings, as there are other relevant characteristics that can influence uptake and effectiveness, including the specificity of the list of diagnoses, the time required to use the system, its availability and access, and its cost-effectiveness [10,12,13].

There have been fewer studies of DDSSs in LMIC settings. Although addressing diagnostic error is complex, suggested approaches and solutions include training in diagnostic techniques for clinicians and the use of electronic diagnostic aids, such as DDSSs, to augment the diagnostic abilities of doctors [10]. In a study conducted in Mexico that looked at a range of clinical patterns, a DDSS was shown to improve the diagnostic accuracy of family medicine residents for both rare and common illnesses alike; they achieved an accuracy of 82.4% (SD 8.5%) with the DDSS and 74.1% (SD 9.4%) without the DDSS [14].

DDSSs may have a role in upskilling health workers and in supporting doctors' decision-making in the medium term. However, health-related artificial intelligence solutions developed in and for high-resource settings should not simply be used in an LMIC setting without adequate clinical investigation. Due to their development in settings with different health care structures and health care worker education levels, and their development on a base of medical data biased toward these settings, one cannot simply extrapolate data from HICs to LMICs. Instead, it is important to carry out clinical evaluations that specifically demonstrate the safety and performance of the technology for individual LMIC settings and its underlying medical reasoning before its use can be extended to new LMIC locations and use cases.

Mid-level Health Care Workers

This study will be conducted in a district hospital in Tanzania, where the main entry point for patients into the health care system is primary care [15]. Primary care is delivered in an outpatient setting that includes dispensaries, health centers, and district hospitals [16]. In Tanzania, the health care staff shortage is severe; staffing is estimated to be 52% of the actual need [17]. Mid-level health care workers compensate for the insufficiency of qualified medical doctors by carrying out some aspects of the roles of doctors. Mid-level health care workers are a group predominantly found in LMICs [18]. They are defined as health care workers who undergo shorter training than physicians, but who nonetheless perform some roles generally considered part of a physician's responsibilities [18]. In Tanzania, mid-level health care workers include clinical officers (COs) and assistant medical officers (AMOs) [19].

After graduating from secondary school, COs receive 3 years of practical and theoretical training. A CO's responsibility is diagnosing and treating common conditions and performing

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minor surgeries. After gaining 3 years of practical experience, a CO can undergo a further 2 years of training to become an AMO. The position of an AMO involves a wider scope of medical practice; they can perform surgeries such as appendectomies and cesarean sections. Additionally, AMOs can act in leadership roles in medical facilities, especially in rural areas [19]. The prototype DDSS in our study will be used by COs. If there is no CO available for the patient consultation, then it will be used by an AMO. By evaluating the use of the prototype DDSS by mid-level HCPs, we aim to assess its potential to improve the performance of HCPs who have received less medical training than fully-qualified medical doctors.

Objective and Hypotheses

This study is part 2 of the AFYA (Artificial Intelligence-Based Assessment of Health Symptoms in Tanzania) study series [20]. The current study will explore the potential of the prototype DDSS to empower HCPs in LMICs. The objective is to measure to what degree the prototype DDSS can enhance the diagnostic accuracy of mid-level HCPs. This will be done by comparing, in an observational study setting, the diagnostic accuracy of HCPs who use the study tool to HCPs performing usual care, henceforth referred to as usual HCP, and by comparing the accuracy of diagnoses submitted before and after input from the DDSS. Since impracticality is a common barrier to CDSS adoption [8,9], we will also collect qualitative data on the usability, usefulness, and acceptance of the prototype DDSS. These measurements will provide insights on the appropriateness of the prototype DDSS interface.

There are two study hypotheses: (1) a "chatbot"-based DDSS, which is similar to a symptom assessment app (SAA) as it asks a series of questions about the patient's symptoms using a sequential "question flow," is an appropriate interface for improving the accuracy of decision-making by mid-level HCPs in sub-Saharan Africa; and (2) the diagnostic accuracy of mid-level HCPs will be improved by the use of a "question flow" DDSS based on a chatbot.

Methods

This study is the second of 2 studies in the AFYA study series, and is a prospective, 2-arm observational study conducted at Mbagala Rangi Tatu Hospital, Dar es Salaam, Tanzania. The first study was a general, prospective, observational assessment of a symptom assessment platform named "Ada" (Ada Health GmbH) that is used directly by patients. That study used the same clinical setting as the present study and a separate clinical study protocol that has been described previously [20].

The development of the trial protocol was conducted in accordance with the current Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Multimedia Appendix 1) [21].

The Ada Prototype DDSS Specifications and Rationale of Use

The prototype DDSS evaluated in this study is being developed through an iterative user-centered design approach [22]. It has been modified from a CE (Conformité Européenne)-marked SAA [23] that was developed to provide laypeople the opportunity to determine what might be causing their health problems.

As part of the iterative user-centered process, we have explored different tools reported in various past studies, including by a study conducted in a British primary care waiting room that investigated the usability, acceptability, and utility of an SAA [24], a study conducted in a German emergency department that assessed urgent-care advice provided by an SAA [25], and another study in a German emergency department that gathered patients' relevant symptoms and presented them to their physicians [26]. Additionally, Ada Health GmbH has developed a prototype HIC DDSS that uses the same underlying Ada medical intelligence platform but does not utilize a chatbot interface; it allows HCPs to update symptoms in real time without relying on a question flow. It also allows HCP-level clinical symptom and test-finding information to be entered. We have conducted careful formative usability research in collaboration with academic expert centers; this has also contributed to the iterative user-centered design process [27]. This HIC HCP-facing DDSS has shown potential for assisting early diagnosis of rare diseases [28], with the potential for economic benefits to health care systems [29] and potentially longer-term transformational benefits for rare disease management [30]. In cooperation with usability researchers and user interface designers, we have incorporated the findings from these studies into the further development of a DDSS prototype.

We determined that the HIC prototype DDSS explored in past studies [27-29] may not be optimal for low-resource settings, as it is less suited to the mobile phone interface and relies on physician training for effective use. We therefore explored the development of a simpler chat-based DDSS for lower-income settings, where the question-flow prompting of the HCP could provide clinical histories and diagnostic benefits.

The prototype DDSS used in this study was created for use by LMIC health care workers, initially in an observational clinical study setting, to investigate the hypotheses of this study and to further understand the DDSS requirements of mid-level HCPs. The "chatbot" prototype DDSS interface asks the HCP to enter the patient's age and their presenting complaint, followed by basic health information, such as the presence or absence of diabetes and hypertension, smoking, and pregnancy status (if relevant). It then asks a series of questions about the patient's symptoms, with the optimal question asked at each point of the question flow so as to determine the most relevant information in a manner that is dynamically updated based on each answer provided by the patient. In this study, the chatbot is used on a handheld tablet, but it can be used in real world settings on any device with an internet connection, including smartphones, desktops, and laptops. The prototype DDSS will use the English language. This was decided after consultation with the HCPs involved in the study. The user interface of the study tool can be seen in Figure 1.

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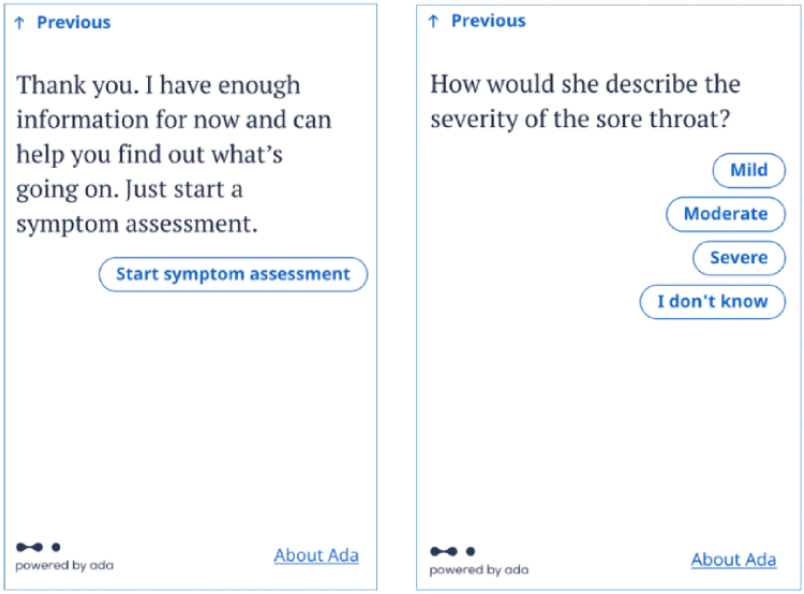
Figure 1. Screenshots showing the user interface of the tool in this study.



Dynamic questioning is delivered by the system's underlying medical intelligence using a medical knowledge base built by medical doctors to define a Bayesian network. This Bayesian network allows approximate inference to be carried out. Based on a user's answers, the system dynamically decides which questions to ask next in order to generate a list of potential conditions [24]. In this study, the Ada assessment was used to help mid-level HCPs gain relevant insights into the patient's condition during their consultation by asking questions about the patient's symptoms in an order determined by the system's underlying reasoning engine. After the assessment, the HCP received a list of possible "condition suggestions" determined by the reasoning engine based on the patient's presenting complaint and their symptoms. Along with these condition suggestions, the HCP was provided with additional information regarding the presentation of the disease, so that the HCP was able to make a more informed diagnosis.

The accuracy and comprehensiveness of the Ada platform has been validated in several studies of the Ada SAA [31-33]. In 2020, the Ada SAA, which uses the same medical reasoning as the prototype DDSS, was shown to be market leading in the accuracy of its condition suggestions and urgency advice compared to 7 other SAAs, and it had condition suggestions and safety performance comparable to United Kingdom general medical practitioners [31]. In a more recent study comparing 12 tools, the Ada SAA had the highest diagnostic accuracy at the first diagnosis (72%), while the next best SAAs achieved accuracies of 68% and 59.5%, respectively. Overall, the mean accuracy of all 12 SAAs was 37.7% [33]. When evaluating urgency advice, the Ada SAA was rated third best, with an accuracy of disposition of 64% (accuracy was 90% and 66.7%, respectively, for the first- and second-best SAAs), while the mean accuracy achieved by all SAAs was 57.7% [33].

Study Optimization Phase

Before continuing on to the pilot study, there will be a feasibility and process optimization phase in which 15 patients will be recruited. This phase is for the optimization of general study procedures, patient tracking, and information recording in the busy clinical environment. In this phase, we will also be able to determine if staff training has been adequate and if the assessment is properly optimized for use by health care workers. Any deficiencies in the study process or staff training will be identified and a period of up to 2 weeks will be allowed for the rectification of any identified issues. Usual care for the patients will not change, and the data from these patients will not be included in the study analysis. After the optimization phase, at least 50 patients will be recruited for the pilot study.

Patient Population and Eligibility Criteria

In this study, children, adolescents, and adults who arrive at the study site will be assessed for eligibility. The study site will be a busy district hospital waiting room at Mbagala Rangi Tatu Hospital in Dar es Salaam, Tanzania. Any person who enters the clinic and is willing or able to provide consent will be included, except for (1) patients who are not capable of completing a health assessment (eg, due to mental impairment, inebriation, or another incapacity) (2) patients with severe injury or illness that requires immediate treatment, or (3) patients with traumatic injury. Data from patients dropping out of the study or deviating from the protocol will be excluded from analysis.

In order to ensure that the study has a sample of patients with a comprehensive spectrum of symptom constellations and conditions, inclusion of patients will be monitored throughout the study; doing so will ensure that this pilot study does not just provide detailed testing for the most commonly presenting patient scenarios, but also provides testing for the performance of the prototype DDSS for a broad range of medical conditions. There will be a target of enrolling between 2 to 5 patients for conditions related to (1) abdominal pain or gastrointestinal issues, (2) the lower respiratory system, (3) the upper respiratory system, (4) mental health, (5) vision, (6) orthopedic issues, (7) the cardiovascular system, (8) the genitourinary system, (9) the neurological system, (10) the skin, (11) obstetrics and gynecology, and (12) the ear, nose, and throat. We plan to include at least one adult and one child in each category, where

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reasonable, and once a total of 5 patients have been enrolled for a given category, no further patients will be included. In cases in which the presenting complaint does not match the condition category with which the patient is ultimately diagnosed, the physician's diagnosis will be aggregated on a dashboard adapted to optimize recruitment according to the categories listed above.

The maximum of 5 patients in one condition category is only an aim, but one that should be readily attainable. The study trackers hired for this study, that is, the workers who will recruit the patients, have CO and nurse midwife education and training, meaning that they are able, to a great extent, to determine these classifications.

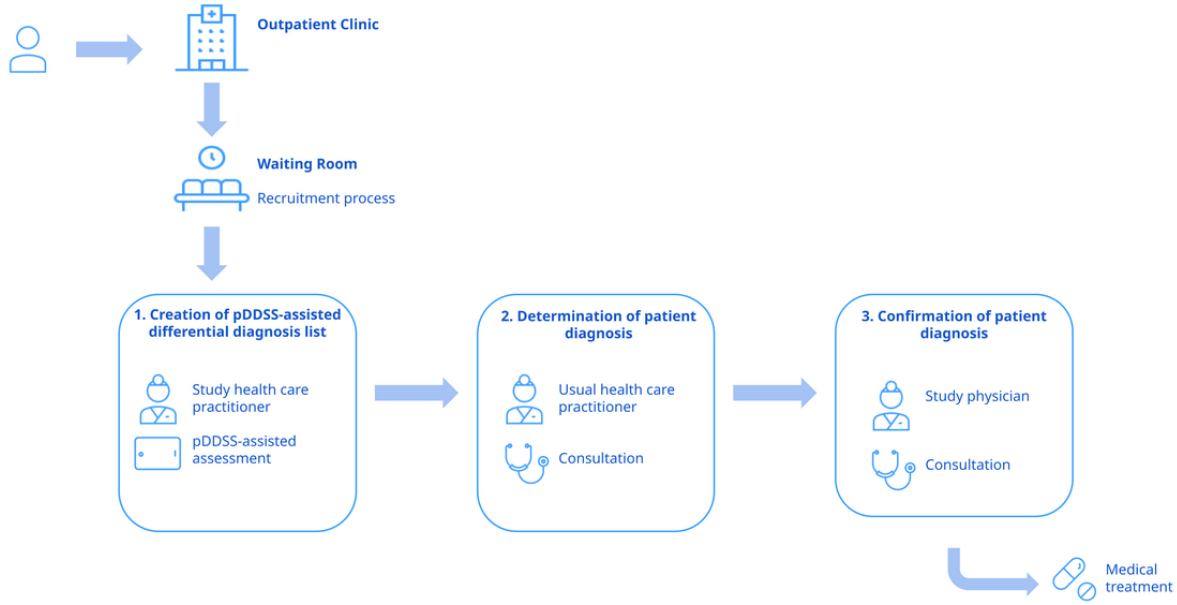
Interventions

This is an observational, prospective study. There will be no experimental or control interventions.

Description of Study Visits and Assessment Schedule

The patient's journey in the study will consist of 3 stages (Figure 2 shows an overview).

Figure 2. The patient journey in the study. Step 1: using the study tool, a differential diagnosis list is created by the study health care practitioner (clinical officer or assistant medical officer). Step 2: using a structured electronic case report form (eCRF), the patient consults with the usual health care practitioner for the determination of a diagnosis. Step 3: using a structured eCRF, the patient consults with a study physician to confirm the findings in step 2 with higher objectivity and a gold standard diagnosis. DDL: differential diagnosis list; pDDSS: prototype diagnostic decision support system.



Patient Presenting to the Clinic (Recruitment Process)

For the recruitment process, the study staff will work in close cooperation with the hospital staff in order to identify potentially eligible patients in the waiting room. Patients assessed as potentially eligible will be approached by the study staff. The study staff will provide them with detailed information about the study and obtain written informed consent if the patients decide to enroll in the study. In addition to their parent's or caretaker's consent, children aged between 9 and 18 years will be requested to sign an assent form themselves. Enrolled patients will receive a unique study ID that is not part of the usual health care record and will be allocated alternately to the 2 study arms.

Ada Assessment by Study HCP (Stage 1)

After the recruitment process, the patients will consult with a study HCP, who is a mid-level HCP and will not be involved in the patient's care. The study HCP will assess the patient using the prototype DDSS and create a differential diagnosis list. Depending on the patient allocation, there will be a difference in the synthesis of the final differential diagnosis list in the assessment (Figure 3): In arm 1, the study HCP will submit a preliminary list before seeing the prototype DDSS's condition suggestion list. Once the preliminary list is submitted, the study HCP cannot change it. After being able to review the preliminary list and the prototype DDSS's condition suggestion list, the study HCP will pick his or her top 5 differential diagnoses from both lists and submit a final differential diagnosis list. Conversely, in arm 2, the study HCP will see the prototype DDSS's condition suggestion list before submitting a final differential diagnosis list. This will give the study HCP the opportunity to consider differential diagnoses from the prototype DDSS and add their own differential diagnoses to create a final differential diagnosis list. The degree to which these lists match the gold standard diagnoses will be judged in a later step by an unbiased physician panel, after the completion of patient recruitment and study data recording.

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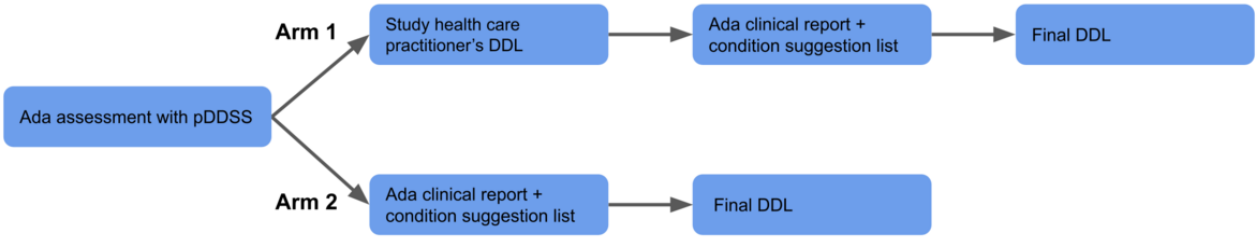
Figure 3. Comparison of study arms in stage 1. pDDSS: prototype diagnostic decision support system; DDL: differential diagnosis list.



Our limit of 5 differential diagnoses is a pragmatic limit based on Ada's limit of 5 condition suggestions; it is similar to the approach taken in many other papers in the medical literature, which have used comparisons with a gold standard diagnosis and a maximum of 5 to 10 differential diagnoses [33-35]. The reasoning for this is that the length of a diagnostic list has been found to be a key predictor of accurate diagnosis retrieval; long diagnostic lists are less specific and hence problematic for clinicians using differential diagnosis tools in a busy clinical setting [10].

Patient Examination by Usual HCP (Stage 2)

Having finished step 1, the patients will continue on to a consultation with a usual HCP. In this step, the patient's diagnosis and a further diagnostic plan for them will be determined as a part of usual care. The usual HCPs will be COs, AMOs, or medical doctors. The usual HCPs in stage 2 will not be the same HCPs that performed the interview in stage 1. During the consultation, the usual HCPs will fill out a standardized electronic form and a structured consultation report form through a tablet-based electronic case report form (eCRF). Afterwards, they will complete the standard hospital forms, record vital signs, and request laboratory or diagnostic procedures as part of usual care.

Patient Examination by Study-Provided Physician (Stage 3)

After laboratory and diagnostic procedures, the patient will proceed to a consultation with a study-provided physician. This physician will, as in Stage 2, complete a structured consultation form through a tablet-based eCRF. The results of this consultation will amend the one from stage 2 in the gold standard panel. Adding a study physician not involved in the patient's care to confirm the patient's diagnosis ensures a higher degree of objectivity in the generation of the gold standard. The study physician will be able to refer to the usual HCP's notes from stage 2, although this will be only allowed at the end of the consultation in order to minimize bias and ensure patient safety.

Although the interaction time between health care staff and the patient in the investigation will be about three times as long as the standard hospital process, this extra time will be compensated for by the study participants being moved forward in the waiting-room queue for examination, clinical testing, and receiving test results (when relevant). The overall effect is that the study participants will have a longer period of interaction at the clinic (with study trackers and study physicians), but will have a similar total visit length at the clinic (ie, less passive waiting time in the waiting room).

Measurement Methods

Overall, there will be 5 stages in the process of data collection and physician panel assessment (Figure 4 shows an overview). The first 3 stages in this process have already been described: (1) the study HCP will use the prototype DDSS; (2) the patient will consult with a usual HCP; and (3) the patient will consult with the study-provided physician. There are then 2 additional steps: (4) generation of a differential diagnosis by the physician panel, and (5) matching of conditions by the physician panel.

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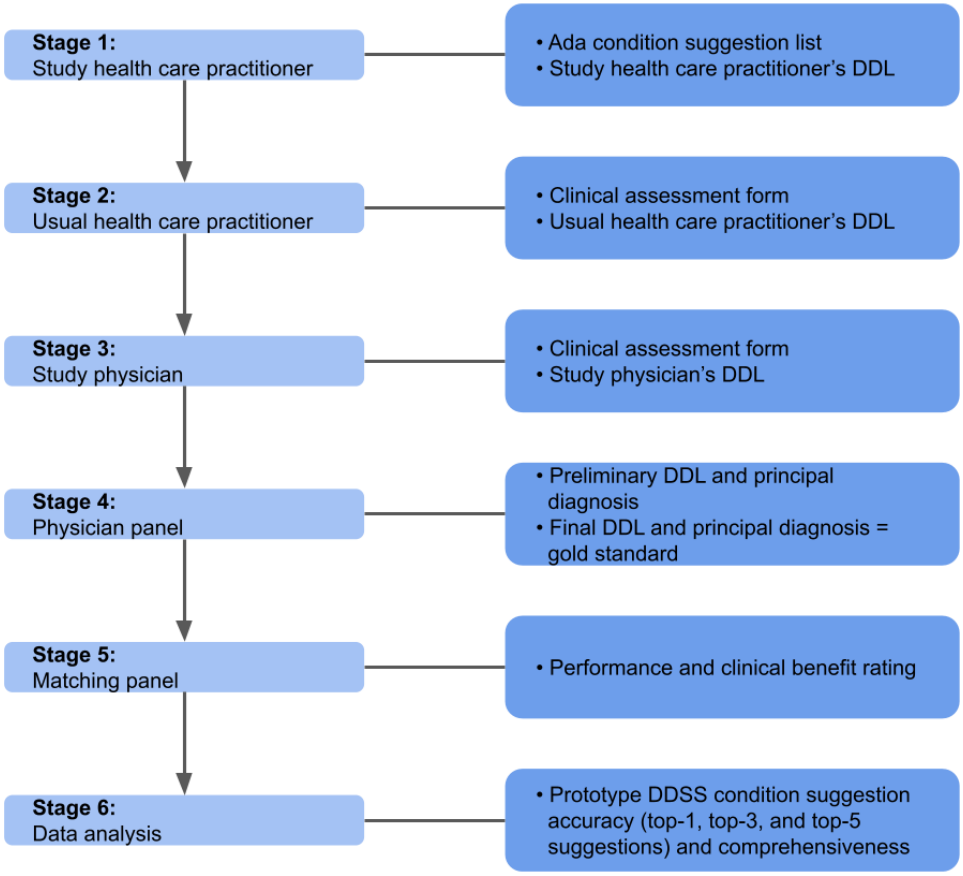
Figure 4. Data flowchart. DDL: differential diagnosis list; DDSS: diagnostic decision support system.



The physician panel in step 4 that makes the differential diagnoses will be made up of 3 local physicians, each with at least 3 years of full-time clinical experience (the majority in general medicine), who will carry out a review process; this process will yield the gold standard differential diagnosis list for each case. The physician panel members have been thoroughly screened and chosen by the principal investigator of this study, who is a native Tanzanian doctor with over 20 years of experience as a medical doctor and several additional years of experience as an instructor at Muhimbili University of Health and Allied Sciences. All physician panelists are required to have an active medical license and to be available for at least 9 hours per week during the physician panel process in order to be immersed enough in the process. Two independent "reviewer" physicians on the panel will review the diagnoses from the usual HCP and the study-provided physician, the pseudo-anonymized medical history, and the symptoms of each patient. They will assign a preliminary differential diagnosis list and a principal diagnosis to each case based on history and symptoms alone and then assign a final differential diagnosis list and principal diagnosis based on the full patient clinical file (this will include vital signs and results from medical examinations and diagnostic tests). In case of disagreement between the 2 differential diagnosis lists, a third reviewer will make a final decision. The tenth revision of the International Statistical Classification of Diseases and Related Health Problems will be used to determine all diagnoses.

The matching of conditions by the physician panel in step 5 will involve matching the diagnoses made by the usual HCP and study-provided physician with the diagnoses made by the reviewer physicians on the physician panel. The same procedure for the DDSS condition list will be carried out by the reviewer physicians. As in step 4, a third reviewer physician will make a final decision if there is disagreement between the 2 reviewer physicians. The primary comparator of the Ada assessment is the differential diagnosis obtained before the addition of vital sign measurement, physical examination, and additional diagnostic tests. Looking at the differential diagnosis list at each point in the patient's clinical journey is still a relevant point of comparison.

Finally, the data collection performed in these 5 steps will be analyzed (details are in the "Data Analysis" section). In order to determine the usability, usefulness, and acceptability of the prototype DDSS, the usual HCP questionnaires, in addition to the patient questionnaires, will be analyzed and described using methods appropriate to modified Likert-scale questionnaire data [26].

Endpoints

Primary Endpoints

The first endpoint will be the condition suggestion accuracy and comprehensiveness of the prototype DDSS, evaluated against the gold standard differential diagnosis determined by the review panel, reported in the context of the accuracy of the usual HCP. The second endpoint will be the study HCP's condition suggestion accuracy and comprehensiveness, which will be compared between arm 1 (in which the HCPs determine their own list of condition suggestions before seeing the

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prototype DDSS's condition suggestions, then create a final ranked list of condition suggestions) and arm 2 (in which they see the prototype DDSS's condition suggestions before determining their list of overall ranked condition suggestions). The third endpoint will be a comparison of the study HCP's condition suggestion accuracy and comprehensiveness in arm 1 in the preliminary and final DDLs.

Additional Data of Interest

Additional data of interest will include qualitative data on the usability, usefulness, and acceptability of the prototype DDSS.

Outcomes and Outcome Measures

The design of this study is based on the literature on pilot study design, as it will serve as a guide for a larger trial in the future [36,37]. The sample size of a minimum of 50 participants was a pragmatic determination of a number of participants that could be used to assess the ability to recruit patients across a spectrum of conditions in a clinic of this type and in this setting, to evaluate the feasibility of collection of the complete study data, and to allow an accurate analysis. There are multiple aspects of study design and operation that will be explored in this pilot study: (1) investigating if it is feasible to determine the accuracy and comprehensiveness of the Ada DDSS for a large range of symptoms and conditions in multiple different age groups; (2) establishing how many patients and HCPs can be recruited and the likely number of completed patient and HCP questionnaires; (3) trialing new methods and enabling power calculations intended to be used in a later single- or multicenter randomized controlled trial; and (4) evaluating the general feasibility, both technical and logistical, of a full-scale study, including issues of data collection and questionnaire design. The pilot has not been powered to definitively accept or reject the scientific hypotheses, as a pilot is required before the sample size for a definitive study can be estimated.

Risk-Benefit Assessment

This study does not pose any risk to the patients, as it is solely observational; therefore, there is no need for additional safety management. Patients requiring immediate medical care and clinically unstable patients will be excluded. If patients are called into their appointment before the study HCP finishes the prototype DDSS assessment, they will be excluded from the study process and analysis and proceed to usual care, meaning there will be no delay in the diagnosis or treatment of any patient. Although there will be 2 extra consultations for patients enrolled in the study, these consultations will generally require less than 10 minutes; therefore, it is highly unlikely to delay a patient's diagnosis or treatment.

Data Management and Data Safety

This study has a data management plan that outlines the guidelines by which data entry will take place. All consent forms will be paper based; the rest of the data will be collected electronically. Paper records will be kept in a locked cabinet in the facility only accessible by study-specific personnel, while for electronic data, a clinical-trial electronic data capture (EDC) system (REDCap) will be used. Overall, study-site data collection will go through a secured local area network, allowing data sharing on site. Study personnel, who will be provided unique usernames and passwords, will be trained on the EDC system. Before committing data to the EDC system, the research assistant will first verify that the data are correct. After this, the research assistant will not have access to the data, as they will be automatically locked after each commit. Storage of the data will last a minimum of 3 years from the date that the last patient is seen at Muhimbili University of Health and Allied Sciences; 10% of the digitized usual care consultation notes will undergo source-data verification.

Data Analysis

Applying the definition from Gilbert et al [31], we will assess the accuracy and comprehensiveness of the top-1, top-3, and top-5 suggested conditions by the prototype DDSS in comparison to the gold standard differential diagnoses. Data analysis will also be carried out as presented by Gilbert. In short, descriptive tests and statistics appropriate for categorical data will be utilized to compare condition suggestion accuracy. To analyze if the proportion of correct condition suggestions from the prototype DDSS, from the usual HCPs, and from the study-provided physicians are drawn from the same distributions, the chi-squared test will be applied. If there is a significant difference, we will apply a 2-sided post hoc pairwise Fisher exact test to compare the prototype DDSS and the practitioners. Due to the low sample size of this pilot study, it may be the case that the chi-squared tests will not produce significant results. As the study goal is the comparison of the prototype DDSS to usual care, the ratings of the usual HCPs will be strictly anonymized.

Patient and Public Involvement

No patients or members of the public were directly involved in the development of the research hypotheses or study design. However, feedback and learnings from patients and other individuals from past, related studies of the Ada SAA, as well as previous studies carried out at the study site, were used to help design the study and patient interaction protocols [24,26,27,31].

Ethics Approval

The pilot study received ethics approval from the ethics committee of Muhimbili University of Health and Allied Sciences (MUHAS-REC-09-2019-044) and the National Institute for Medical Research (NIMR/HQ/R.8c/Vol. I/922). All amendments to the protocol have been reported and adapted on the basis of the requirements of the ethics committee. The trial has been registered at ClinicalTrials.gov with the registration number NCT04958577.

Results

Patient recruitment started in October 2021 in the outpatient clinic of the Mbagala Rangi Tatu Hospital. Participants will be recruited directly in the waiting room of the outpatient clinic. Data collection will conclude in May 2022. Data analysis is planned to be finished by the end of June 2022. The results will be submitted to peer-reviewed journals and local and international stakeholders and will be communicated in editorials and articles by Ada Health GmbH.

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Discussion

As this is the first study of a chatbot-based DDSS on a broad range of conditions conducted in an LMIC, we expect that our pilot results will show variable accuracy compared to DDSSs used in HICs. Nevertheless, we expect good overall usability and acceptance of the prototype.

Development of a New DDSS for LMICs

While health care systems in HICs can also benefit from DDSSs, there is a substantially higher need for improvement in the delivery of qualitative health care in LMICs [2,4]. Due to their high scalability, digital solutions such as mobile health tools can be cost-effective in mitigating these problems. Web-based applications have hardware requirements that are quite low. Internet connectivity is still required, but while there are gaps, especially in rural settings, the quality of internet connectivity is increasing in many LMIC settings [38]. Additionally, this approach makes it possible to update the DDSS without extensive maintenance on the HCP side. Artificial intelligence–based and short message service–based health tools have already been used in different areas of medicine in Africa [39-42].

Widespread adoption of CDSSs requires high usability and integration into the clinical workflow with minimal disruption. This study is an important step in the iterative, user-centered design process that we will use to develop a DDSS for LMIC health care workers. On one hand, this study will provide insights into the accuracy of the app and enable us to improve our medical database based on real-world experience in the setting of an African clinic. On the other hand, the qualitative data on the usability, usefulness, and acceptability of the prototype DDSS will give us the opportunity to further develop the current prototype to match the needs of our target users (health care workers, in this case) and thus increase acceptance of the tool.

This study will test one cycle of a design process and will gather further information on the appropriateness of a chatbot-based DDSS for mid-level HCPs. The study outcomes will allow further ideation and definition of the requirements in later prototypes.

Strengths and Limitations of the Current Study

There are several strengths and limitations to this study. It is prospective, unlike previous assessments of DDSS performance, which have mostly been retrospective [10]. The Tanzanian outpatient clinic setting will provide a heterogeneous patient population. Through the application of broad inclusion criteria, we aim to include a diverse patient population with varied conditions covering a wide range of age groups. Another strength of this design is the approach to determining the gold standard diagnosis, which is based on the methods in Gilbert et al [31] and Semigran et al [43] and will use a physician panel and voting methods to achieve high objectivity and independence.

This is a single-site study in the outpatient clinic of a Tanzanian district hospital; therefore, the study's findings may not be applicable to other LMICs. The relatively small enrollment target of a minimum of 50 participants is another limitation, but as this is a pilot study, this sample size is adequate to enable the design of a definitive later study. The study questionnaires filled out by the participants and the usual HCPs are not based on previously validated instruments and thus response bias cannot be excluded.

Considering the pilot character of this study, the limitations are appropriate, as the findings of this study can be used in the conception of a larger trial that will validate the accuracy and usefulness of a chatbot-based DDSS.

Acknowledgments

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Authors' Contributions

MS, NS, HA, MB, LO, EM, PB, ET, RV and SG contributed to planning (study conception and protocol development). All authors contributed to commenting on drafts of the protocol. SG is the guarantor for this work. The corresponding author, SG, attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Conflicts of Interest

MS, HA, LO, EM, PB, ET, RV and SG are or were employees, contractors, or equity holders in Ada Health GmbH. All should be considered to have an interest in Ada Health GmbH. HA is a director of the Ada Health Foundation GmbH. The Ada Health GmbH research team has received research grant funding from Fondation Botnar and the Bill & Melinda Gates Foundation.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 83 KB - resprot_v11i6e34298_app1.pdf]

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Abbreviations

AFYA: Artificial Intelligence-Based Assessment of Health Symptoms in Tanzania
AMO: assistant medical officer
CDSS: clinical decision support system
CO: clinical officer
DDSS: diagnostic decision support system
eCRF: electronic case report form
EDC: electronic data capture
HCP: health care practitioner
HIC: high-income country
LMIC: low- and middle-income countries
SAA: symptom assessment app

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Protocol

Advancing Posttraumatic Stress Disorder Diagnosis and the Treatment of Trauma in Humanitarian Emergencies via Mobile Health: Protocol for a Proof-of-Concept Nonrandomized Controlled Trial

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Abstract

Background: Decentralized health systems in low- and middle-income countries (LMICs) affected by humanitarian crises lack resources and a qualified workforce to attend to the overwhelming demand for mental health care in emergencies. Innovative approaches that are safe, cost-effective, and scalable are needed to address the burden of traumatic stress caused by emergencies. High mobile phone ownership rates combined with the precision of neural, cognitive, and biometric measures of trauma and their feasible integration with artificial intelligence makes digital app interventions a promising pathway to promote precision diagnosis and high-impact care.

Objective: This study aimed to advance methods for the objective diagnosis and treatment of trauma in emergencies across LMICs by examining neural, cognitive, and biometric markers and the efficacy of the eResilience app, a neuroscience-informed mobile health mental health app intervention, via changes in clinical symptomatology, cognitive performance, and brain activity.

Methods: Trauma-exposed African refugees residing in Australia were selected for this study. A research software version of the eResilience app with advanced monitoring capabilities was designed for this trial. Participants completed the eResilience app at home during a 7-day period. Clinical, cognitive, and electrophysiological data were collected at baseline, along with posttest measurements to examine biomarkers of trauma and the efficacy of the proposed digital intervention for the treatment of trauma and its potential outcomes, including depression, anxiety, physical symptoms, self-harm, substance misuse, and cognitive impairment. In addition, biofeedback, well-being, and subjective stress data points were collected via the app during the treatment week, followed by clinical interviews at 1, 3, 6, and 12 months after the intervention.

Results: Data collection was conducted between 2018 and 2020. A total of 100 participants exposed to war were screened; 75 (75%) were enrolled and assigned to a trauma-exposed control (38/75, 51%) or posttraumatic stress disorder condition (37/75, 49%); and 70 (70%) completed all baseline, treatment, and posttest assessments. A total of 89% (62/70) of those who completed the intervention opted to enroll in the 3-, 6-, and 12-month follow-ups. Data collection is complete. As of May 2022, the results of all proposed analyses are being prepared for publication. If proven efficacious, this proof-of-concept clinical trial will inform fully powered randomized clinical trials in LMICs to further develop artificial intelligence–powered, app-based diagnostic and prognostic features and determine the app's cross-cultural efficacy for the treatment of trauma in emergency settings.

Conclusions: This protocol provides researchers with a comprehensive background of the study rationale, a detailed guideline for replication studies interested in examining the feasibility and efficacy of the eResilience app across varied demographics, and a robust framework for investigating low-cost objective diagnostic markers in mental health interventions. Methodological limitations and suggestions are also provided.

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International Registered Report Identifier (IRRID): RR1-10.2196/38223

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KEYWORDS

posttraumatic stress disorder; PTSD; trauma; humanitarian; emergencies; mobile health; mHealth; technology; neuroscience; electrophysiology; electroencephalogram; EEG; cognition; health system; biometric; health application; mental health; cognition; trauma; health intervention; mobile phone

Introduction

Background

Nations worldwide face the continuous challenge of addressing the complex and varied consequences of past, current, and evolving humanitarian emergencies. The United Nations Office for the Coordination of Humanitarian Affairs estimates that there are currently 234 million vulnerable people across 56 countries affected by war and conflict, climate change, hunger, and the COVID-19 pandemic [1]. Humanitarian emergencies, whether man-made, natural hazards, or public health crises, are often characterized by loss of life, mass-scale displacement, security risks for aid workers, economic crises, political tension, and wearying of public health systems leading to constraints in the provision of large-scale health care for the affected population. Although the psychological aftermath of disasters is still overlooked in emergency responses, the growing global recognition of the burden of mental health [2] disease has prompted many scientific studies on the long-term implications of psychological distress in humanitarian crises. This burden is well-documented across the domains of justice, peace and reconciliation [3-7], policy and legislation [8], and its impact on the economy [9,10], with a presumably accentuated economic impact in low- and middle-income countries with fragile health systems [11]. Therefore, understanding and addressing the mental health outcomes of disasters can not only promote the health of populations affected by adversity but also alleviate the burden across all societal domains affected. However, to address such issues, innovations are needed to resolve some of the core pressing clinical challenges faced by humanitarian actors, such as discrepancies in subjective diagnostic tools and costly mental health treatment protocols that require specialized clinicians and that, for the most part, lack cultural sensitivity.

Mental Health Apps for Humanitarian Emergencies

Accelerated by the COVID-19 pandemic, investments in digital health are increasing markedly. In 2020 alone, >90,000 new health apps emerged in a market that already surpasses 350,000 apps, of which 22% account for mental health apps promoting the management of behavioral disorders via cognitive behavior therapy (CBT) strategies, mindfulness, meditation, stress and anxiety management, and sleep hygiene practices and monitoring [12]. However, despite the fast growth in the digital health field, very few apps are suitable or have been designed for use in emergency response as promising innovations are, for the most part, incentivized by the monetization of sophisticated trends in digital technologies such as artificial intelligence, automated therapies, and virtual reality–based treatments [13].

Although not trauma-focused, an example of a successful digital adaptation of CBT-based care for humanitarian settings is Problem Management Plus (PM+), an initiative by the World Health Organization as part of the mental health Gap Action Programme [14] developing mental health solutions for low- and middle-income countries that can be scaled to attend to large populations. PM+ was designed to promote brief psychological interventions for adults with sessions once per week during a 5-week period, promoting behavioral, stress management, and everyday problem-solving tools [15]. Emerging data from feasibility trials and randomized controlled trials in Pakistan [16-18], Nepal [19,20], and Kenya [21,22] indicate that PM+ is promising for the effective management of psychological distress, including trauma symptoms, and problems in daily life via app in emergency settings. Alongside additional studies on PM+ taking place in Europe to attend to the needs of refugees and asylum seekers [23-27], the European Union STRENGTHS program is also a promising initiative examining the efficacy of PM+ in attending to the psychological needs of Syrian refugees across Europe and Middle Eastern countries [28]. However, developers emphasize that PM+ is a low-intensity intervention for adults with depression, anxiety, or stress in areas affected by adversity and is not designed to address the full range of challenges brought on by adversity; thus, it is recommended for use in conjunction with other support systems. Moreover, the World Health Organization stresses that PM+ is not suitable to address suicidality and other severe mental, neurological, or substance use disorders. Further limitations reported include challenges in scalability in Kenya [29] and cost-efficacy in Pakistan [30].

Overall, only 2 studies on app-based interventions designed specifically for trauma in a humanitarian context were identified. A randomized clinical trial examined the efficacy of Sanadak, a CBT-based self-help trauma app in Arabic for Syrian refugees [31]. In comparison with a control condition, the Sanadak app was not more effective in reducing posttraumatic stress disorder (PTSD) symptomatology and, furthermore, it was not likely to be a cost-effective solution. An additional study protocol has been recently published aimed at conducting an examination of another CBT-based trauma app for Syrian refugees in Germany, but the results have not yet been published [32].

Study Objectives and Relevance

This study was focused on 2 primary objectives. First, it aimed to investigate novel neural and cognitive diagnostic and prognostic markers of clinical and subclinical PTSD with the

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potential for future integration in portable technology. We proposed that objective markers, when integrated into artificial intelligence, could aid lay humanitarian actors in the fast and accurate screening of individuals in need of care, guide best practices, assist with precision impact evaluation, and serve as predictive measures in prevention initiatives. Second, this proof-of-concept study introduced a trauma-focused digital mental health intervention, the eResilience app. Although the intervention's clinical rationale presents a transdiagnostic approach targeting basic physiology and neurocircuitry affected by stress, hence potentially having clinical utility to address a range of mental health conditions, this study examined its feasibility as a primary treatment for clinical and subclinical PTSD. The examination outcome assessment process for the intervention was based on psychological, cognitive, and neurobiological systems via (1) electrophysiological activity during a state of rest, (2) neuropsychological testing, and (3) clinical symptomatology.

eResilience App

Core Features

The eResilience app was proposed as a stand-alone intervention. The clinical curriculum is personalized for communities living under the poverty line, categorized by earning <US $5 per day. Moreover, it is low-intensity, without the involvement of specialists; it is trauma-focused, based on core components of complex trauma interventions including safety, self-regulation, self-reflective information processing, relational engagement, and positive affect enhancement [33]; it adheres to nonexposure practices as a safety measure; it is standardized in a toolkit format; it is 10 hours long and designed for completion during a short period of 5 to 7 consecutive days; it uses a clinical multimodal approach combining a diversity of clinical tools; it is culturally adaptable and neuroscience-informed; and, finally, it is designed to scale and reach large vulnerable populations.

Clinical Rationale

In alignment with the core components of complex trauma interventions, the curriculum was based on three clinical aims established for the eResilience protocol: (1) the creation of a safe and personal therapeutic space to hone skills of autonomic nervous system (ANS) control and awareness, (2) the enhancement of core cognitive functions affected by trauma, and (3) building or restoring relational engagement. The clinical tools in the curriculum that aim to build ANS awareness and control are rooted in theoretical and biological processes in the sympathetic and parasympathetic branches of the nervous and somatosensory systems. The method includes (1) building body awareness skills, (2) training one's ability to shift awareness between somatic sensations, and (3) identifying internal and external resources for top-down and bottom-up self-regulation, altogether aiming to promote a sense of safety that has been disrupted by trauma in the body and the environment. The clinical tools selected for building ANS awareness and control included breath work, progressive muscle relaxation, biofeedback, rhythm-focused exercises (music therapy, binaural beats, and bilateral tapping), yoga nidra, guided imagery, and grounding techniques. Therapeutic tasks primarily targeting cognitive function in the prefrontal cortex introduce the practice of exteroception skills, including engaging attention shifting from external surroundings, such as objects and sounds, and a short written task (which may also be adapted to accommodate the needs of individuals with low literacy levels) to identify internal and external resources for coping with adversity, as well as self-reflective information processing, positive affect, meaning making, and gratitude practice aimed at enhancing overall executive function capacities disrupted by trauma. For relational systems, selected tasks were informed by the biological principles and neural circuitry of social behavior and included the introduction of subjective and real-life safe interpersonal experiences, support system identification, building a sense of purpose in the community, and engagement in altruistic behavior, altogether aiming to promote environmental safety, interpersonal relatedness, planning, decision-making, initiation, and pleasure in the context of social interactions.

Software

In total, 3 software versions of the eResilience app have been created. The first prototype, also known as a minimum viable product, along with its first field version designed for groups, was created for and piloted by an international charity in West Africa. For this clinical trial, the eResilience research version 1.0 (Multimedia Appendix 1) was created and optimized to include clinical trial safety measures, accommodate individual participant use, and collect biometric and self-report data during the intervention week. The software specifications are detailed in the *Methods* section.

Research Questions and Hypotheses

On the basis of the evidence presented for anomalies in electrophysiological and cognitive performance in PTSD, this study questioned whether resting-state electrophysiological activity and neuropsychological performance were reliable objective measures for diagnosing clinical and subclinical PTSD and predicting intervention outcomes. It was hypothesized that, at baseline, (1) the PTSD cohort would present statistically significant differences in quantitative electroencephalograms (EEGs) compared with the controls and that (2) the PTSD group would perform more poorly than the control participants on the cognitive tests. Moreover, in questioning the feasibility of the proposed treatment for clinical and subclinical PTSD, we hypothesized that, at posttest measurements, the intervention would (1) reduce PTSD severity according to the Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; CAPS-5), Past-Month Edition, between baseline and posttest measurements (3-, 6-, and 12-month follow-up time points) and (2) improve participant performance in cognitive measures.

Methods

Ethics Approval

The study was approved by the Human Research Ethics Committees of the University of Sydney and the University of the Sunshine Coast, Australia. This trial was conducted in compliance with the ethics committee approval conditions, the National Health and Medical Research Council Statement on

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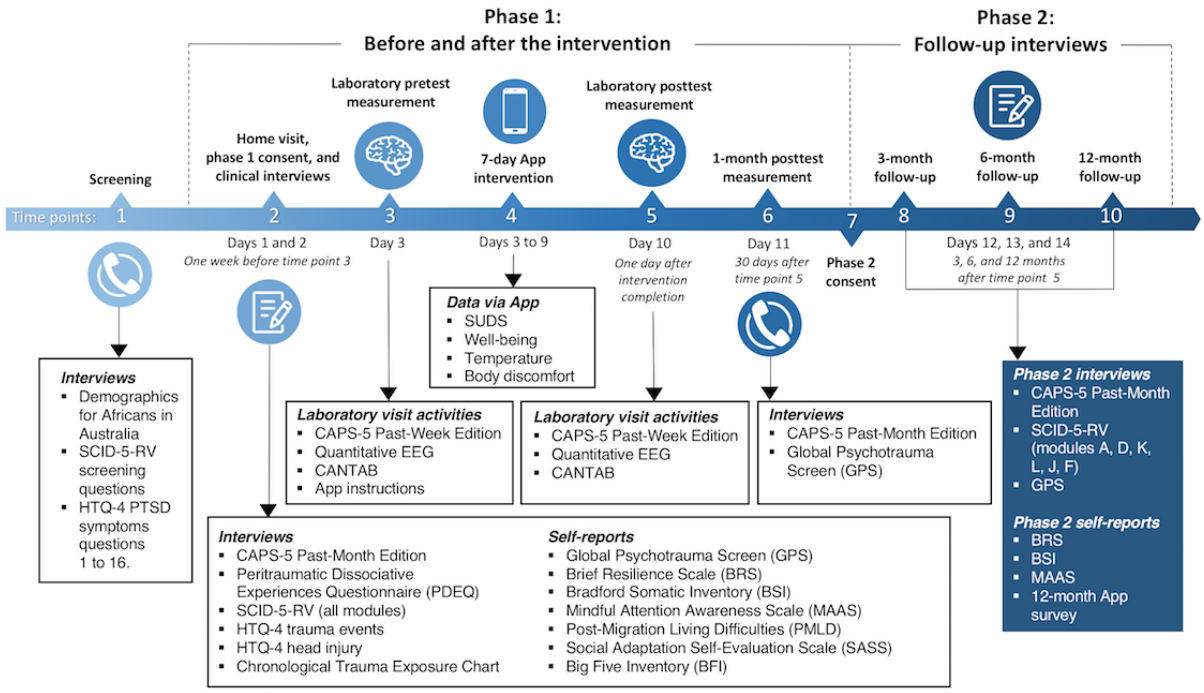
Ethical Conduct in Human Research (2007), and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

Study Design

This proof-of-concept study was designed as a nonrandomized controlled trial, including 10 time points across the 2 study phases. The first phase involved a 10- to 11-day commitment, comprising intake (time point 1), 1 or 2 baseline home visits to complete clinical interviews (time point 2, within 2 weeks of time point 1), a baseline university laboratory visit (time point 3, after 7 days of time point 2), the eResilience app intervention (time point 4, for 7 consecutive days starting the day of time point 3 upon laboratory data collection completion), a posttest university laboratory visit (time point 5, the day after time point 4 completion), and the 1-month follow-up (time point 6, after 30 days of the time point 5 laboratory visit). The second phase of the study included a new informed consent (time point 7, within 2 months of completing time point 6) to collect 3-, 6-, and 12-month follow-ups (time points 8, 9, and 10). The interventions at each time point are summarized in Figure 1. In total, participants in both phases of the study committed between 13 and 14 days to complete the trial within a 12-month period.

Figure 1. Study design. CANTAB: Cambridge Neuropsychological Test Automated Battery; CAPS-5: Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EEG: electroencephalogram; HTQ-4: Harvard Trauma Questionnaire-4; PTSD: posttraumatic stress disorder; SCID-5-RV: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Research Version; SUDS: Subjective Units of Distress Scale; TBI: traumatic brain injury.



Electrophysiology Paradigm and Acquisition

Paradigm

Quantitative EEG signals were collected in a sound-attenuated room during a resting state with 4-minute eyes-open and 4-minute eyes-closed paradigms and a 1- to 5-minute break between recordings to check and fix impedance as needed. The participants were instructed to fixate on a dot in the center of a television monitor during the eyes-open collection and rest quietly during the eyes-closed paradigm.

Participant Protocol

The participants followed instructions to not consume alcohol, caffeinated drinks, or nicotine on the day of the quantitative EEG recordings. Moreover, they were instructed to wash their hair with only shampoo the evening before the laboratory visits and avoid conditioners, gels, oils, and hair spray to increase electrode adherence to the scalp.

Data Acquisition and Export

Data were acquired at a sampling interval of 4000 µS and sampling rate of 250 Hz using the Electrical Geodesics' (EGI) Geodesic EEG System 400 [34]. A scalp EEG was recorded from 32 electrode sites according to the standard 10-20 International System [35,36] with the 32-channel HydroCel Geodesic Sensor Net which includes 2 link mastoids and 4 electrodes for vertical and horizontal eye movement tracking. Impedance was kept <5 kΩ. Raw EGI data were exported in a binary format with integer precision for preprocessing in the BrainVision Analyzer Software (version 2.2.1) [37]. A software solution was installed to read the original Cartesian electrode positions used in the EGI system.

Clinical Interviews

Several diagnostic clinical interviews as well as psychosocial and self-report questionnaires were selected for this study. All clinical interviews were conducted by a masters-level clinician with 12 years of experience conducting trauma assessments with African refugee communities (JVP) and a trained clinical

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research assistant with experience collecting and evaluating trauma assessments of 400 refugees across Uganda (Elsa Goninon). Challenging diagnostic decisions were discussed among senior researchers in the team (CH and BOT).

The CAPS-5 was chosen as a primary outcome measure for PTSD, possessing excellent convergent and discriminant validity (κ=0.84) [38], interrater reliability (κ=0.78-1.00), and test-retest reliability (κ=0.83). The full version of the Structured Clinical Interview for the DSM-5, Research Version [39], was collected face to face for diagnostic assessments of additional psychiatric conditions, including mood, anxiety, obsessive-compulsive disorder and related conditions, substance use, sleep, feeding and eating, somatic symptoms and related conditions, and externalizing disorders. To the best of our knowledge, there are currently no studies examining the psychometric properties of the Structured Clinical Interview for the DSM-5, Research Version; however, the clinical version of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders has demonstrated excellent interrater reliability for most diagnoses (κ values reported to be ≥0.75, diagnostic sensitivity >0.70, and specificity >0.80) [40]. The Global Psychotrauma Screen (GPS) [41] is a new, 22-question screening instrument designed to identify reactions to a potentially traumatic event or severe stressor within the month before assessment, demonstrating robust concurrent validity and good internal consistency, with acceptable Cronbach α coefficients across several studies [41-43]. The GPS data collected in this study will be used to examine the clinical validity of the instrument among refugees.

Additional clinical interviews included items 1 to 6 of the Peritraumatic Dissociative Experience Questionnaire [44], a self-report questionnaire that assesses dissociation (test-retest reliability: r=0.77; internal consistency: α=.89) [45]; the Harvard Trauma Questionnaire (HTQ) [46] to assess torture, trauma, traumatic brain injury, and trauma-related symptoms (test-retest reliability: 0.89; interrater levels: 0.098; test-retest reliability: 0.92; internal reliability for varied ethnic backgrounds, eg, 0.98 for Indochinese groups) [46]; the Social Adaptation Self-Evaluation Scale [47], a 20-item questionnaire measuring social motivation and behavior (Cronbach α=.74; no significant changes in test-retest reliability between the 2 first releases of the measure; P>.05) [47]; the Post-Migration Living Difficulties [48,49], a 17-item checklist assessing postmigration difficulties encountered by refugees proposed to serve as a predictor for poor mental health in refugee groups [50-52]; the Mindful Attention Awareness Scale [53], a 15-item self-report survey designed to assess levels of dispositional trait mindfulness (internal consistency among African American populations: α=.90 [53]; convergent validity negatively correlating with a measure of overall psychological distress [r=−0.38] and positively correlating with a measure of psychological flexibility [r=0.45] [54]); the Big Five Inventory [55], a 44-item self-report scale used to assess the prevalence of the 5 dimensions of personality (internal consistency among African American populations across the five subscales: agreeableness, α=.70; extroversion, α=.83; conscientiousness, α=.79; openness, α=.72; and neuroticism, α=.70) [56]; the Brief Resilience Scale [57], a 6-item questionnaire designed to assess one's ability to bounce back from stress (internal consistency: α=.80-.91; 1-month test-retest reliability interclass correlation coefficient=0.69; convergent and predictive validity positively correlating with measures of active coping, positive reframing, and planning [r=0.27-0.42] and negatively correlating with a range of poor health-related outcomes such as perceived stress, negative affect, anxiety, and depression [r=0.34-0.60]) [57]; and, finally, the Bradford Somatic Inventory [58], a multiethnic inventory that assesses the presence and severity of somatic symptoms related to anxiety and depression (internal consistency: α=.86 [59] and good test-retest reliability within a British care population).

Finally, 3 instruments were created for this study. The Demographics for Africans in Australia (Multimedia Appendix 2) is a 27-item questionnaire designed to collect demographic data specific to the experiences of African refugees resettled in Australia. The Chronological Trauma Exposure Chart (Multimedia Appendix 3) was created to supplement the assessment of trauma history. Considering that many participants in the communities selected for recruitment are commonly not aware of their exact birth date and that the long-term exposure to traumatic experiences during extended years of war presents a challenge in remembering precise years and dates, the chart contains a table with a range of years of interest on the x- and y-axes, x representing the participant's year of birth and y outlined by year in accordance with the main war-related events in each country. This way, the chart allows researchers to accurately identify the year of a described traumatic exposure that may have only been recalled according to a particular event in the war (eg, the fragile peace period in Liberia in 1997 or the state conflicts in 2012 in Sudan), thus pragmatically allowing the researchers to immediately identify and confirm with the participant their estimated age at the time of the reported event. The second half of the chronological chart attempts to aid in identifying the age, frequency, and duration of 8 traumatic experiences common among the target participants, including exile, bush hiding, malnourishment, sexual assault or rape, physical torture, cannibalism, and fighting in the war as adults or children. Finally, to examine the long-term qualities of the intervention according to both quantitative and qualitative subjective reports, a 7-item app survey (Multimedia Appendix 4) was developed for administration at the 12-month follow-up for participants who completed all stages of the study. The survey asks participants if they practiced, told others, or taught others the skills they learned during the previous year, including details such as frequency and mode of practice, recall of favorite activities, and perceived life improvement. In total, 2 exteroceptive questions also ask participants to check what resources they have often found most helpful throughout life to overcome adversity and the role religion may have played in adapting to difficult life situations.

Cognitive Tests

The Cambridge Neuropsychological Test Automated Battery [60] is a computerized and standardized assessment administered via tablet to measure the key cognitive processes of (1) information input into the brain, such as attention and processing speed; (2) information representation in the brain, such as memory; and (3) use of stored information to guide behavior, also known as executive function. The Cambridge

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Neuropsychological Test Automated Battery system has been used in other trials examining cognitive function in PTSD [61-69]. The tests are language-independent and suitable for cross-cultural experiments. The following tests were selected for this study for identification of diagnostic and prognostic cognitive markers: Motor Screening Task, Reaction Time, Rapid Visual Information Processing, Paired Associates Learning, Delayed Match to Sample, Spatial Working Memory, One Touch Stockings of Cambridge, and Emotion Recognition Test.

Intervention

At time point 3, the participants were individually taken through a 30-minute Microsoft PowerPoint introduction to the eResilience app. The session included handling a take-home kit containing printed safety guidelines, a smartphone with software, soundproof headphones, biofeedback equipment for temperature measurements, and the printed app response booklet (Multimedia Appendix 5). The participants were guided step by step on how to set up the biofeedback equipment at home and open and use the app and its features and provided with safety briefings and a short demonstration of each clinical task. Finally, the researchers programmed the software in the presence of each participant to activate the daily app alarm at the preferred time as chosen by the participant in the following 7 days. Once programmed, the smartphone app activated daily reminder alarms at 1 hour and 15 minutes before the time specified to commence the program each day. The participants were instructed to leave the phone always plugged at home and with the volume on. For time point 4, all participants took the app kit home and followed instructions on the smartphone screen to complete a sequence of daily tasks for 7 consecutive days. During the treatment week, the participants completed the tasks by themselves and at their own pace with a time frame ranging between 90 and 100 minutes, given the pause button option across all intervention blocks. Access to the tasks for each day was unlocked every 24 hours at the hour selected by the participant during time point 3 to prevent participants from potentially attempting to complete more than one session per day in the same 24-hour period.

Software Specifications

The eResilience app research version (Multimedia Appendix 1) designed for this study includes 2 user dashboards: one for researchers and the second one for study participants. The researcher dashboard presents features to (1) add participants and schedule their intervention commencement time; (2) a user-friendly database of participant activity; (3) a management system for the allocation of smartphones and other research equipment; and (4) a real-time participation monitoring feed including mobile SMS text message notifications each time a participant commences, concludes, or skips a task. Once the researcher launched the participant dashboard on the app, a secure log-in was needed to switch back to the researcher dashboard, thus making it impossible for participants to make changes. The participant dashboard home screen displayed a user-friendly layout with a simple 1-click motion to start each of the 7 days of the intervention. Although it displayed all 7 buttons for the 7 days of the intervention, only the current day was activated for access each day. This feature unlocked the curriculum every 24 hours at the daily time stipulated by the participant at baseline, preventing participants from attempting to complete the curriculum in <7 days. A daily alarm set by the researcher reminded the participant to complete the tasks at 1 hour and at 15 minutes before the elected starting time.

Once the intervention was launched, the clinical tasks were presented via visual and audio instructions recorded in a pitch-controlled, text-to-speech software. Advanced features to promote participant safety included well-being, body discomfort, and stress checks added at the start and end of the day and in between blocks of exercises, automating SMS text messages that were sent to researchers on standby whenever a participant reported elevated levels of distress during the intervention. As part of the study design, the software also presented integration for external biofeedback equipment for temperature check-ins as part of the objective stress measurements. The data set collected via software during the intervention week included time-tracking features to register precise individual participation (eg, when a clinical task had been paused, skipped, or not played). Data were secured and accessed via a password-protected researcher account.

Recruitment

Participants were recruited in collaboration with the following local African community organizations in the state of Queensland: the *Federation of Liberian Communities in Australia*, the *Liberian Association of Queensland*, the *Congolese United for Peace and Reconciliation in Australia*, *Together We Are Powerful Inc*, and the *South Sudanese Youth Council*. Further recruitment support was also received from three nonprofit charities: *Second Chance Africa*, *Sync Body-Brain Health*, and *Welcoming Australia*. Building rapport with community leaders was imperative for successful recruitment, managing cross-cultural expectations, and ensuring that the project aim was well understood before approaching community members. Each community leader held meetings with researchers and other nonprofit staff for several months to discuss the details of the project. They also visited the neuroscience laboratory to understand all the data collection procedures before introducing the project to their community members. All African community leaders mutually agreed to assist the study motivated by the project's potential outcome to disseminate effective trauma care worldwide across regions of disaster via our supporting charities and sponsored 7 recruitment social events to introduce the opportunity to their members. The events included free cultural activities such as live music, sports, dance, and traditional food proposed by the community leaders. During the events, the researchers, along with the community leaders, adhered to the approved study advertisement materials, distributed handouts of the participant information statement (Multimedia Appendix 6) to provide information about the study, and provided opportunities for those interested to ask questions regarding participation. An expression-of-interest sign-up sheet was also used during events for contacting prospective participants. Most participants who completed the project also referred other friends and family members to participate in the study.

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Study Phase 1 Eligibility and Consent

Inclusion Criteria

Participants were eligible if they were Liberian, Congolese, or Sudanese refugees who had migrated to Australia after the age of 18 years. All participants were required to have English proficiency and have fled emergency in Africa between 1989 and 2018. The participants were divided into two groups: a PTSD group, including clinical and subclinical PTSD cases according to the diagnostic specifications outlined in Textbox 1, and a trauma-exposed control group who did not meet the criterion for clinical or subclinical PTSD or other mental health disorders.

Textbox 1. Posttraumatic stress disorder (PTSD) diagnostic inclusion criteria.

Inclusion criteria

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) threshold: Clinician-Administered PTSD Scale for the DSM-5 (CAPS-5) criteria A+B+C+D+E+F+G
- DSM-5 subthreshold: CAPS-5 criteria A+(at least one threshold symptom at B, C, D, and E)+F+G
- DSM-5 subsyndromal: CAPS-5 criteria A+B+(meets criteria for cluster C or D or E or any 2 of the 3 clusters, but not C+D+E combined)+F+G
- DSM-5 other stress or trauma-related disorders: CAPS-5 criteria A+F+G (and no overlap with DSM-5 Subsyndromal cases)
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) threshold: Clinician-Administered PTSD Scale for the DSM-IV (CAPS-4) criteria A+B+C+D+E+F
- DSM-IV subthreshold: CAPS-IV criteria A+(at least one threshold symptom at B, C, and D)+E+F
- DSM-IV subsyndromal: CAPS-4 criteria A+B+(C or D)+E+F
- DSM-IV Harvard Trauma Questionnaire (HTQ) risk screen: HTQ mean score of items 1 to 16 ≥2.5 (symptomatic for PTSD)
- DSM-IV threshold: CAPS-IV criteria A+B+C+D+E+F
- DSM-IV subthreshold: CAPS-4 criteria A+(at least one threshold symptom at B, C, and D)+E+F

PTSD Group Diagnostic Inclusion Criteria

Considering the reported limitations of the Diagnostic and Statistical Manual of Mental Disorders in identifying trauma among refugee populations [70], we broadened the PTSD symptom profile in the inclusion criteria (Textbox 1) to include clinical (threshold) and subclinical (subthreshold, subsyndromal, other stress or trauma-related disorders, and risk screening) profiles. Researchers ensured that two core characteristics were met for all participants enrolled in the PTSD group: (1) the presence of trauma symptomatology in response to a humanitarian event and (2) the reported trauma-related cause significant life impairment.

Exclusion Criteria

Exclusion criteria for both groups included a self-reported severe medical condition, genetic disorder, or concurrent drug or alcohol abuse or dependency within the month before the intervention trial.

Additional exclusion criteria for the PTSD group included current use of psychotropic medication or use within the 2 months preceding the intervention, concurrent psychotherapy for PTSD, and acute risk of suicide or homicide.

Considering the various levels of trauma symptomatology proposed for the PTSD group, additional exclusion criteria for the trauma-exposed control group included not meeting the threshold, subthreshold, subsyndromal, or other stress- or trauma-related disorders criteria on either the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or the DSM-5 as well as not meeting PTSD risk or symptom criteria on the HTQ.

Study Phase 1 Consent

All participants enrolled provided oral and written consent and signed a participant consent form at time point 2 (Multimedia Appendix 7).

Study Phase 2 Eligibility and Consent

Participants were contacted 30 days after completion of the 1-month posttest measurement, invited to participate in the study phase 2—involving 3-, 6-, and 12-month follow-up interviews—and given a copy in person or via email of the second participant information statement (Multimedia Appendix 8). Eligibility to participate in the second phase of the study included having completed the first phase. Those who opted to join provided oral and written consent and signed the second participant consent form (Multimedia Appendix 9) at time point 7.

Statistical Analyses

Overview

Study measures will be compared between the PTSD and control group participants. Descriptive statistics and 2-tailed *t* tests will be used to describe the sample and compare changes between groups.

All time-domain quantitative EEG recordings will be plotted into a frequency power spectrum using fast Fourier transform. The grand average for each segment of data for the control and experimental conditions will be calculated at pre- and posttest measurements across both paradigms to generate topographical distributions of spectral power values in the delta, theta, alpha, peak alpha, beta, peak beta, and gamma frequency bands. The results will be presented in the form of power values (uV2).

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On the basis of the respective data distribution, McNemar nonparametric tests, *t* tests, and repeated ANOVAs will be used for all quantitative EEG, neuropsychological, and clinical data collected across time points to identify statistically significant changes after the intervention. Changes in selected variables of both groups between the baseline and postintervention conditions will be investigated via additional independent sample *t* tests and Wilcoxon nonparametric tests. Linear regression analyses and chi-square tests will be used to identify predictors of treatment response between the subjective and objective variables. Further correlation analyses will be conducted to assess the relationship between clinical and cognitive variables in the experimental condition to explore associations between the app, PTSD symptomatology, and cognitive and electrophysiological variables. Additional post hoc analyses will be conducted as needed.

Statistical Power and Sample Size Estimation

The proposed sample size of 60 for this study (PTSD: 30/60, 50%; controls: 30/60, 50%) was based on the effect size computation of a quantitative EEG measure previously used to investigate the dimensional complexity of the EEG between the PTSD and control groups [71]. This produced a mean of 11.991 (SD 0.1760) for the non-PTSD group and of 11.1689 (SD 0.2437) for the PTSD group based on EEG leads that yielded significant results (frontal electrodes on both hemispheres Fp1, F8; central electrodeC4 and parietal electrode P4 on the right hemisphere; temporal electrodes T3, T4, T5, and T6 on the right and left hemispheres, and occipital electrode O1 on the left hemisphere) [49]. An SD estimate of 0.612 for the control and PTSD groups and a mean difference of 0.822 between the PTSD and control groups indicated an effect size of 1.343 and a 100% statistical power estimation with a sample size of 30 per condition. Clinical studies on PTSD have often achieved large effect sizes with samples of 30 patients per condition in accordance with the recommendations of the International Society of Traumatic Stress Studies Treatment Guidelines [72].

Results

Recruitment Results

For the recruitment results (Figure 2), at the first time point (time point 1), a total of 100 individuals were screened for this study, of whom 20 (20%) did not meet the inclusion criteria because they were control participants with comorbid psychiatric conditions (7/20, 35%); PTSD group participants with reported substance use (6/20, 30%); or participants between groups with poor English fluency (4/20, 20%), outside the target age range (1/20, 5%), or unable to be contacted (2/20, 10%).

In the first phase of baseline assessments, time point 2, a total of 80 participants consented and were fully assessed, and 75 (94%) chose to enroll in the intervention. All enrolled participants (75/75, 100%) completed the second baseline phase (time point 3) and took the eResilience app home to complete the intervention during the 7-day period (time point 4). In total, 7% (5/75) of the participants withdrew consent before commencing the intervention because of lack of time (4/5, 80%) and a disclosure of alcohol abuse (1/5, 20%); thus, their data will be removed from the analyses. All 70 participants who completed the intervention returned to the laboratory for postintervention assessments (time point 5) and completed the 1-month follow-up assessment (time point 6) via telephone. Upon completion of the 1-month follow-up, the participants were contacted and extended an invitation to participate in the 3-, 6-, and 12-month follow-ups for the study. In total, 89% (62/70) of the participants who completed the trial consented and opted to enroll again (time point 7). Of the 8 participants who did not join the follow-ups, 2 (25%) were part of the PTSD group and opted out without disclosing reasons, and 6 (75%) were unable to be reached because of changes in phone numbers, addresses, or email (PTSD: 2/6, 33%; controls: 4/6, 67%). All participants enrolled in the follow-ups (62/62, 100%) completed the interviews at the 3 time points (time point 8, time point 9, and time point 10). In summary, the final data sample includes 70 participants at baseline, 1-week, and 1-month posttest analyses and 62 participants in the 3-, 6-, and 12-month follow-ups.

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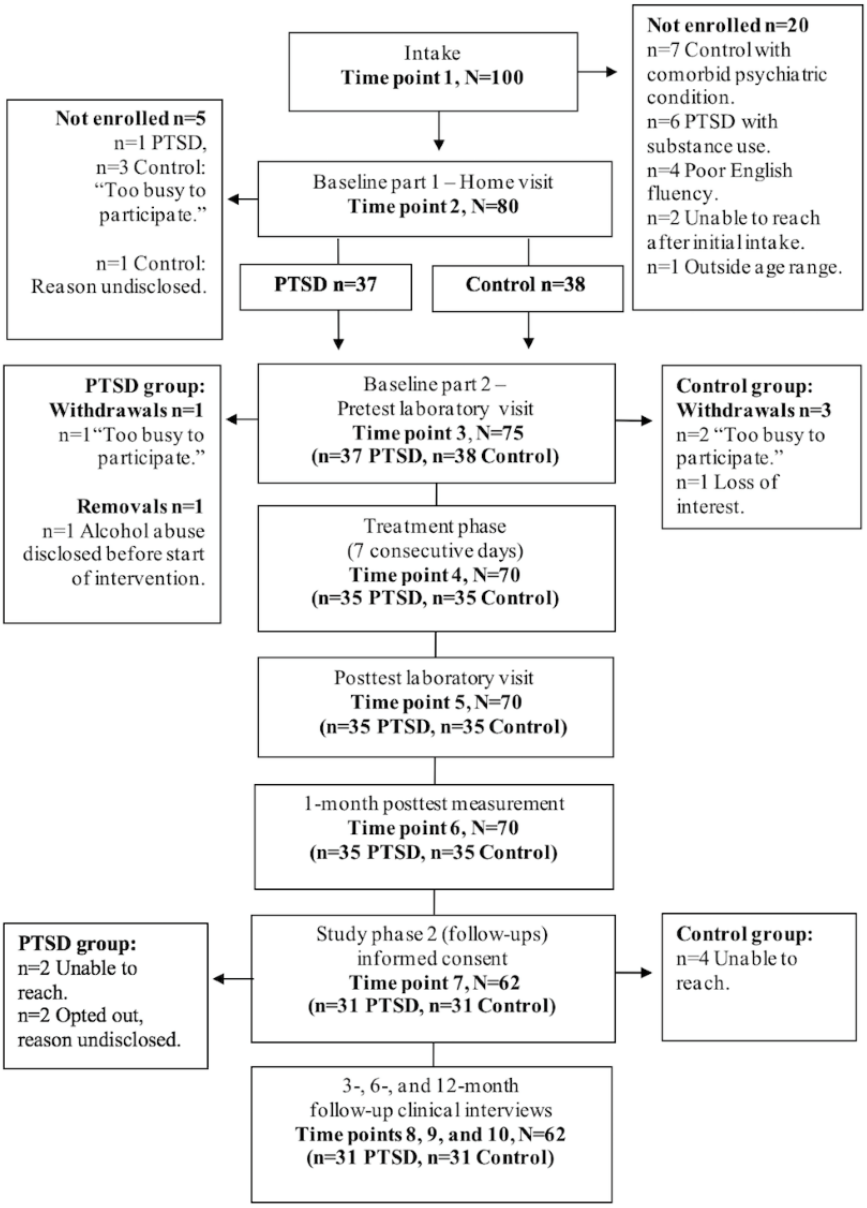
Figure 2. Study recruitment results flowchart.



Participant Profiles

The final sample that completed the treatment phase (n=70) included 44% (31/70) men and 56% (39/70) women aged 18 to 54 years (mean 33.64, SD 10.54 years). The participants were Congolese (Democratic Republic of the Congo; 23/70, 33%), Liberian (22/70, 31%), and Sudanese (25/70, 36%) and altogether represented 26 African ethnic groups. The PTSD cohort (35/70, 50%) included 69% (24/35) of participants who met the full DSM-5 PTSD diagnostic criteria based on the CAPS-5, 14% (5/35) who met the DSM-5 subthreshold criteria, and 17% (6/35) who met the DSM-5 subsyndromal criteria, as detailed in Textbox 1. When translating the reported symptomatology of the PTSD cohort to the DSM-IV–based criterion, 63% (22/35) met the threshold, 34% (12/35) met the subthreshold, and 3% (1/35) met the subsyndromal criteria. On the basis of the DSM-IV HTQ risk screening, only 43% (15/35) of the PTSD group participants had scores indicating being symptomatic for PTSD. In the trauma-exposed control group (35/70, 50%), 40% (14/35) presented no PTSD symptoms, 23% (8/35) presented 1 mild symptom, and 9% (3/35) presented more than one mild symptom but no threshold symptoms. Moreover, 29% (10/35) of the controls presented one or more threshold symptoms but disclosed not being bothered by them. None of the control participants met the clinical or subclinical PTSD criterion. Most importantly, none of the control participants who presented trauma symptoms (21/35, 60%) reported levels of impairment or trauma-related distress.

Data Collection Adaptations

The participants were asked to complete the GPS on their own at the end of the home visit. Nevertheless, upon noticing that several participants mistakenly responded to the GPS based on lifetime experiences, the researchers conducted a second GPS interview within 24 hours to ensure that all answers corresponded to the symptoms experienced within the previous 30 days.

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Continuation of Therapy

None of the participants requested referral for the continuation of mental health care. Many participants expressed an interest in downloading the app to continue the intervention tasks when it became available.

Adverse Events

No adverse events were reported during the study.

Additional Results

Additional results for all analyses proposed are being prepared for publication as of May 2022.

Discussion

Principal Findings

We anticipate that this proof-of-concept trial will provide evidence of the preliminary efficacy of the proposed intervention in treating trauma and will identify novel cognitive and electrophysiological diagnostic and prognostic markers of clinical and subclinical PTSD. Although the results of this trial are being prepared for publication, the enrollment outcomes were presented in this protocol. On the basis of the sample size estimation, the aim of this study was to recruit 60 participants. However, refugee community members' interest in joining the trial exceeded the study capacity. Moreover, the dropout rates were unusually low for PTSD clinical trials, with only 3% (1/35) of the PTSD participants dropping out before treatment initiation and none dropping out during or after treatment. In contrast, other intervention studies have indicated dropout rates >20% [73-75].

Strengths and Limitations

This study design presents strengths and limitations. First, it is essential to acknowledge that our healthy control group, although not presenting PTSD or other psychiatric disorders, was exposed to similar war and conflict-related traumatic events as the PTSD group. The recruitment of nonexposed controls, although most suitable, was not possible considering that all 3 African refugee communities involved in this study migrated to Australia because they were fleeing conflict. Moreover, between both groups, traumatic brain injury, medication washout, and other medical conditions were only self-reported via the approved clinical interviews. Thus, it is possible that trauma exposure among controls, along with brain injury, unreported use of medications, or other undetected medical conditions between both groups, could affect response to the intervention, cognitive test scores, and quantitative EEG recordings. Particularly in the PTSD group, quantitative EEG recordings can also be affected by the dysregulation of sleep often present in traumatic stress; therefore, this must be considered during the analyses.

Although one of the strengths of this study is the combination of objective and subjective diagnostic and prognostic measures, owing to restricted resources, the follow-up phase did not include the collection of quantitative EEG, biometric data, or cognitive tests. In addition, although the proposed design does not include randomization of participants and a no-intervention group as a proof of concept, this feasibility study serves a vital role in subjectively and objectively examining the preliminary efficacy of the eResilience app before directing resources toward large randomized controlled trials. It is also important to note that, although the proposed app intervention was designed for cross-cultural use, the sample recruited for this study, primarily represents African cohorts exposed to war and conflict-related trauma. Finally, the COVID-19 pandemic coincided with the 12-month follow-up mark, potentially causing additional stress after the intervention.

Clinical Intervention Design Challenges

To date, apps are unlikely to address all complexities of mental health disorders and, thus far, evidence supports that they are best used to supplement care rather than as first-line interventions. The development of the eResilience app as a high-impact intervention and the proposed study design are challenged by the fact that the populations for which this intervention is designed are likely never to have access to adequate professional help in their lifetime, and an app such as the one proposed may be the only help they will ever access. Moreover, recognizing that PTSD is not the sole mental health concern among our target populations and that the eResilience app should aim toward a transdiagnostic approach, this proposed study lacks the power and resources to examine outcomes across diverse domains. Another considerable challenge relates to designing a tool suitable for large-scale dissemination while not compromising safety and quality of care.

Notably, one of the promising strengths of this intervention design for individual or group use is the cost efficacy projected to be relatively lower than existing programs. In addition, the simplicity and safety of the designed clinical tools aim to eliminate the need for training and supervision of local lay staff. Finally, the week-long time frame would also further reduce costs in extensive community outreach efforts, thus boosting its scalability potential.

Future Directions

If successful, this trial will provide a foundation for large-scale, cross-cultural studies to further examine the efficacy of the proposed app intervention and biomarker precision as well as to better understand how brain data may inform other cost-effective biometric measures for software integration, serve as a digital aid for the precision diagnosis of PTSD and related disorders, and measure treatment response.

The research software version used in this study is available upon request to all external researchers interested in conducting future trials. Recommendations for future designs include (1) the inclusion of healthy controls that have not been exposed to traumatic stress, particularly as it pertains to the identification of diagnostic markers; (2) the inclusion of objective measures to examine physiological regulation skills at long-term follow-ups; (3) the use of smartphones with sensor technology for biometric data collection, including heart rate variability; (4) the investigation of the efficacy of the app for other disorders as primary outcome measures, such as depression and generalized anxiety; and (5) the expansion of the sample diversity to include non-African communities and demographics

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affected by other types of humanitarian emergencies besides war and conflict. Finally, although the design and results of this trial may be premature in assessing the cost-efficacy and scalability qualities of the app, we also strongly recommend that those qualities be considered in future study protocols. Further considerations will be discussed alongside the publication of the study results.

Conclusions

This study protocol introduces a novel digital app for the treatment of posttraumatic stress in emergencies. Its nonreliance on the DSM-5 constructs of PTSD and greater focus on the neural substrates of traumatic stress as an attempt to target the cause of symptoms may increase the likelihood of cross-cultural adaptability, promoting long-term sustainable change on a neurobiological basis rather than via the reduction and ongoing maintenance of symptoms. The potential identification of diagnostic markers could yield further advances for the humanitarian sector, contributing toward the cost-effectiveness of large-scale programs by making the best use of limited resources when identifying persons in need and objectively monitoring impact via automated health data feedback. Overall, we conclude that the successful enrollment and low dropout results presented indicate a strong interest from the Liberian, Sudanese, and Congolese refugee communities in Australia to be involved in research to contribute toward the development of novel approaches to address global mental health challenges caused by war and adversity.

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Authors' Contributions

The first author JVP contributed to study conceptualization, design, and manuscript writing. The second and third authors CH and BOT provided expert supervision and revision. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
eResilience app research version 1.0.
[PDF File (Adobe PDF File), 2745 KB - resprot_v11i6e38223_app1.pdf]

Multimedia Appendix 2
Demographics for Africans in Australia.
[PDF File (Adobe PDF File), 95 KB - resprot_v11i6e38223_app2.pdf]

Multimedia Appendix 3
Chronological trauma exposure chart.
[PDF File (Adobe PDF File), 137 KB - resprot_v11i6e38223_app3.pdf]

Multimedia Appendix 4
App survey for 12-months post-test assessment.
[PDF File (Adobe PDF File), 256 KB - resprot_v11i6e38223_app4.pdf]

Multimedia Appendix 5
eResilience app response booklet.
[PDF File (Adobe PDF File), 2759 KB - resprot_v11i6e38223_app5.pdf]

Multimedia Appendix 6
Participant information statement.
[PDF File (Adobe PDF File), 495 KB - resprot_v11i6e38223_app6.pdf]

Multimedia Appendix 7
Participant consent form.

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[PDF File (Adobe PDF File), 348 KB - resprot_v11i6e38223_app7.pdf]

Multimedia Appendix 8
Participant Information Statement - Phase 2.
[PDF File (Adobe PDF File), 224 KB - resprot_v11i6e38223_app8.pdf]

Multimedia Appendix 9
Participant Consent Form Phase 2.
[PDF File (Adobe PDF File), 190 KB - resprot_v11i6e38223_app9.pdf]

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Abbreviations

ANS: autonomic nervous system
CAPS-5: Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
CBT: cognitive behavioral therapy
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG: electroencephalogram
EGI: Electrical Geodesics
GPS: Global Psychotrauma Screen
HTQ: Harvard Trauma Questionnaire
PM+: Problem Management Plus
PTSD: posttraumatic stress disorder

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Protocol

Assessing Trauma Management in Urban and Rural Populations in Norway: A National Register-Based Research Protocol

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Abstract

Background: Time is considered an essential determinant in the initial care of trauma patients. In Norway, response time (ie, time from dispatch center call to ambulance arrival at scene) is a controversial national quality indicator. However, no national requirements for response times have been established. There is an ongoing debate regarding the optimal configuration of the Norwegian trauma system. The recent centralization of trauma services and closure of emergency hospitals have increased prehospital transport distances, predominantly for rural trauma patients. However, the impact of trauma system configuration on early trauma management in urban and rural areas is inadequately described.

Objective: The project will assess injured patients' initial pathways through the trauma system and explore differences between central and rural areas in a Norwegian trauma cohort. This field is unexplored at the national level, and existing evidence for an optimal organization of trauma care is still inconclusive regarding the impact of prehospital time.

Methods: Three quantitative registry-based retrospective cohort studies are planned. The studies are based on data from the Norwegian Trauma Registry (NTR; studies 1, 2, and 3) and the local Emergency Medical Communications Center (study 2). All injured patients admitted to a Norwegian hospital and registered in the NTR in the period between January 1, 2015, and December 31, 2020, will be included in the analysis. Trauma registry data will be analyzed using descriptive and relevant statistical methods to compare prehospital time in rural and central areas, including regression analyses and adjusting for confounders.

Results: The project received funding in fall 2020 and was approved by the Oslo University Hospital data protection officer, case number 18/02592. Registry data including approximately 40,000 trauma patients will be extracted during the first quarter of 2022, and analysis will begin immediately thereafter. Results are expected to be ready for publication from the third quarter of 2022.

Conclusions: Findings from the study will contribute to new knowledge regarding existing quality indicators and with an increasing centralization of hospitals and residents, the study will contribute to further development of the Norwegian trauma system. A high generalizability to other trauma systems is expected, given the similarities between demographical changes and trauma systems in many high-income countries.

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KEYWORDS

trauma; emergency medicine; prehospital care; trauma registries; epidemiology; quality of health care

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Introduction

Background

Traumatic injuries constitute a major global health problem [1]. According to the Global Burden of Disease study conducted by the World Health Organization in 2013, 973 million people sustained injuries that required health care, and injuries accounted for 4.8 million deaths. Although mortality from injuries has been reduced in the last four to five decades because of injury prevention and better trauma care, it is still one of the leading causes of mortality and morbidity among younger age groups [2].

There is broad agreement that a well-functioning trauma system, with a seamless treatment chain from accident site to completed rehabilitation, is essential for optimal patient outcomes [3]. In November 2015, the Norwegian government published a new health and hospital plan that aimed at ensuring a coherent system of emergency services in and outside hospitals that provides adequate security and quality of health care throughout the country [4]. Parallel to this, an updated national trauma plan has been developed and implemented. The plan includes all stages of the chain of survival, from first aid at the scene of injury; criteria for suspecting serious injury; and destination for definite care, treatment, and rehabilitation [5,6].

In Norway, the scattered population, long distances, seasonal cold, and a rough climate challenge the organization and provision of acute care medical services [7]. There is an ongoing debate regarding the optimal configuration of today's trauma systems, and there has been a tendency toward the centralization and closures of emergency hospitals with trauma wards. In 2002, 52 hospitals had a trauma ward, and today, there are only 38 hospitals with one. The debate must be held considering the increased availability of advanced prehospital treatment, which might counteract the long transport time for trauma patients. More centralized emergency medical competence may affect where the patient is transported and treated.

Prehospital Time

As the distance between injury site and trauma center increases, the choice between whether to transport patients directly to definite care or stabilize patients either at the accident scene or in nontrauma center hospitals with a subsequent transfer to a trauma center becomes increasingly pertinent [8].

Several studies on the effect of prehospital transport time on mortality have been conducted in the last two decades. In 2020, a scoping review by Bedard et al [9] on the effect of prehospital time on trauma outcomes was published. They reported on positive, negative, and neutral associations between prehospital time and inhospital mortality. The relationship between prehospital time and mortality thus seems to be unclear. However, most of the included studies in this scoping review did not differentiate between blunt and penetrating trauma. Other studies, including a systematic review by Harmsen et al [10] in 2015 and individual empirical studies, have found a clear positive effect of prehospital time on survival for penetrating and traumatic brain injuries [11]. In the case of blunt injuries, the results remain mixed. In the same systematic review, short emergency response time and transport time from scene to hospital were associated with better survival. Moreover, a longer on-scene time had favorable odds for survival [10]. On the contrary, Waalwijk et al [12] found an association between prolonged on-scene time and mortality in their recently published article.

Furthermore, studies included in the 2020 scoping review by Bedard et al [9] were largely based on urban areas with a high population and hospital density. For rural areas, both the incidence and the consequence of traumatic injury exceed those of urban areas, while evidence for the optimal organization of trauma care is less conclusive. By comparison, a large 4-year registry study from a trauma register in Quebec, Canada, reported on mortality differences between rural and urban areas. They collected data from nearly 80,000 registered trauma patients and concluded there was an increased mortality in rural areas [13]. These findings suggest that rural areas are associated with higher mortality due to longer prehospital times.

Norwegian Trauma System

Norway has a scattered population of 5.4 million people [14]. Approximately 80% of its inhabitants live in urban areas, while the rest live in rural areas [15]. It is a high-income country with a publicly funded health care system and a national trauma system.

According to the national trauma plan, 34 acute care trauma hospitals and 4 trauma centers receive and treat trauma patients in Norway. All acute care trauma hospitals offer general surgical and orthopedic services and are capable of stabilizing severely injured patients before transferring them to trauma centers if necessary. The acute care trauma hospitals do not offer neurosurgery, intervention radiology (except for a few), or other specialized services. The trauma centers offer all medical specialties, including neurosurgery, and can manage all types of injuries. Both emergency hospitals and trauma centers have criteria for trauma team activation (TTA). In addition, there are several competence requirements for trauma team members, including passing an Advanced Trauma Life Support course and having a minimum of 4 years of surgical experience for the team leader [6,16].

In Norway, emergency medical communications centers (EMCCs) are organized as several public centers spread across the country with their own emergency contact number. The emergency call receivers use predefined criteria for triage and dispatch of resources based on the caller’s information.

National Quality Indicators

The Norwegian trauma plan defines the following quality indicators related to patient transport:

- Rate of patients with transport time to trauma center less than 45 minutes (otherwise the patient should go to an emergency hospital with a trauma ward)
- Proportion of correct destination from scene for all patients with a suspected serious injury

Norwegian authorities have defined national quality indicator for prehospital *response time* as the time interval from when an EMCC is notified until the ambulance arrives on scene [17].

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Until recently, this quality indicator was merely a recommendation, but in March 2021, the Norwegian Parliament agreed on a resolution to fix the response time by law [18]. The quality indicator for response time is as follows:

- In urban areas, the ambulance should arrive at the scene within 12 minutes in 90% of emergency events.
- In rural areas, the ambulance should arrive at the scene within 25 minutes in 90% of emergency events.

Aim

The overall aim of the project is to assess how trauma system configurations in urban and rural areas affect the initial management of trauma patients. Injured patients' initial pathways through the Norwegian trauma system will be described, and urban-rural differences will be explored. We will also determine the association between prehospital time and outcomes in trauma patients.

First, the project will examine dispatch time, prehospital time, interventions given, patient destination, and modes of transport in a Norwegian trauma population with data from the Norwegian Trauma Registry (NTR) for 2015 to 2020. Differences in gender and age will be examined along with injury mechanism. Second, we will investigate to what extent ambulance services, including emergency medical services (EMS) and helicopter EMS (HEMS), reach severely injured patients within an acceptable time frame according to national quality indicators. Third, we will investigate the time spent on primary care in acute care trauma hospitals compared to trauma centers and time spent transferring patients between hospitals and trauma centers. For one of our studies, we will investigate response dispatch for severely injured patients (Injury Severity Score [ISS]>15) with additional data from the EMCC journal [19].

Methods

This project consists of 3 quantitative registry-based retrospective cohort studies using data from the NTR studies 1, 2, and 3 and the local EMCC data (study 2).

Hypotheses and Objectives

The specific objectives and hypotheses of the project are as follows.

Study 1

The following are the objectives, outcome measures, and hypothesis for study 1:

- Objectives
  - To assess how response times to suspected severely injured patients comply with national quality indicators [17]
    - Examine differences between urban areas compared to rural areas using the Statistics Norway centralization index [20]
    - Compare prehospital time for: (1) primary admissions to acute care trauma hospitals and (2) primary admission to trauma centers
    - Examine transfers between hospitals
- Primary outcome measures
  - Response time: time interval from dispatch to ambulance at scene
- Secondary outcome measures
  - Time spent at scene
  - Prehospital time for primary admissions to emergency departments (ED) at trauma centers
  - Prehospital time for primary admissions to ED at acute care trauma hospitals.
  - Total prehospital time from dispatch to ED admission at trauma centers and acute care trauma hospitals
  - Time from primary to secondary hospital admission
- Hypothesis: We hypothesize shorter response time in urban areas compared to rural areas.

Study 2

The following are the objectives, outcome measures, and hypothesis for study 2:

- Aim
  - To conduct an in-depth analysis of dispatch dynamics in a subgroup of severely injured patients (ISS≥9/ISS>15) and explore potential differences in urban and rural areas by linking data from the NTR with local EMCC data. The decision-making process at the EMCC is an unexplored but important part of the chain. The analysis will include:
    - Coherence between initial information and patient physiology (including Glasgow Coma Scale)
    - Evolution of initial and subsequent resource utilization
    - Prehospital medical interventions according to level of service provider
- Primary outcome measures
  - Response
  - Emergency
  - Resources utilized
  - Triage (triage to hospital and triage to TTA)
- Secondary outcome measures
  - More precise location data
- We will look at the possibility of cooperation with other Nordic counties.
- Hypothesis: Over- and undertriage occur to a greater extent in patients with moderate to severe injuries. In the trauma system, accuracy is difficult both in relation to where the patient is to be transported and in connection with TTA.

Study 3

The following are the objectives, outcome measures, and hypothesis for study 3:

- Aim
  - To explore potential differences in quality of trauma care in severely injured patients between urban and rural areas.

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    - To examine ground EMS compared to HEMS on scene competence, interventions given, and transport type for patients with severe injury (ISS≥9/ISS>15).
- Primary outcome measures
    - Mortality
    - Length of hospital stay/intensive care day/intubations days
    - The Glasgow Outcome Scale Extended/The American Society of Anesthesiologists physical status classification [21].
- We will adjust for the following possible confounding factors:
    - Gender/age
    - Injury severity
    - If the data quality allows it, it may be relevant to adjust for physiological data.

We may consider extracting supplementary data from the Norwegian Cause of Death registry to verify the mortality rate.

Due to the exploratory design of the study, no hypothesis is formed.

Study Setting

This a national population-based study including the entire mainland of Norway and its population. The emphasis is initial trauma management including the prehospital phase and emergency departments belonging to the 34 acute care trauma hospitals and 4 trauma centers that comprise the Norwegian trauma system.

Study Population

All injured patients admitted to a Norwegian hospital and registered in the NTR between January 1, 2015, and December 31, 2020, will be included in the analysis. Textbox 1 shows the inclusion and exclusion criteria. The registry data will include approximately 40,000 trauma patients.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- All patients admitted with trauma team activation (TTA) on arrival to the emergency department in all acute care trauma hospitals and trauma centers in Norway, irrespective of Injury Severity Score (ISS) and New Injury Severity Score (NISS)
- All patients treated at an acute care trauma hospital or trauma center in Norway without TTA and with one or more of the following injuries:
    - Penetrating injury to the head, neck, torso, or extremities proximal to elbow or knee
    - Head injury with Abbreviated Injury Score ≥3
    - NISS>12
- All patients with trauma-related death at site of trauma or during transportation to hospital who are referred to hospital, but where prehospital management/treatment was initiated

Exclusion criteria

- Patients with chronic subdural hematoma without other trauma-related injuries
- Patients with injuries from drowning, inhalation, hypothermia, and asphyxia without concomitant trauma
- Patients who die on scene without the activation of prehospital resources.
- “Walk-in” traumas, meaning patients who present to hospital via private vehicle, police vehicle, or other/unknown
- Patients who are not registered with the emergency medical communications centers

Variables

Time Variables

The primary variables are time intervals in different prehospital phases determined by time points extracted from the NTR. The time points include time of trauma, time of EMCC call registration, time of resource dispatch, time of arrival on scene, time of departure, and time of arrival at a hospital (Figure 1).

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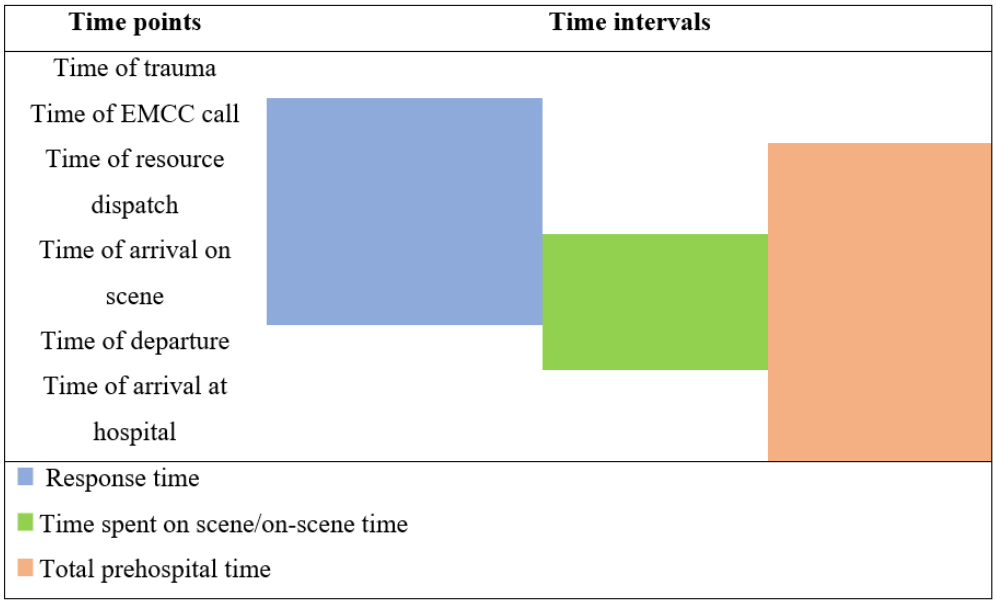
Figure 1. Time points and time intervals illustrated.



Patient Characteristics

Secondary variables describe the study population and include:

- Age, gender, preinjury health status, injury mechanism, ISS, New Injury Severity Score (NISS), discharge health state, discharge destination, and mortality [22]
- Municipal code for further determination of centralization index
- Physiological data (prehospital and emergency room data)
- Prehospital data: prehospital stabilizing interventions, prehospital treatment level, and transport type
- Intrahospital data: emergency department stabilizing interventions

Triage

For our one-year cohort study from a selection of hospitals, the variable triage (triage to hospital and triage to TTA) will also be investigated. The aim is to examine the accuracy of resource utilization, triage, and severity of injuries of trauma patients.

Data Analysis

Registry data for studies 1 and 2 will be analyzed using descriptive statistical methods and relevant statistical methods to compare prehospital time in rural and central areas. The studies will comply with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology Statement) checklist. Categorical variables will be analyzed with Pearson chi-square test, continuous variables with normal score distribution with *t* tests, and skewed distributions with the Mann-Whitney *U* test. We will consider using Fisher exact test for smaller subgroups. For study 3, we intend to use logistic regression analysis for the dependent variable mortality. Independent variables will be centralization index, gender/age, ISS, and likely physiological data. This model will allow us to identify the effect of rurality/centrality (centralization index) on patient mortality, adjusted for covariates. The strength of association will be reported as an odds ratio (OR) with 95% CIs. Low statistical power due to small groups and few events could result in some significant differences with broad 95% CIs. We plan to test correlations between the centralization index with Spearman rank correlation test. The significance level is set at $P<.05$. The analyses will be performed with SPSS software version 27 or higher (IBM Corp).

Ethics Approval

Research will be conducted according to the ethical guidelines of the Helsinki Declaration. The study protocol and delivery of data according to the March 2020 application were approved by the Oslo University Hospital data protection officer (number 129324), who is the data controller for the NTR. After assessment, the study was exempted from formal ethical approval by the regional committees for medical and health research because it is health service research and thus is not required to be presented. The NTR has concession from the Norwegian data protection authority to include patients without their consent because large parts of those included have temporarily limited consent competence upon contact with the health trust. Nevertheless, all patients have a reservation right, which means that patients can withdraw consent to be registered. For study 2, we will apply for approval from the regional committee for medical health research to collect local EMCC data.

Results

According to its annual report for 2019, the NTR registered 7948 patients that same year. Several patients were treated at more than one hospital; therefore, the total number of trauma records is higher at 8788. This is due to the organization of the trauma system in Norway, where patients are often transported to the nearest emergency hospital for initial stabilization before being transferred to a trauma center. According to the same report, approximately 13% (n=1051) of the patients had an ISS>15 and approximately 21% (n=1689) had an NISS>15. Of the patients, a total of 67% were male, and the age group with the highest incidence of trauma was 16-24 years for both genders. The average age was 43 (median 44) years. Motor

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vehicle accidents were the most common cause of trauma (45%), followed by falls (42%) and sports injuries (22%) [23].

Based on the data from 2019 and the annual reports from the years prior, we assume we will extract data on approximately 40,000 patients registered in the NTR for further analysis, and this will be sufficient for us to carry out statistical analyses and draw our conclusions. Power analysis will be carried out for each individual study and outcome measure. For some subgroup analyses and outcome measures, we will consider doing power analysis before further analyses.

Discussion

Summary

We aim to explore to what extent ambulance services (including HEMS) in Norway reach severely injured patients within an acceptable time frame according to national quality indicators. We also want to examine differences between prehospital time, interventions, and triage in urban and rural areas in Norway. This field is unexplored at the national level, and existing evidence for the optimal organization of trauma care is still inconclusive regarding the impact of prehospital time. There is an ongoing debate on the relevance and importance of prehospital time in Norway.

Relevance

Findings from this study will contribute to new knowledge regarding existing quality indicators, and with the increasing centralization of hospitals, this study will contribute to the further development of the Norwegian trauma system. The project adheres closely to the thematic priorities of the call to generate new knowledge about structural, organizational, and economic factors that impede and promote integrated, coherent patient and user pathways to trauma patients and services. Given the similarities between demographical changes and trauma systems in many high-income countries, we expect that our study findings will have an impact on other trauma systems outside of Norway.

Strengths and Limitations

The NTR is a national quality registry that provides information about potentially severely injured patients in Norway. The main objective of the registry is to monitor trauma treatment and contribute to an increased quality of trauma care throughout the country [23]. This makes the registry well designed for research. There are several strengths in these studies: data needed for analysis already exist, and the data collection has been done independently of the study. A large sample size gives good statistical power and will help detect small effect sizes and true differences [24].

According to the NTR's annual report for 2019, all 38 hospitals with a trauma ward in Norway delivered data to the registry, and the coverage is estimated to be >95% [23].

Limitations are inherent to the retrospective design of the quantitative studies, with a risk of bias and the fact that causal factors cannot be explored. As registers may be missing data on important factors, this research design may be prone to confounding errors [24].

The NTR specifically has known deficiencies in prehospital physiologic data due to missing data and, to some extent, coding and import issues. The challenge of collecting prehospital physiological parameters exists for many countries [25]. Severely injured patients in this project will thus be selected based on injury severity (ie, retrospective determination of ISS). These data obviously were not apparent at the scene, leading to suboptimal possibilities for the selection of destination, treatment priorities, and provider level.

Hospital-based registry data are very likely to cause a risk of selection bias. The majority who die following trauma die prehospitally, and the proportion of prehospital deaths is higher in rural than urban areas [26,27]. We can assume that patients are included in data registries as "survivors" to a greater extent in rural areas, as opposed to central areas where truly unstable patients die to a greater extent in hospital.

Dissemination Plan

Findings from the studies will be presented at national and international conferences and published in three peer-reviewed international medical journals.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

ED: emergency department
EMCC: emergency medical communications centers
EMS: emergency medical services
HEMS: helicopter emergency medical services
ISS: Injury Severity Score
NISS: New Injury Severity Score
NTR: Norwegian Trauma Registry
OR: odds ratio
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology Statement
TTA: trauma team activation

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Protocol

The Novel Data Collection and Analytics Tools for Remote Patient Monitoring in Heart Failure (Nov-RPM-HF) Trial: Protocol for a Single-Center Prospective Trial

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Abstract

Background: Heart failure remains a leading cause of mortality and a major driver of health care utilization. Despite numerous medical advances in heart failure, associated hospitalizations continue to increase, owing largely to suboptimal outpatient management. Remote patient monitoring (RPM) aims to further address this current need in heart failure care by providing data to clinical teams to act pre-emptively to address clinical decompensation. However, to date, RPM approaches using noninvasive home-based patient sensors have failed to demonstrate clinical efficacy.

Objective: The Novel Data Collection and Analytics Tools for Remote Patient Monitoring in Heart Failure (Nov-RPM-HF) Trial aims to address current noninvasive RPM limitations. Nov-RPM-HF will evaluate a clinician co-designed RPM platform using emerging data collection and presentation tools for heart failure management. These tools include a ballistocardiograph to monitor nocturnal patient biometrics, clinical alerts for abnormal biometrics, and longitudinal data presentation for clinician review.

Methods: Nov-RPM-HF is a 100-patient single-center prospective trial, evaluating patients over 6 months. The outcomes will include patient adherence to data collection, patient/clinician-perceived utility of the RPM platform, medication changes including the titration of guideline-directed medical therapy to target doses, heart failure symptoms/performance status, and unplanned heart failure hospitalizations or emergency department visits.

Results: This prospective trial began enrollment in March 2020 and anticipates enrollment completion by June 2022, with trial completion by December 2022.

Conclusions: This trial protocol aims to provide a systematic framework for the evaluation of heart failure RPM strategies, which are currently heavily used but seldom robustly studied. The trial results will help to inform the role of noninvasive RPM as a viable clinical management strategy in heart failure care.

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KEYWORDS

heart failure; remote patient monitoring; clinical innovation; digital health; mHealth; mobile health; cardiology

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Introduction

Heart failure (HF) remains a leading driver of morbidity and mortality in the United States, affecting 6.5 million Americans [1]. Despite numerous medical innovations in HF over the past decade, per capita rates of HF hospitalizations have actually increased from 2010 to 2017 [2]. This population is expected to increase by 50% by 2030, placing an increasing burden on the US health care system and highlighting the need for innovations in HF care [3]. HF care also carries significant economic implications, with over US $30 billion spent in direct HF care in 2020, primarily driven by HF hospitalizations, and estimated to double by 2030 [4-6].

Effective HF care requires vigilance for indications of clinical HF decompensation. Failure to detect and manage these indicators can result in unplanned emergency department (ED) visits and hospitalizations. Although patients and care teams attempt to detect signs of impending decompensation with conventional techniques such as daily weight measurements, these approaches have not demonstrated consistent clinical efficacy [7].

Optimal HF care also relies on maximizing guideline-directed medical therapies (GDMTs). Several pharmacotherapies such as renin-angiotensin-aldosterone system inhibitors and beta-blockers have demonstrated mortality benefit in patients with HF with reduced ejection fraction (HFrEF) [8,9]. However, consistent provision of these therapies, at maximally tolerated dosing, does not occur [10]. Logistical challenges of conventional outpatient care contribute to this implementation gap. These include reliance on ambulatory visits for medication titration, which often occur months apart, and insufficient vital sign information to allow for medication up-titration between visits.

Remote patient monitoring (RPM) aims to address these gaps in current HF care. RPM is a strategy that allows care teams to monitor and manage patients outside of traditional in-person health care encounters. The strategy could enhance current efforts for more rapid medication titration and avoidance of clinical decompensation and unplanned acute care visits. RPM has demonstrated a reduction in HF hospitalizations, but only by using an invasive hemodynamic patient sensor (CardioMEMS) [11]. RPM strategies using noninvasive patient sensors such as blood pressure (BP) cuffs, scales, and wearable biosensors have reduced cost, lower risk, and greater applicability to the HF population. However, the clinical evidence supporting noninvasive RPM is mixed, with the majority of clinical trials failing to demonstrate a similar clinical benefit [12]. This lack of clinical efficacy in trials is likely attributable to multiple factors, including poor patient adherence [13], lack of clinically actionable patient data and alerts [14], and lack of clinician engagement [15].

The field of noninvasive RPM continues to evolve, with recent advances in data collection and monitoring now demonstrating improved predictive power for clinical decompensation [16]. However, there is a paucity of studies evaluating these emerging tools as part of RPM interventions.

The Novel Diagnostic Tools for Remote Patient Monitoring in Heart Failure (Nov-RPM-HF) Trial aims to address these limitations through the design and evaluation of a novel RPM platform for HF management that incorporates these emerging data collection tools. The trial will evaluate the perceived utility of the RPM platform, its impact on timely GDMT optimization and medication changes, and its impact on unplanned ED visits and hospitalizations.

Methods

Overview

The Nov-RPM-HF trial is a single-center prospective study of an RPM platform and its adoption, clinical utility, and ability to optimize GDMTs and reduce unplanned acute care events among patients with HFrEF. Specifically, the trial will evaluate patient adherence with passive and active data collection, patient-perceived usability and utility of the RPM platform to monitor their health status, clinician-perceived usability and utility of the RPM platform for HF management, clinical utility of the RPM clinical alerts, impact of RPM on medication changes and titration of HF GDMT, and impact of HF RPM on clinical outcomes (ED visits, hospitalizations).

Full inclusion and exclusion criteria are summarized in Textbox 1. Inclusion criteria include history of HFrEF with a HF hospitalization or ED visit in the last 12 months. This criteria selects for a HFrEF population with a baseline event rate that mirrors the trial population in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial. Such an event rate should allow for increased power to detect clinical outcomes among our study population. Prior noninvasive RPM trials have included a relatively stable population of patients with HF with low clinical event, and this was thought to have contributed to the inability to demonstrate clinical efficacy [13]. End-stage HF with a life expectancy <1 year or requiring advanced therapies including left ventricular assist devices or cardiac transplantation were excluded. Patients with barriers precluding them from obtaining monitored data (eg, wearable defibrillator use preventing ballistocardiograph sensing) were also excluded.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age≥18 years
- HF (heart failure) hospitalization or emergency department visit in last 12 months
- HF with reduced ejection fraction: most recent left ventricular ejection fraction (LVEF) of <50% and at least 1 recorded LVEF of <40%
- New York Heart Association Functional Class II-IV
- Sleeps in same bed ≥4 days per week
- Ambulatory
- Willingness to complete the required surveys, measurements, and study activities

Exclusion criteria

- Advanced HF therapies: inotrope therapy, left ventricular assist device or cardiac transplantation
- Wearable defibrillator or other worn device that may affect ballistocardiogram measurements
- End-stage renal disease on chronic dialysis
- Malignancy undergoing active therapy
- Weight >385 lbs at time of enrollment
- Living in a skilled nursing facility or other chronic care facility
- Planned major surgeries or procedures requiring hospitalization in next 6 months
- Hospice care or life expectancy <1 year

Patients were prospectively screened and recruited from the Advanced Heart Failure clinic at the Washington University School of Medicine's Division of Cardiology. This clinic specifically treats patients with HF, with a focus on implementation of GDMTs and evaluation for advanced therapies including mechanical circulatory assist devices and cardiac transplantation when indicated. The trial was approved by the institutional review board at Washington University for either written or phone-based informed consent. The trial began recruitment in March 2020.

Ethical Considerations

The trial was approved by the ethics review board of the Washington University Office of Ethics and Integrity, with all information for patient informed consent reviewed. The trial was deemed to be in equipoise with current standard of care for heart failure management.

RPM Platform

The RPM platform for the trial was provided by a third-party vendor, Myia Health (San Francisco, CA). The platform consists of patient biometric sensors, a digital "Home Hub" tablet to aggregate data from the sensors and transmit to the vendor for analysis, and a web-based clinical interface for clinicians to review data. The clinical interface was co-designed with the advanced HF clinicians to incorporate clinician priorities in its design. To ensure that the RPM platform was optimally designed for clinician and patient needs, Myia conducted clinician and patient interviews (n=51), and incorporated their input into the design of the RPM platform (Figure 1). These interviews identified the following priorities for the prospective RPM platform: home sensors that collected data with minimal or no actions from the patient, optimizing ease-of -use clinical monitoring platform for clinicians with integration into current workflows, and data curation through smart triaging to minimize information overload for the clinical teams.

The RPM platform (Figure 1):

- Patient biometric sensors: Sensors include a weight scale, BP cuff, and a ballistocardiograph. The ballistocardiograph is a pressure-based sensor that is placed under a patient's bed mattress. It measures ballistic forces related to heart and lung movement to derive heart rate (HR), respiratory rate (RR), and other associated physiologic parameters. Importantly, the ballistocardiograph is always "on" and only requires the patient to lie in bed to collect data, thus minimizing the data collection burden for patients.
- Home Hub tablet: An Android (Google) LTE-enabled tablet loaded with the Myia application serves as a data aggregation and transmission point for collected vital sign sensor data. It also includes a user interface to solicit, collect, and transmit patient-reported outcomes.
- Clinical interface: The clinician interface displays sensor data for all patients currently enrolled in the trial. The interface includes a data visualization workspace that juxtaposes longitudinal health data (vital signs, symptoms) with event data (ED visits, hospitalizations) to aid in clinical management. Patient data is prioritized for clinical review using alerts. Alerts are customized based on patient-specific thresholds (eg, vital signs outside of predefined range), with deviations outside normal range triggering an alert. Additionally, among patients on submaximal GDMTs, medication-specific alerts are included to allow for rapid HF medication up-titration.

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Figure 1. Remote patient monitoring platform used in the Novel Data Collection and Analytics Tools for Remote Patient Monitoring in Heart Failure Trial. BP: blood pressure; ECG: electrocardiogram.

Study Protocol

Following enrollment, study participants have the Home Hub and sensors shipped to their homes. Once the kit is delivered, the technical support team will reach out to assist with home monitoring and sensor setup.

As part of the study, patients will take measurements daily from all study sensors. The first 7 days for each patient will be a run-in period where patient data is collected. If sufficient data is collected and transmitted, study participants will transition to the active management phase. Sufficient data is defined as transmission from both BP cuff/weight scale and ballistocardiograph sensors in at least 4 of the 7 days. If minimum requirements are not met, patients are continued in the run-in period for an additional week (up to 3 weeks maximum). Technical support will contact patients to determine if lack of transmission represents a technical issue versus nonadherence. If patients were unable to meet minimum data requirements after 3 weeks, then they were disenrolled from the study.

Following run-in period completion, study participants will enter the 6-month active management phase of the study. A designated research nurse is responsible for daily monitoring of the RPM clinical interface. This includes monitoring the RPM clinical interface daily for clinical alerts, contacting patients to assess clinical status in response to alerts, and escalating to the patient's HF cardiologist if clinical status warrants management changes. This research nurse will also be responsible for contacting study participants for issues with data transmission or poor adherence to patient data collection.

On a monthly basis, enrolled patients will have their clinical data reviewed by a multidisciplinary team including a triaging nurse and an HF cardiologist. The purpose of these reviews is to assess participant's clinical status and adherence to data transmissions, and to identify opportunities for optimized medical management, including maximizing GDMT. RPM platform monitoring is outlined in Figure 2.

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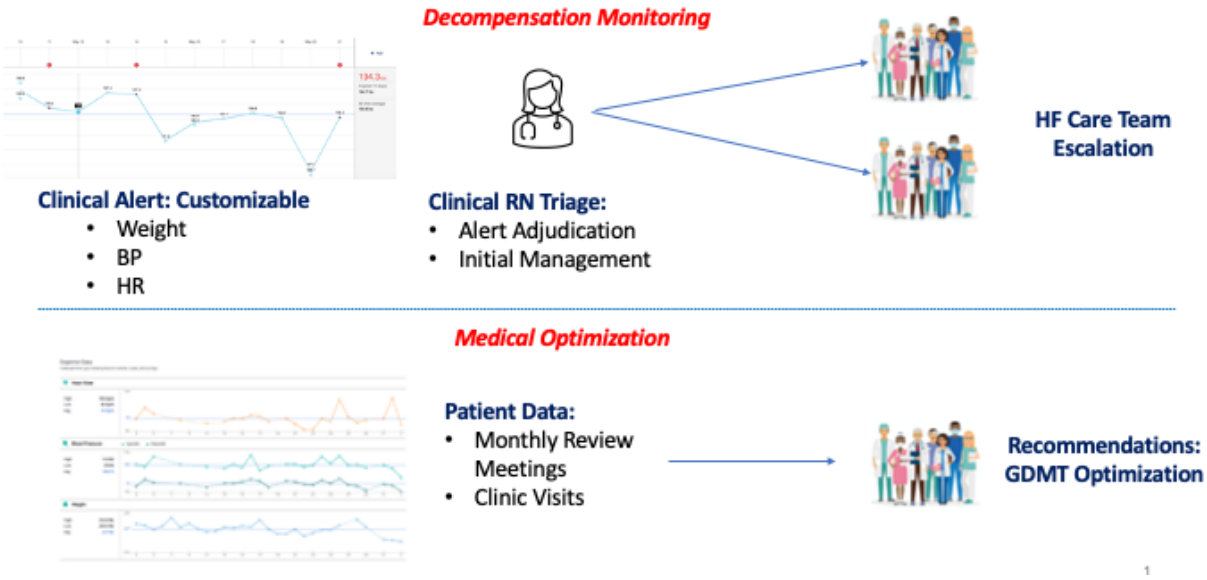
Figure 2. Remote patient monitoring platform monitoring strategies. BP: blood pressure; GDMT: guideline-directed medical therapy; HF: heart failure; HR: heart rate.



Clinical Alerts and Thresholds

Several clinical monitoring alerts will be used prospectively during the management phase of the study. Each alert has default thresholds that are customizable to individual study participants. Absolute threshold alerts will be turned on by default in all patients, while GDMT alerts can be opted-in by the clinical team for patients deemed to be on submaximal GDMT. Default values are shown in Textbox 2. All alerts are required to be addressed within 24 hours by the monitoring nurse and escalated to the clinical team if indicated. Actions taken by the clinical team in response to the alerts were documented.

Textbox 2. Remote patient monitoring clinical interface parameters with default values.

Absolute thresholds alerts

High and low thresholds for weight, blood pressure (BP), and heart rate (HR). Thresholds include both default absolute values and patient-specific deviation from baseline values.

- Weight
  - >3 lbs over 1 day
  - >5 lbs over 3 days
- BP
  - Systolic blood pressure (SBP)>200 mmHg
  - SBP>180 mmHg each day for 3 consecutive days
  - SBP<80 mmHg
- HR
  - HR<35 bpm average in 1 night
  - HR>150 bpm

Guideline-directed medical therapy (GDMT) alerts

These alerts are generated for patients on submaximal GDMT. They are designed to permit rapid up-titration of GDMT, customized based on drug class.

- Beta-blocker
  - HR>80 bpm (nightly average) and SBP>100 mmHg for 3 consecutive days
- Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, angiotensin receptor neprolysin inhibtor, and mineralcorticoid receptor antagonist
  - SBP>110 for 3 consecutive days

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Outcomes

Trial outcomes were designed to both directly evaluate the perceived utility of the RPM platform and to assess its impact on clinical outcomes.

Patient Adherence to Data Collection and Transmission

Patient data collection adherence will be measured for all home BP cuff, scale, and ballistocardiograph sensors as percentage of days with data transmission from each device over the 6-month trial duration. "Minimally-useful data profile" is defined as the percentage of weeks with at least 4 days of data transmission from both an *active* (BP cuff or weight scale) and *passive* (ballistocardiograph) sensor.

Patient-Perceived Usability and Utility of RPM Platform

Patients' assessment of the RPM platform utility and usability will be assessed through a series of surveys (survey timeline in Multimedia Appendix 1). Surveys will be conducted at 2, 4, and 6 months. Surveys will have scaled numerical responses 1 to 7, with 17 total questions. Questions will assess RPM platform components (scale, BP cuff, ballistocardiograph) usability, platform setup, and the platform's perceived utility in augmenting clinical care. The sum of the numeric responses for each question will combine into an "overall utility score." This score will be assessed for change throughout the study duration for each participant. Surveys will be reviewed at the time of submission by the research nursing group. Patients will be contacted regarding any significant RPM platform concerns. Scores will also be analyzed to assess for RPM platform strengths/weaknesses and to evaluate for change in perceived utility over the trial duration.

Clinician-Perceived Usability and Utility of RPM Platform

Along with patients, clinicians will also be assessing the RPM platform's utility and usability through a series of surveys (survey timeline in Multimedia Appendix 1). Surveys will be conducted at 3 and 6 months, with scaled numerical 1 to 7 ratings of 14 components of the RPM platform, with a focus on the clinical interface.

Clinical Utility of RPM-Generated Clinical Alerts

The number of absolute threshold clinical alerts (Textbox 2) generated by the RPM platform will be reported, along with its accompanying clinical action. Clinical actions include medication changes (adding/holding medications), scheduling a follow-up appointment, advising immediate medical care (ED visit or hospitalization), or no action. The clinical utility of each absolute threshold alert will be measured as the percentage of clinical alerts prompting clinical action and categorized by physiologic measure (ie, weight, BP, and HR).

Medication Changes

Clinician-directed changes will be tracked during trial duration for the following HF medication classes: beta-blockers, angio-converting enzyme (ACE)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitors (ARNIs), magnetic resonance angiographies (MRAs), hydralazine, nitrates, and loop diuretics. The distance to target dose will also be assessed for GDMT medications, beta-blocker, ACE/ARB/ARNI, and MRA drug classes. Based on previously established methodology [10], baseline doses of each of these drug classes will be the classified percentage of target dose: 0% to 25%, 25% to 50%, 50% to 75%, and 75% to 100%. This target dose category will be compared for each participant between 0 and 6 months to assess for changes in GDMT dosing. Change in proximity to target dose over trial duration will be compared to that of matched controls (see "Statistical Considerations" for matching methodology). For all drug classes, the absolute number of medication changes will be recorded and compared to that of the matched controls.

HF Symptoms and Performance Status

Study participants' symptoms and performance status will be evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) at 0, 3, and 6 months (Multimedia Appendix 1), with absolute results and change over study duration reported.

HF Clinical Events

The study's primary clinical end point is HF hospitalizations. Secondary clinical events include other unplanned hospitalizations and ED visits. Clinical events will be obtained through monthly electronic health record review by the research team and with monthly patient surveys. All hospitalizations will be adjudicated by the clinical team as either HF or other unplanned hospitalizations. Clinical end points will be compared to those of matched controls.

Statistical Analysis

Patient medication changes and clinical events will be compared to 100 matched historical controls. Controls will be patients with HFrEF matched on an HF hospitalization in the past year, age within 5 years, sex, race, and comorbidities (coronary artery disease, diabetes mellitus, hypertension, renal disease).

Statistical analysis for clinical end points will be in comparison with matched controls. For survey data, including RPM platform utility and patient symptom assessments, these will be evaluated for change over the trial's 6-month duration. Continuous variables will be assessed via sample *t* tests, and categorical variables will be assessed via chi-square tests.

Power Calculation

Medication Changes

This trial is powered at 99% to assess for 50% more medication changes in the study arm compared to historical controls. We will use a type I error of 0.05, assuming Poisson distribution [17]. This medication change rate was selected based on prior work in the CHAMPION trial, in which monitored patients had over double the number of medication changes (n=2468 for 270 patients vs n=1061 for 280 patients; $P<.001$) [18].

HF Symptoms and Performance Status

This trial is powered at 84% to assess for a 6-point increase (SD 20) in KCCQ scores for trial participants over the trial duration. We will use a type I error of 0.05. This improvement in KCCQ scores was based on the Minnesota Living with Heart Failure symptom assessments improvements observed in the CHAMPION trial [19].

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HF Hospitalizations

Regarding HF hospitalizations, Nov-HF-RPM is underpowered for this end point. Power calculation for clinical HF events was conducted using the baseline event rates observed in the CHAMPION trial given similar inclusion criteria [19]. Effect size was estimated to be roughly 50% that observed with CardioMEMS. Using type 1 error of 0.05, the study would require 1054 recruited patients (with 1054 matched controls) to obtain 80% power. We will nonetheless plan to collect this clinical end point to better understand if there is a positive trend with RPM. Future studies with larger patient populations will be required to obtain adequate statistical power for hospitalizations.

Results

This prospective trial began enrollment in March 2020 and anticipates enrollment completion by June 2022, with trial completion by December 2022.

Discussion

Optimal HF care requires the ability to effectively monitor and treat impending clinical decompensation so as to prevent ED visits and hospitalizations. RPM aims to address the current gaps in outpatient clinical care. To date, the only RPM strategy using an invasive hemodynamic sensor (CardioMEMS) has demonstrated the ability to reduce HF hospitalizations [11]. RPM strategies using noninvasive biometric sensors are a potential lower risk and lower cost approach to RPM. However, prior trials evaluating noninvasive approaches to RPM have not demonstrated clinical efficacy [12,20].

Several limitations of noninvasive RPM strategies are thought to contribute to the lack of demonstrated efficacy in these prior studies. These include poor patient adherence to monitoring, a lack of clinically actionable patient data and alerts, and a lack of clinical buy-in. The design of the Nov-RPM-HF study seeks to overcome these limitations.

Poor patient data collection adherence was observed in the majority of noninvasive RPM clinical trials and is thought to have contributed to neutral outcomes [12]. Both patient-perceived utility and ease-of-use of RPM platforms are believed to be contributing factors to nonadherence. Accordingly, Nov-HF-RPM will assess if improved adherence can be observed through the use of *passive* sensors for patient data collection that do not require direct patient action. The trial will also directly compare data collection adherence between *passive* (ballistocardiograph) and *active* sensors (BP cuff, scale). The ballistocardiograph adds a novel component to the home sensor collection, with the potential to augment adherence and provide continuous nightly data for HR and RR. To date, several studies using ballistocardiograph data-derived algorithms have demonstrated the ability to effectively classify compensated versus decompensated disease states in HF [21,22]. However, the role of the ballistocardiograph in an HF management strategy has not been studied.

A lack of clinically actionable RPM alerts has been commonly observed in prior noninvasive RPM studies. A systematic review of noninvasive RPM trial clinical alerts revealed patients were contacted only 39% (range 29%-52%) for follow-up and management changes [14]. Furthermore, RPM alerts with high false-positive rates have previously led to unnecessary office visits and hospitalizations [23]. Nov-RPM-HF will assess clinical utility of all absolute threshold alerts based on if there is a corresponding clinical action. Alert utility will be broken down by alert type (weight, BP, HR) to assess comparative utility of each physiologic measure.

Although seldom measured in RPM clinical trials, adoption and buy-in from the clinical team is essential for maximal and effective RPM use. Factors affecting clinical adoption include perceived utility of RPM-provided patient data and integration into existing clinical workflows [15]. Nov-RPM-HF evaluates a clinician-designed RPM platform, and clinical utility will be assessed through structured surveys, broken down by RPM platform components, and evaluation of clinical actions motivated by RPM alerts.

Nov-RPM-HF will provide an important contribution to the field of RPM for patients with HFrEF. Its design attempts to overcome prior limitations of prior RPM strategies and determine its impact on patient engagement and satisfaction, clinical satisfaction, and HF medical optimization. Insights from the study will inform the future role of noninvasive RPM as a viable HF clinical management strategy.

Conflicts of Interest

TM discloses current grant funding from the National Institutes of Health National Center for Advancing Translational Sciences (1U24TR002306-01: A National Center for Digital Health Informatics Innovation); current consulting for Creative Educational Concepts, Inc and Atheneum Partners; and honoraria or expense reimbursement in the past 3 years from the University of Utah (May 2017), New York Presbyterian (Sept 2017), Westchester Medical Center (Oct 2017), Sentara Heart Hospital (Dec 2018), the Henry Ford health system (March 2019), and the University of California San Diego (Jan 2020). He is currently employed as a cardiologist and the executive director of the Healthcare Innovation Lab at BJC HealthCare/Washington University School of Medicine. In this capacity, he is advising Myia Labs, for which his employer is receiving equity compensation in the company. He is receiving no individual compensation from the company. He is also a compensated director for a New Mexico–based foundation, the JF Maddox Foundation.

Multimedia Appendix 1
Study survey timeline for patients and clinicians.

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Abbreviations

ACE: angio-converting enzyme
ARB: angiotensin receptor blocker
ARNI: angiotensin receptor-neprilysin inhibitor
BP: blood pressure
CHAMPION: CadioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes In NYHA Class III Heart Failure Patients
ED: emergency department
GDMT: guideline-directed medical therapy
HF: heart failure
HFrEF: heart failure with reduced ejection fraction
HR: heart rate
KCCQ-12: Kansas City Cardiomyopathy Questionnaire
MRA: magnetic resonance angiography
Nov-RPM-HF: Novel Data Collection and Analytics Tools for Remote Patient Monitoring in Heart Failure
RPM: remote patient monitoring
RR: respiratory rate

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Protocol

Development and Validation of Population Clusters for Integrating Health and Social Care: Protocol for a Mixed Methods Study in Multiple Long-Term Conditions (Cluster-Artificial Intelligence for Multiple Long-Term Conditions)

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Abstract

Background: Multiple long-term health conditions (multimorbidity) (MLTC-M) are increasingly prevalent and associated with high rates of morbidity, mortality, and health care expenditure. Strategies to address this have primarily focused on the biological aspects of disease, but MLTC-M also result from and are associated with additional psychosocial, economic, and environmental barriers. A shift toward more personalized, holistic, and integrated care could be effective. This could be made more efficient by identifying groups of populations based on their health and social needs. In turn, these will contribute to evidence-based solutions supporting delivery of interventions tailored to address the needs pertinent to each cluster. Evidence is needed on how to generate clusters based on health and social needs and quantify the impact of clusters on long-term health and costs.

Objective: We intend to develop and validate population clusters that consider determinants of health and social care needs for people with MLTC-M using data-driven machine learning (ML) methods compared to expert-driven approaches within primary care national databases, followed by evaluation of cluster trajectories and their association with health outcomes and costs.

Methods: The mixed methods program of work with parallel work streams include the following: (1) qualitative semistructured interview studies exploring patient, caregiver, and professional views on clinical and socioeconomic factors influencing experiences of living with or seeking care in MLTC-M; (2) modified Delphi with relevant stakeholders to generate variables on health and social (wider) determinants and to examine the feasibility of including these variables within existing primary care databases; and (3) cohort study with expert-driven segmentation, alongside data-driven algorithms. Outputs will be compared, clusters characterized, and trajectories over time examined to quantify associations with mortality, additional long-term conditions, worsening frailty, disease severity, and 10-year health and social care costs.

Results: The study will commence in October 2021 and is expected to be completed by October 2023.

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Conclusions: By studying MLTC-M clusters, we will assess how more personalized care can be developed, how accurate costs can be provided, and how to better understand the personal and medical profiles and environment of individuals within each cluster. Integrated care that considers "whole persons" and their environment is essential in addressing the complex, diverse, and individual needs of people living with MLTC-M.

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KEYWORDS

artificial intelligence; social care; multimorbidity; big data; protocol; mixed method; long-term health

Introduction

Background

Multiple long-term health conditions (multimorbidity) (MLTC-M) have been defined in the 2018 Academy of Medical Sciences policy report [1] as "The coexistence of two or more chronic conditions, each one of which is either a physical noncommunicable disease of long duration, such as a cardiovascular disease or cancer; a mental health condition of long duration, such as a mood disorder or dementia; an infectious disease of long duration, such as HIV or hepatitis C." Globally, 1 in 4 people have MLTC-M, although estimates vary [2,3]. Prevalence increases with age from 54% for those over 65 years to 83% for those over 85 years [3]. MLTC-M are associated with decreased quality of life for each additional LTC, worse mental health, reduced functional status, and more severe morbidity [4]. Mortality risk increases, with meta-analyses reporting hazard ratios of 1.73 (95%CI 1.41-2.13) and 2.72 (95%CI 1.81-4.08) with 2 or more and 3 or more LTC, respectively, compared to people without MLTC-M [5]. The economic burden consumes 70% of the National Health Service budget, 65% of hospital bed days, and 50% of general practice (GP) appointments [3]. Societal and economic impacts include a lower likelihood of full-time employment and a greater likelihood of receiving assistance for unemployment and housing needs [6].

These impacts emphasize the need for a deeper understanding of MLTC-M in relation to physical health, mental health, and social well-being. Integrated care may have the potential to address MLTC-M more effectively, although current evidence offers a mixed picture of the efficacy of integration in addressing the complex care needs of this cohort of patients. Previous MLTC-M research in the United Kingdom shows that integrated services in MLTC-M contributes to higher patient satisfaction [7], increased perceived quality of care, and increased or improved patient access; it may potentially contribute to lower costs, although evidence related to reductions in the cost of provision is inconsistent [8]. An umbrella review reported that integrated care had limited costs of care by reducing emergency admissions and the length of hospital stay along with increasing care in the patients' own homes; however, some of these findings are based on limited evidence [9]. Integrating health and social needs also has the potential to address growing health inequalities, as MLTC-M are more prevalent in low socioeconomic groups and require earlier social care input [10]. This might include, for example, poverty alleviation through support with benefits, citizen's advice, housing, and literacy, alongside input to facilitate access to disability allowances.

Data sets comprising millions of patient records including measures of health and socioeconomic determinants alongside subsequent health and social needs over the life course of a patient with MLTC-M are increasingly available. This provides opportunities to advance the understanding of MLTC-M toward the delivery of truly person-centered and holistic care. At present, efforts to improve care focus on approaches that primarily address biological needs, rather than considering the impact of wider health and social determinants on individuals living with several conditions at the same time [11]. This is because MLTC-M can be determined by and lead to socioeconomic and psychosocial barriers to health [12]. For example, poor cognitive function impacts treatment adherence, finances, or housing, and physical limitations impair access to health, healthy food, or green spaces for physical activity. A shift toward holistic and integrated care, alongside a preventative approach to health and social needs [13] could be effective in reorienting health and social care inputs to manage the complications, consequences, and costs of MLTC-M.

Operationalizing holistic and integrated care is challenging due to the level of personalization required across the health and social care continuum. At an individual level, it is costly and difficult to implement. Clustering heterogeneous populations into relatively homogenous subgroups with similar health and socioeconomic determinants and needs and then tailoring appropriate interventions to each cluster could offer a pragmatic solution. Studies have demonstrated the potential of clustering for integrating health and social care using expert-driven segmentation [14]. These methods face challenges in combining volumes of disparate data such as that found across social and community services. Evidence on population clustering uses expert-driven approaches based on a priori criteria [14]. This is limited by uncertainty regarding the completeness of the included variables and the number of natural clusters. Our recent review [15] and work by others show that a priori methods are more commonly used to group populations by single diseases as well as sociodemographic and clinical characteristics, and that these are within limited sectors rather than across the health and social care continuum [16]. Although studies report the potential of expert clustering approaches for integration of care [14], these have faced challenges in processing volumes of unlinked data across services with poor distinction between clusters and trajectories over time [17]. Data-driven approaches could process large amounts of disparate information to generate homogenous clusters [16,18].

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Data-driven approaches include unsupervised artificial intelligence (AI) algorithms, including metric learning or variational autoencoder frameworks. The feature selection and engineering process will initially be informed by expert- and patient-proposed variables, but deep ML can extend these using self-learning. Clusters generated by deep artificial neural networks (ANNs) are more likely to be homogenous and predict trajectories. For example, a study of 2449 participants in Taiwan combined medical and socioeconomic data to generate data-driven clusters that accurately predicted service usage and expenditure [19]. In the Netherlands, biopsychosocial needs of the elderly were combined from 25 data sets across health, welfare, and elderly associations to generate data-driven clusters that informed resource allocation and finances [20]. Another study from Singapore (N=146,999) collated data from health and social care services using ML to produce clusters that were sensitive to changes in health status and progression toward disability [6]. Validity was supported by the ability of clusters to discriminate between longitudinal health care usage and mortality. Global evidence suggests that data-driven clustering using AI has the potential for understanding MLTC-M and establishing care systems based on the principles of person-centered care. Such systems are expected to provide opportunities for better and more timely interventions, a reduction in disease burden, and better use of scarce resources, and these now need to be examined in the United Kingdom.

Advances in data-driven processing paradigms could overcome previous limitations in methodology using unsupervised or semisupervised deep embedded clustering [16,18,21]. ML can process rich longitudinal records to discover natural groupings of data points with or without knowledge from human experts in the form of ground truth labels or feature constraints. Traditional algorithmic approaches include k-means, Gaussian mixture models, hierarchical and Bayesian network–based clustering, whereas recent approaches use deep ANNs [22]. Such algorithms can provide cohesive groupings based on self-learned features and are more likely to predict trajectories toward disease progression, frailty, and mortality [23]. Detailed characterization and comparison of clusters by “whole person” parameters can be analyzed that are unbiased by human understanding and consider sociodemographic and clinical profiles, service usage patterns, critical time points for change in needs, and deviation in comorbid disease severity. Using a “whole person” approach could inform the development of an intervention that would support health and social care providers to address the needs pertinent to each MLTC-M cluster and potentially provides an opportunity for efficient implementation of person-centered care.

Objectives

We aim to develop and validate population clusters that consider health and social care determinants and subsequent health and care needs for people with MLTC-M using data-driven AI methods compared to expert-driven approaches, followed by evaluation of cluster trajectories and their associations with health outcomes and costs.

Methods

We will carry out a longitudinal mixed methods study with 3 parallel work streams including (1) qualitative interview study, (2) modified Delphi, and (3) cohort study. They are described below.

Qualitative Interview Study

Recruitment and Sampling

Email and postal invitations will be sent to participants who have expressed interest through advertisements viewed on social media, local community centers, the university website, charity newsletters, caregiver support networks, and through word of mouth. Given the complex structure of health and social care, an iterative and a proactive recruitment approach will be necessary. To include hard-to-reach and underrepresented groups that reflect diversity in social needs, we will recruit at events, such as those held in local authority facilities and community or faith centers, as well as seek additional expert input through established Black and minority ethnic networks. We will aim for a representative sample of <30 interviews, as our pilot interview study [24] showed that this number is achievable within the study timelines and data saturation was achieved with a sufficiently diverse sample of stakeholders across a range of geographies. Purposive sampling will be employed to capture a wide range of participant perspectives from across a diverse range of settings, as well as snowball sampling from the initial round of 10 interviews to identify further participants.

Data Collection

Semistructured interviews will explore views on health and social needs over the course of living with or supporting MLTC-M and views on possible intervention components identified from our preliminary work. Telephone or internet-based video interviews will be conducted by trained researchers. An interview schedule will be designed covering broad open questions to enable similar topics to be addressed across the sample. The design of the interview schedule will be informed by our study aims, our previously published scoping review, and the expertise of team members; it will then be tested prior to use. Furthermore, the development of the interview schedule will be iterative; insights from earlier interviews may inform additions or amendments to the interview schedule in the later interviews. A flexible approach will be used to ensure that related subjects of importance can be raised. Interviews will be digitally recorded and transcribed verbatim and the content anonymized.

Analysis

We will use inductive reflexive thematic analysis [25,26]. Throughout the analytical process, a form of constant comparative analysis will be used to identify key differences or similarities in the data, between professions, and sectors or geographies. Discussion of the evolving analysis within the research team will enable us to explore and incorporate alternative perspectives that may challenge and enrich initial interpretations of the data. Additionally, we will use deviant case analysis to further broaden (or confirm) the patterns identified in the data, adding rigor to our analytical conclusions.

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A summary of our findings will then be sent to a sample of participants who had agreed to receive them to ensure that we have appropriately captured relevant points of view. QSR NVivo software (version 12) will be used to manage the data and the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist will guide reporting [27].

Modified Delphi

Theoretical Framework

Integrated care with co-ordination, continuous health, and social input is set out by the SELFIE (Sustainable intEgrated care models for multi-morbidity: delivery, FInancing and performancE) framework [28]. This conceptual model considers patients with MLTC-M, emphasizing holistic understanding of individuals in their own environment at its core. The micro-, meso- and macroenvironments branch from this central point. By starting at the core and moving around the framework, researchers, policy makers, and practitioners are guided through considerations of individuals, their health, social context, and the wider environment.

Recruitment and Sampling

A "virtual Delphi panel" will be established. Participants will be invited to join, including experts from health and social care, service managers, researchers, caregivers, patients, and database managers. We will convene a panel of >20 members. A purposive sampling approach will be used to recruit the panel.

Method and Analysis

A modified Delphi technique [29] conducted over 3 rounds will be used to collect expert views on clinical and socioeconomic determinants, and subsequent needs over the life course of MLTC-M. Throughout, the process will use the SELFIE framework that conceptualizes integration of care at the micro, meso, and macro scales according to the 6 key (World Health Organization) components (service delivery, leadership and governance, workforce, financing, technologies and medical products, and information and research) [28]. This conceptual framework is presented diagrammatically in a layered pie chart model, with the individuals with multimorbidity and their environment placed at its core. Radiating out from the core, concepts pertaining to integrated care for multimorbidity are grouped at the micro, meso, and macro levels. They are further split according to the 6 key components of health systems used to describe, understand, and compare different global health systems.

Discussion among panelists related to the potential clustering of specific variables will be guided and structured by the SELFIE conceptual framework. In particular, the extent to which variables are applicable within existing databases or obtainable through new health and social care data linkages will be considered in detail by the panel. Initially, participants will be supplied with a ranked list of variables generated from our preliminary review, followed by discussion and the qualitative study described above. Then, similar ideas emerging from these discussions will be grouped. Potentially relevant variables will be collated by the research team, fed back, and subsequently rated or ranked by panelists at the next round (phase II), with a "free text" option available for clarification. The most highly rated variables will be taken forward (phase III).

The panelists in round 1 will make their initial judgments individually without any interaction with other panelists, and these "ratings" will be fed into subsequent rounds. Web-based interactions with other panelists will occur during the deliberation rounds of the Delphi panel, a process spanning 1 to 2 days. At each stage, researchers experienced in the Delphi method will moderate the panel. The research team will take notes of these discussions to track the decision-making process and determine how and why specific decisions are reached. No attempt will be made by researchers to hasten discussion or compel the panel to reach a consensus.

Cohort Study

Data Sources

We will use the Clinical Practice Research Database (CPRD) GOLD and Aurum [30] to identify clusters. To test the validity of our approach and clusters identified, we will run our code on additional databases (eg, Secure Anonymised Information Linkage [SAIL]) and local data sets (eg, English Longitudinal Study of Ageing [ELSA]).

CPRD GOLD and Aurum include 50 million registered GP patients with high levels of heterogeneity in ethnicity, deprivation, and morbidities. Primary care–linked records include Hospital Episode Statistics Admitted Patient Care (HES APC) data on hospital admissions, discharges, accident and emergency (A and E), and outpatients in England, socioeconomic status (Index of Multiple Deprivation [IMD] or Townsend score), and death data from the Office for National Statistics.

SAIL is a nationwide repository of routinely collected electronic data on health and social care in Wales, United Kingdom. It includes over 2 billion anonymized records linked with hospital admissions and primary care data [17].

The ELSA collects data from people aged over 50 years covering physical and mental health, well-being, finances, and attitudes around aging and how these change over time. The Health Survey for England is an annual survey that looks at changes in the health and lifestyle of people. Local area data sets allow local authority data linkage with health information using health determinants from the census and social determinants, such as wealth and the IMD (a score calculated for each participant's neighborhood based on social indices such as income, education, and employment).

The same variable definitions will be applied to all data sets, wherever possible, to ensure consistency and comparability of findings from the respective data sets.

Population

Participants must be aged 18 years and over when entering the study. They must be diagnosed with MLT-C (defined by Guthrie et al, forthcoming) that included the following 59 conditions: stroke, coronary heart disease, heart failure, peripheral arterial disease, heart valve disorder, arrythmia, venous thromboembolic disease, aneurysm, hypertension, diabetes, Addison disease,

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cystic fibrosis, thyroid disease, chronic obstructive pulmonary disease, asthma, bronchiectasis, Parkinson disease, epilepsy, multiple sclerosis, paralysis, transient ischemic attack, peripheral neuropathy, chronic primary pain, solid organ cancer, hematological cancer, metastatic cancer, melanoma, benign cerebral tumors that can cause disability, dementia, schizophrenia, depression, anxiety, bipolar disorder, drug or alcohol misuse, eating disorder, autism, posttraumatic stress disorder, connective tissue disease, osteoarthritis, osteoporosis, gout, long-term musculoskeletal problems due to injury, chronic liver disease, inflammatory bowel disease, chronic pancreatic disease, peptic ulcer, chronic kidney disease, end-stage kidney disease, endometriosis, chronic urinary tract infection, anemia (including pernicious anemia, sickle cell anemia), visual impairment that cannot be corrected, hearing impairment that cannot be corrected, Meniere disease, HIV/AIDS, chronic Lyme disease, tuberculosis, postacute COVID-19, congenital disease, and chromosomal abnormality.

Follow-up

The participants within the data sets will be followed-up until the earliest occurrence of the following: developing the outcomes of interest, transfer out of the practice, death, practice stopping data contribution to the database, and end of data linkage to HES APC and the ONS.

Clustering Variables

Variables for inclusion in the clustering models will be generated by the qualitative study and Delphi, including but not limited to sociodemographic variables (eg, age, sex, ethnicity, and IMD), clinical variables (eg, blood pressure, cholesterol, medication use defined as repeat medication only), social needs (eg, social services, physiotherapy, or occupation health input), health and social care usage (eg, hospitalization, outpatient appointments), mortality and health care costs (eg, inpatient costs of admissions to hospital as a day case [31] or as an inpatient for ≥1 night), outpatient and A and E costs, noninpatient costs (costs of all GP contacts and outpatient clinics) and for all other purposes, including primary care and social care, and Personal Social Services Research Unit costs [32].

Outcome Variables

The initial core variables that we have included are as follows: all-cause and cause-specific mortality, deterioration to worsening MLTC-M (ie, number of conditions), worsening frailty score, inpatient costs (admission to hospital as a day case or as an inpatient for ≥1 night), outpatient costs, A and E cost, GP contract cost, social care contact cost, referral to community services (occupational therapy, district nurses, physiotherapy) cost, nursing home cost, and respite care costs. Additional outcome variables could be added depending on the results of the parallel qualitative and Delphi work package.

Analysis

Traditional Statistical Modeling

Participant characteristics will be summarized with appropriate summary statistics. Using generalized linear models, we will describe multimorbidity rates and frailty over time. Survival models will be used to investigate all-cause and cause-specific mortality. For expert-driven clustering, we will carry out latent class modeling considering profiles over at least a 10-year follow-up period. We will model trajectories of multiple long-term conditions, as well as health and social care needs over time using group-based multitrajectory modeling in Stata (StataCorp). We will conduct complete case analyses for all models and separately evaluate the models in multiply imputed data (sensitivity analysis). Under the "missing at random assumption," where appropriate, we will use multiple imputation with chained equations to generate 5 imputed data sets. Continuous values may need transformation before imputation. Imputation models will include all exposure and outcome variables; statistical models will be developed on each of the 5 imputed data sets and the estimates pooled using Rubin's rules. Data will be analyzed using Stata (version 17). We will conduct our study and report the findings in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (The REporting of studies Conducted using Observational Routinely collected health Data) guidelines for observational studies using routinely collected health data.

AI-Based Modeling

A variety of data mining and ML methods will be used for data-driven knowledge elicitation regarding the concept of social care needs, patient social care need trajectories over time, outcomes associated with the trajectories, and interventions (modifiable exposures) that can be used to modify the trajectories and the respective the final outcomes. This information will be included in a report on intervention strategies and policies.

The sequence of ML-based analytic tasks will be as follows:

1. The variables defining the concept of social care needs, which are generated by the modified Delphi study, will be entered for clustering and cluster interpretation to discover naturally occurring classes of social care needs. The clustering approach will exploit the ability of the ML methods to process high-dimensional and high-volume data using data science pipelines composed of dimensionality reduction, unsupervised clustering, supervised learning, and model interpretation algorithms. These pipelines are further described below.
2. Using longitudinal data, patients' social care need trajectories (ie, sequences of social care need class membership) will be composed, and these trajectories will be clustered with respect to outcomes of interest, including mortality, worsening frailty, accrual of critical LTCs of interest, and costs. For trajectory clustering, we will apply hierarchical clustering with custom distance measures based on the outcomes of interest using the HDBSCAN (Hierarchical Density-Based Spatial Clustering of Applications with Noise) algorithm] in Python.
3. Trajectory clusters will be analyzed by experts for identifying clusters of interest (ie, clusters with undesirable outcomes). Further, intervention points will be identified aiming at trajectory modification so that trajectory outcomes can be positively modified.

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4. Predictive and causal associations between exposures (these variables will be selected during the modified Delphi study) and trajectories will be modeled at the points for interventions previously selected. For predictive modeling, we will use the XGBoost algorithm in Python. For causal modeling, we will use directed acyclic graphs and linear models.

For the ML-based clustering in step 1 of the above procedure, we will develop, apply, and evaluate 2 ML clustering pipelines. Pipeline 1 is semiautomated based on shallow ML clustering using expert- crafted features calculated from raw data. Here, the expert is added by ML tools for data visualization by low-dimensional embedding. Pipeline 2 is a fully automated pipeline based on deep ANNs and explainable AI techniques, where the pipeline takes raw data as the input and provides clusters and interpretations as the output. In addition, prior to feeding data into the clustering pipelines, data will be preprocessed by rescaling of the numerical data (such as standardization or min-max scaling) or transformations for mixed categorical and numerical data (such as Gower transformation) or calculating dissimilarity measures for categorical data (such as the simple matching coefficient). The precise data preprocessing method will be finalized after a descriptive analysis of the selected variables.

Pipeline 1 uses semiautomated ML motivated mainly by the work of Becht et al [22] through applying Uniform Manifold Approximation and Projection (UMAP), t-Distributed Stochastic Neighborhood Embedding (t-SNE), and specialized variational autoencoder (SCVIS) algorithms based on biological cell type and cell differentiation trajectory clustering.

In phase 1, we interactively assess the propensity of the data for clustering and topology using low- dimensional (2D and 3D) embeddings with parameterized t-SNE and UMAP [22] and quantitative measures of goodness of clustering. If t-SNE and UMAP produce clusters, this would naturally mean that the input feature space contains the necessary information for separating the data into naturally occurring clusters and classes. If clusters cannot be observed in the low-dimensional space, new features derived by experts will need to be introduced. The t-SNE and UMAP algorithms expose information about the number of natural clusters in the data and the shape of the clusters, which will inform the selection of models to be used for fitting the clusters of data. In this role, it is generally reported that UMAP performs better when t-SNE [22] with a notable exception being nested cluster extraction (ie, a tight, dense cluster inside a wide, sparse cluster), where t-SNE performs better and UMAP fails to separate the clusters [33].

The data in the low-dimensional (2D/3D) output space of t-SNE and UMAP will be clustered using HDBSCAN; the quality of these clusters will be quantitatively evaluated using measures for cohesion and separation (eg, sum of squared errors, silhouette coefficient, Calinski-Harabasz and Davies Bouldin Indexes). The observed natural clusters in the low-dimensional (2D/3D) space are not explicitly and directly interpretable, as UMAP and t-SNE perform highly nonlinear transformations and further interpretable ML methods will be used in the next phase to facilitate their interpretation.

Phase 2 selects data features (<20) and interpretable ML classification algorithms to fit models onto the natural clusters in the data. Algorithms with interpretable models are, for example, decision trees, rule learners, naive Bayes, k-nearest neighbors, generalized linear models, Gaussian mixture models, or ensembles of these, each generally performing differently depending on the density, shape, and separation boundaries of the data classes. We will output interpretations of individual clusters based on the derived decision boundaries of the best performing classification model learned for the clusters.

Pipeline 2 is fully automated and builds on the approach by Ding et al [23] for applying deep generative models (autoencoders) to derive interpretable low-dimensional features for discovering biological cell types, states, and development lineages [23]. We will use this approach to discover homogenous patient groups and their health care–related states and trajectories. Pipeline 2 will be compute-intensive and use existing high-performance computing infrastructure including servers with graphic processing unit arrays.

In phase 1, automated dimensionality reduction will be performed with a deep learning autoencoder neural network, followed by clustering in the lower-dimension space, based on the work of Xie et al [34].

The autoencoder is given the raw data (even if it is very high-dimensional) and features are successively generated automatically by the layers of the autoencoder, as well as low-dimensional embedding for clustering. Importantly, the mapping of input features (the high-dimensional space) and output features (the low-dimensional space) is captured by the weights of the encoding and decoding neural networks of the autoencoder; we can make transformations between the 2 spaces, which are needed for deriving cluster interpretations using explainable AI techniques in phase 2. Further, in the low-dimensional space, automated clustering will be performed using HDBSCAN, where metrics for cohesion and separation (as in pipeline 1) will be used to select the best clustering.

In phase 2, explainable AI (XAI) algorithms will be used for deriving cluster interpretations. We will use the XGBoost algorithm coupled with the SHAP (SHapley Additive exPlanations) XAI algorithm [35] for building and interpreting models of the clusters derived in phase 1.

Beyond the approach and methods described above, and in the course of ongoing data analysis work, further refinement of our approach would be considered when addressing the specific concerns explained below.

Causality

Statistical dependences between the studied variables will be inferred from the data, which will then be appraised by a multidisciplinary team for the type of relation (causal or not) and factored in dynamic epidemiological models. Interpretable ML will be used for determining dependences between variables, where the techniques will include Bayesian network inference from data, SHAP estimation, and local surrogate model inference (local interpretable model-agnostic explanations [LIME]) over learned and possibly nonlinear,

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models. Dictionary learning of sparse coding techniques will also be researched for selecting candidate causalities.

Sparsity

This can naturally occur in high-dimensional spaces. However, some or many dimensions will not generally be mutually independent and there will be redundant dimensions to some degree with respect to a given learning task. This type of data sparsity will be addressed using dimensionality reduction techniques (eg, principal component analysis, UMAP) in the ML pipeline. Sparse data will also be interpreted by topological data analysis (eg, with the KeplerMapper tool) and manifold learning. For cases with sparse labeled data, but denser unlabeled data, semisupervised learning and the transfer learning pipeline will be specifically explored and designed for specific characteristics of the problem.

Temporality

Time series and sequence learning for predicting the sequence of accrued conditions and cluster trajectory prediction will be performed with the long short-term memory (LSTM) and transformer ANN algorithms.

Networked Data

We assume that some known relations between the studied variables exist and are machine readable. These relations will be used to create a graph representation of the related variables. The graph will be used with graph neural networks for learning better latent representations for the downstream learning tasks or for inferring unobserved relations.

Explainability

Dimensionality reduction, visualizations, clustering, and topological data analysis will be used for finding naturally occurring structures in the data that can be related to the studied phenomenon. We will initially apply readily interpretable ML techniques such as linear models, decision trees, and inferred Bayesian networks. Furthermore, nonlinear model learning on the labeled data (supervised learning with XGBoost or deep ANN) and interpretation learning (with SHAP and LIME) will be performed for identifying predictor variables that will be further assessed for their epidemiological meaning by a multidisciplinary team.

Bias

Addressing bias is critical to ensure model fairness and to ensure that predictions are not affected by an individual belonging to one of the groups defined by some sensitive attribute(s). An interdisciplinary approach is necessary to ensure that all researchers adopt principles of fairness and responsible AI practices [36,37]. Bias can be an intrinsic property of the data set resulting from sampling procedures and will be addressed qualitatively through engaging experts and data owners. Bias can also be introduced by decisions of data scientists during data preprocessing.

Data set selection, wrangling, and transformation have the potential to remove or inadvertently introduce new bias in data. We will address this challenge by building on our team's existing work in this area including previous algorithms [36,37]. Our approach will apply a formal model of data preprocessing operations (feature selection, feature engineering, imputation and listwise deletion, resampling, outlier removal, smoothing/normalization, and encoding) to record the effect each operator has on the data. Operations will be logged during processing through code instrumentation to produce an end-to-end provenance document that contains a fine-grained history of each data set element in the final training set.

Derived clusters and interpretations from the expert-driven and AI-supported clustering will be summarized with descriptive statistics. This will also allow inequities in care across clusters to be assessed using a proxy of area-level deprivation for socioeconomic status. Clusters will also be analyzed to identify whether they differ statistically between the 2 methods. Appropriate regression models (depending on data distribution) will be constructed to quantify the association between population clusters and outcomes. Finally, we will compare outcomes between the derived population clusters with respect to key covariates and between the clustering methods.

We will conduct segmentation via latent class analysis using Latent GOLD (Statistical Innovations) and data-driven analysis will be performed with R (version 4 or later) and Python (version 3 or later). The Delphi panel will be reconvened for algorithmic stewardship that permits an additional layer of quality control to discuss AI outputs in terms of safety, fairness, effectiveness, and practicality and to determine which clusters to take forward [38].

We will ensure FAIR (Findable, Accessible, Interoperable, and Reusable) stewardship of data, curation of models, and research integrity through robust governance, as the pipeline develops processes building on the blueprint outlined for the Social Data Foundation, which has been written by one of the authors of this protocol [39]. Each AI pipeline will be developed using microservices deployed in containers (Kubernetes, Cloud Native Computing Foundation) and described using container orchestration for repeatable and continuous testing and deployment. Models will be developed in interactive environments such as Jupyter and built into software libraries for integration into automated workflows (eg, TensorFlow). Artifacts such as software libraries, images, and notebooks will be made available through open-source licenses allowing results to be replicated by others and research outputs repeated/compared by others.

Findable data will be indexed and annotated with semantically rich metadata using shared terminologies. Data will be made accessible by publishing them to national data services via application programming interfaces and directly by humans or machines for integration into workflows, whereas interoperable data will be aligned with standards such as Health Level Seven and Fast Healthcare Interoperability Resources. Reusable data require clear licensing including any ethical, legal, and security requirements necessary for usage.

Ethical Approval

Ethical approval was granted from the University of Southampton Faculty of Medicine Research Committee (reference 67953).

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Results

This study is due to commence in October 2021 and we will aim to complete it by October 2023. The study received funding from the National Institute for Health Research.

Our research attempts to offer commissioners and policy makers reliable evidence on a new approach to manage MLTC-M. We will examine the potential of using ML methods to deliver insights into new disease clusters that consider health and social needs. Clusters will be profiled to evaluate differences in sociodemographic, clinical and treatment variables, comorbid disease patterns, and trajectories of disease progression. We will compare associations of disease trajectories with respect to outcomes and then conduct an intervention development phase to examine the feasibility of using advanced AI outputs to tailor the design of an intervention that supports the integration of care needs. This phase will develop the program theory and scope intervention content, as well as identify and address implementation, trust, adoption, and scalability issues to support rapid incorporation into existing service pathways. The generated evidence could provide a powerful tool for delivering holistic care and reducing the human cost and resource burden of MLTC-M.

Discussion

Principal Considerations

In this mixed methods program of work, we will use multiple large national primary care databases alongside qualitative work and a modified Delphi method to identify clusters of MLTC-M populations based on their health and social needs. Understanding these clusters and their trajectories over time will, in turn, help develop evidence-based solutions. These will be aimed at supporting the delivery of interventions tailored to address the needs pertinent to each homogenous cluster. Our evidence will provide key knowledge on how to generate clusters based on health and social needs and how to quantify the impact of clusters on long-term health and costs.

Limitations

For our qualitative work, we will primarily be carrying out telephonic or virtual interviews whereas the modified Delphi method is an exclusively internet-based one. It is likely that respondents will include those able to use virtual technologies for interviews and those able to use and access virtual services to complete the web-based Delphi. People with MLTC-M who are unable to use these technologies, such as the elderly, those with disabilities, or those from lower socioeconomic backgrounds who may not have access to internet-based services, will not be sufficiently represented in our sample. It is plausible that the richer qualitative data could be obtained through in-person interviews.

There are inherent limitations associated with the analysis carried out on secondary data. These data have been collected in the clinical setting and are not for research purposes. They will have variations in entries and coding that are dependent on individual clinicians. Incomplete, missing, and incorrectly coded records are likely to be limitations. The extent to which problem exists in our data and the impact on our findings will require thorough exploration. Although our cohort will include primary care populations from several large national databases across large geographical areas in England and Wales, it may not include a sufficiently diverse sample of people from varying ethnic and socioeconomic status, thus limiting generalizability.

Conclusions

Outputs from the research will offer commissioners and policy makers reliable evidence for a new approach to manage MLTC-M. Using a “whole person” approach could inform tailoring of interventions specific to each MLTC-M cluster. The evidence generated by this research has the potential to serve as a powerful tool for delivering holistic personalized care, thereby reducing the human cost and resource burden of MLTC-M.

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Conflicts of Interest

None declared.

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Abbreviations

A and E: accident and emergency
AI: artificial intelligence
ANN: artificial neural network
CPRD: Clinical Practice Research Database
ELSA: English Longitudinal Study of Ageing
GP: general practice
HDBSCAN: Hierarchical Density-Based Spatial Clustering of Applications with Noise
IMD: Index of Multiple Deprivation
LIME: local interpretable model-agnostic explanations
ML: machine learning
MLTC-M: multiple long-term health conditions (multimorbidity)
SAIL: Secure Anonymised Information Linkage
SELFIE: Sustainable intEgrated care models for multi-morbidity: delivery, FInancing and performancE)
SHAP: SHapley Additive exPlanations
t-SNE: t-Distributed Stochastic Neighborhood Embedding
UMAP: Uniform Manifold Approximation and Projection
XAI: explainable artificial intelligence

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Protocol

Ensuring a Successful Transition From Cytology to Human Papillomavirus–Based Primary Cervical Cancer Screening in Canada by Investigating the Psychosocial Correlates of Women's Intentions: Protocol for an Observational Study

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Abstract

Background: The human papillomavirus (HPV) test has emerged as a significant improvement over cytology for primary cervical cancer screening. In Canada, provinces and territories are moving toward implementing HPV testing in cervical cancer screening programs. Although an abundance of research exists on the benefits of HPV-based screening, there is a dearth of research examining women's understanding of HPV testing. In other countries, failure to adequately address women's concerns about changes has disrupted the implementation of HPV-based screening.

Objective: The aims of the multipart study described in this paper are to develop psychometrically valid measures of cervical cancer screening–related knowledge, attitudes, and beliefs; to examine the feasibility of a questionnaire examining psychosocial factors related to HPV-based screening; and to investigate psychosocial correlates of women's intentions to participate in HPV-based screening.

Methods: We conducted a web-based survey (study 1) of Canadian women to assess the acceptability and feasibility of a questionnaire, including the validation of scales examining cervical cancer knowledge, HPV testing knowledge, HPV testing attitudes and beliefs, and HPV test self-sampling attitudes and beliefs. Preferences for cervical cancer screening were assessed using the best-worst scaling methodology. A second web-based survey (study 2) will be administered to a national sample of Canadian women between June 2022 and July 2022 using the validated scales. Differences in the knowledge, attitudes, beliefs, and preferences of women who are currently either underscreened or adequately screened for cervical cancer will be examined through bivariate analyses. Multinomial logistic regression will be used to estimate the associations between psychosocial and sociodemographic factors and intentions to undergo HPV-based screening.

Results: Between October 2021 and November 2021, a total of 1230 participants completed the questionnaire in study 1, and 1027 (83.49%) responses were retained after data cleaning methods were applied. Feasibility was comparable with similar population-based surveys in terms of survey length, participant attrition, and the number of participants excluded after data cleaning. As of May 2022, analysis of study 1 is ongoing, and results are expected to be published in the summer of 2022. Data collection is expected to begin for study 2 in the summer of 2022. Results are expected to be published between late 2022 and early 2023.

Conclusions: Findings will provide direction for Canadian public health authorities to align guidelines to address women's concerns and optimize the acceptability and uptake of HPV-based primary screening. Validated scales can be used by other researchers to improve and standardize the measurement of psychosocial factors affecting HPV test acceptability. Study results will be disseminated through peer-reviewed journal articles; conference presentations; and direct communication with researchers, clinicians, policy makers, media, and specialty organizations.

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KEYWORDS

human papillomavirus; HPV-based primary screening; cervical cancer; cervical cancer screening; cancer prevention; knowledge; attitudes and beliefs; preferences; HPV test acceptability; HPV self-sampling; Pap testing; cytology; mobile phone

Introduction

Background

Cervical cancer is the fourth most common cancer in women and presents a significant risk to all people with a cervix [1-3]. In 2018, an estimated 570,000 women were newly diagnosed with cervical cancer worldwide, with 311,000 deaths from the disease [4]. In Canada, >1300 women are diagnosed with and >400 women die from cervical cancer each year [5]. Cytology testing using the Papanicolaou smear, commonly referred to as the Pap test, allows for the detection and subsequent treatment of precancerous lesions that may lead to cervical cancer. Canadian women have been widely screened for cervical cancer using the Pap test for >50 years [6]. There are guidelines in each province and territory that currently recommend screening every 1 to 3 years, starting at the age of 21 or 25 years [7], and most Canadian jurisdictions have organized screening programs [8].

Cervical cancer is caused by persistent infection with high-risk human papillomavirus (HPV) types [9]. The HPV test, which detects high-risk HPV DNA in cervical cells, has emerged as a significant improvement over cytology for cervical cancer screening. Compared with cytology-based screening, HPV-based screening has been shown to offer 60% to 70% higher protection against the development of cervical cancer [10,11]. The HPV test shows improved sensitivity, and negative test results have high negative predictive value, thus providing greater reassurance against cervical lesion development [12]. Furthermore, this allows for increased intervals between cervical screenings and reduced testing costs [12]. HPV testing also introduces the possibility for vaginal self-sampling by the patient. This is not possible with cytology, which requires cervical cell collection by a health care provider, a process that can be uncomfortable or invasive [13,14]. Meta-analyses have shown that self-sampling has similar test accuracy when compared with health care provider–administered sampling [15] and could increase uptake among those who are underscreened when provided as a screening option [15,16].

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Therefore, currently, HPV testing is considered the preferred method of screening by the World Health Organization [17] and is recommended by multiple specialty organizations worldwide (eg, United States Preventive Services Task Force [18], European Society of Gynaecologic Oncology, and European Federation of Colposcopy [19]). Several countries have implemented HPV-based organized screening programs (eg, Australia, the United Kingdom, and the Netherlands), including the use of self-sampling as a collection option [20,21]. However, program implementations have encountered challenges. For example, in Australia, before the introduction of HPV testing, a web-based petition against the proposed changes gained widespread support. In an analysis of comments on the petition, Australian women felt that the policy *devalued or threatened women's health* and represented a government cost-cutting measure and that increased screening intervals and later age of screening initiation would prevent early detection of cervical abnormalities [22]. Similarly, in Wales, increase in screening intervals associated with the shift to HPV-based screening has been met with public backlash, with >1.2 million signatures on a web-based petition against the change at the time of writing [23]. Although these guidelines are grounded in evidence, a disconnect has been observed between women's and public health authorities' views on cervical cancer screening changes. These health authorities failed to effectively and proactively communicate why changes were warranted, why screening intervals may change, and what HPV test results indicate [22-26].

Screening Landscape in Canada

In Canada, provinces and territories are in different planning phases for HPV-based cervical cancer screening programs [7,27], and the nationwide introduction of HPV-based primary screening is a key priority of the recent Canadian Partnership Against Cancer (CPAC) Action Plan for the Elimination of Cervical Cancer [5]. Although cytology-based screening is well established in Canada, screening coverage has failed to reach the CPAC target of including ≥80% of women [28]. This suggests that innovative approaches are needed to reach those women who are underscreened (ie, longer than 3 years since their previous Pap test or never screened). Approximately 40% of women in Canada diagnosed with cervical cancer report either never having had a Pap test or not having had one in >3 years [29]. Underscreened women are often members of ethnic, linguistic, gender, and sexual minorities or have lower socioeconomic status [30-33]. In Canada, only 65% of recent female immigrants reported having a Pap test in the previous 3 years, and 26% of non-English or French speakers reported never having a Pap test [29]. In a study of cancer screening registries in Ontario, transgender patients were significantly less likely than cisgender patients to be screened for cervical cancer (56% vs 72%) [32], reflective of barriers faced by transgender and other gender-diverse people in seeking cervical cancer screening [2]. A study by Decker et al [34] comparing screening rates and outcomes between First Nations women and all other women in Manitoba suggested lower screening rates among First Nations women aged ≥40 years and significantly higher rates of cervical lesions and cancers in First Nations women overall. Targeted solutions must consider these factors. For underscreened women, the introduction of HPV self-sampling could be important for ensuring that cervical cancer screening is more accessible and acceptable [13-15,35,36]. A meta-analysis of 37 studies by Nelson et al [37] found that women who used and indicated acceptability of self-sampling for future screening did so because of its convenience, privacy, and ease of use. However, identified barriers include women's lack of confidence in their ability to correctly collect the specimen, lack of confidence in the test result, and discomfort with the procedure [37,38].

The concerns of adequately screened women (ie, <3 years since their previous Pap test) must also be addressed. Clear and open dialogue with these women is needed to prevent confusion and provide reassurance that the switch to HPV-based screening is evidence-based and represents an improvement over cytology-based screening. Currently, there is a dearth of research examining Canadian women's perceptions and understanding of HPV-based screening and potential changes to screening guidelines. To avoid problems that may arise in Canada as program implementations advance, efforts should be made to understand and address the concerns of women.

Measuring Knowledge, Attitudes, and Beliefs About Cervical Cancer Screening

From both theoretical and practical perspectives, knowledge is a determinant of engagement in protective health behaviors [24,39,40]. In a systematic review of psychosocial factors associated with intentions and acceptability of HPV testing, knowledge was associated with greater acceptability of screening using the HPV test [24]. In Canada, poor cervical cancer screening knowledge has been identified as a key barrier to screening in populations such as immigrant women and ethnic minority communities [41-43]. In a recent systematic review, specific attitudes and beliefs about HPV testing have been identified as both barriers to and facilitators of HPV test acceptability [24]. For example, high perceived benefits of the HPV test were associated with greater HPV test acceptability, whereas negative emotions (eg, shame associated with testing for a sexually transmitted infection) related to HPV testing were associated with lower HPV test acceptability. Importantly, these findings and many additional attitudes and beliefs (eg, high perceived susceptibility to cervical cancer, negative perceived emotional reaction to HPV test results, and high perceived severity of HPV infection) have not been studied and confirmed in Canada-wide samples.

Several measures exist for cervical cancer knowledge [44-47], a subscale has been developed for measuring knowledge of HPV testing [48], and 2 measures of HPV testing and self-sampling attitudes and beliefs have been developed [49,50]. However, existing measures have shown insufficient psychometric testing or suboptimal psychometric properties. In addition, in a fast-moving field, many measures are not up-to-date with evidence from the literature on cervical cancer and HPV testing or do not include other important factors associated with HPV test acceptability (eg, negative emotions related to HPV testing [24]). As women's perceptions of cervical cancer and HPV testing are multifaceted, comprehensive and valid measurement tools are crucial for identifying attitudes,

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beliefs, and knowledge gaps that could be barriers to the acceptance and uptake of HPV-based screening.

Measuring Preferences Regarding Cervical Cancer Screening

Preferences refer to a distinct form of attitude that provides information about the relative value and ranking an individual assigns to certain options over others. Measuring preferences is important in the context of cervical cancer screening, as multiple approaches (eg, varying screening intervals and use of self-sampling) are being considered for implementation [5]. Understanding Canadian women's preferences can provide insight into the acceptability of different screening options and illuminate any potential disconnect between women and public health regarding the implementation of HPV-based screening programs. In particular, by examining women's preferences for screening intervals and age of screening initiation, 2 major points of contention observed in other program implementations [22,51,52], public health can optimize communications to address concerns and ensure acceptability of HPV-based screening guidelines [24]. Furthermore, examining the preferences of underscreened women and adequately screened women separately can help to inform targeted communications for these groups.

This Study

The proposed study will use a multistep approach to examine women's knowledge, attitudes, beliefs, and preferences toward HPV testing and self-sampling. A preparatory study (study 1) was focused on the development and psychometric validation of scales measuring cervical cancer screening–related knowledge, attitudes, and beliefs. In addition, given the challenges of investigating women's views toward a screening approach that has not yet been implemented, this study examined the feasibility and structure of a survey that examines these factors in Canadian women. Results of study 1 will yield validated scales to administer to a large sample of Canadian women (study 2) to estimate the associations between psychosocial factors and women's intentions to participate in HPV-based screening programs. Furthermore, study 2 will survey and compare differences in psychosocial factors and HPV test intentions among adequately screened women and underscreened women, providing timely data to address emerging challenges in both groups.

Objectives

The main objectives of study 1 (scale and questionnaire development) are as follows:

1. To develop psychometrically valid scales to assess women's knowledge of cervical cancer and attitudes, beliefs, and knowledge about HPV testing and self-sampling.
2. To evaluate the feasibility and acceptability of using a web-based survey related to Canadian women's knowledge, attitudes, beliefs, and preferences about new HPV testing–based cervical cancer screening programs.

The main objectives of study 2 (expanded population-based survey of Canadian women) are as follows:

1. To estimate differences in HPV and cervical cancer screening knowledge and attitudes, beliefs, and preferences regarding HPV testing between women who are adequately screened and those who are underscreened.
2. To estimate the multivariable associations between psychosocial factors (eg, knowledge, attitudes, beliefs, and sociodemographics) and intentions to use HPV testing and self-sampling in women who are adequately screened and those who are underscreened.

Study 1: Questionnaire Development and Scale Validation

Methods

Study 1: Ethics Approval

Study 1 received approval from the Research Ethics Board of the Centre intégré universitaire de santé et de services sociaux (the Integrated Health and Social Services University Network) of West-Central Montreal (project ID 2021-2632) in March 2021.

Theoretical Frameworks

Questionnaire development and item selection for the development of the scales were guided by relevant theoretical frameworks. The selection of psychosocial factors influencing intentions to engage in HPV testing was informed by 2 theories: the Theory of Planned Behavior (TPB), which suggests that attitudes, beliefs, subjective norms, and perceived behavioral control influence intentions and subsequent health behaviors [53], and the Health Belief Model (HBM), which posits that the likelihood of behavior change is influenced by perceived susceptibility, seriousness and threat of the disease, perceived benefits of adopting protective health behaviors (ie, screening), cues to action (eg, information and social influence), sociodemographics, and knowledge [54].

Study Design

To build robust measures, we followed a rigorous stepwise process involving review of the scientific literature, discussions, and consensus development with our experienced team of researchers and consultation with project collaborators and the population of interest. This process is described chronologically, separated into 3 steps: phase 1A—questionnaire development, phase 1B—questionnaire validation, and phase 1C—survey testing and psychometric validation. As of May 2022, phases 1A and 1B are completed, and data analysis is ongoing for phase 1C.

Phase 1A: Questionnaire Development

Literature Search

We reviewed the literature for existing relevant scales using a validated and updated search strategy that we used for a recently published knowledge synthesis summarizing factors associated with HPV test acceptability in primary screening for cervical cancer [24]. Embase, Global Health, PsycINFO, MEDLINE, and CINAHL databases were searched from January 2017 to October 2019. After removing duplicates, a total of 1477 references were screened by title and abstract, and 89 full-text

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articles were reviewed to identify relevant scales. Our team found and reviewed 13 scales (including 4 scales that were identified in past literature searches [44,45,48-50,55-62]). Our overall conclusions indicated that existing questionnaires were incomplete in the following ways: not including questions about HPV testing in cervical cancer screening (eg, only including items related to the Pap test), having inadequate psychometric validation analyses (eg, no factor analysis, only partial factor analysis with exploratory factor analysis [EFA], or no reliability testing at all), having inadequate psychometric properties (eg, internal consistency <0.6), being unsuitable for our study design (eg, being designed to administer verbally), and having limited sampling characteristics (eg, only adolescents or in a specific culture or context). Nevertheless, many individual items were potentially relevant to our objectives.

Item Selection

To evaluate potentially relevant items together and guide their selection, a large pool of items (n=781) was created, and a questionnaire structure was drafted (Figure 1) with 4 potential scales: cervical cancer knowledge, HPV testing knowledge, HPV testing attitudes and beliefs, and HPV self-sampling knowledge. This large item pool included items from the reviewed scales and new items generated based on the results of a recent mixed methods synthesis of psychosocial factors affecting HPV test acceptability [24] and a systematic review of emotional responses to testing positive for HPV [25]. Items related to sociodemographics and health behaviors were also included.

All 781 items were compiled into an Excel (Microsoft Corporation) spreadsheet to be reviewed by the research team. A flowchart of the item sources is shown in Figure 2. Each item was reviewed individually over several research team meetings, marked as *retained* or *rejected*, and categorized into an appropriate section of the questionnaire (Figure 1). For instance, the item "The HPV test is safe" was categorized as part of *attitudes and beliefs about HPV testing* instead of *knowledge about HPV testing* because this item captures a belief that women may agree or disagree with, which may impact their intentions to engage in cervical cancer screening with the HPV test. Within each of the questionnaire sections, items were further mapped onto constructs from the HBM (eg, "if the HPV test showed I have HPV, it would be serious" in perceived seriousness) and TPB (eg, "my friends' opinion about getting the HPV test would be important to me" in social cues) to ensure comprehensive coverage of these frameworks.

Figure 1. Draft questionnaire structure. HPV: human papillomavirus; PAPM: Precaution Adoption Process Model.

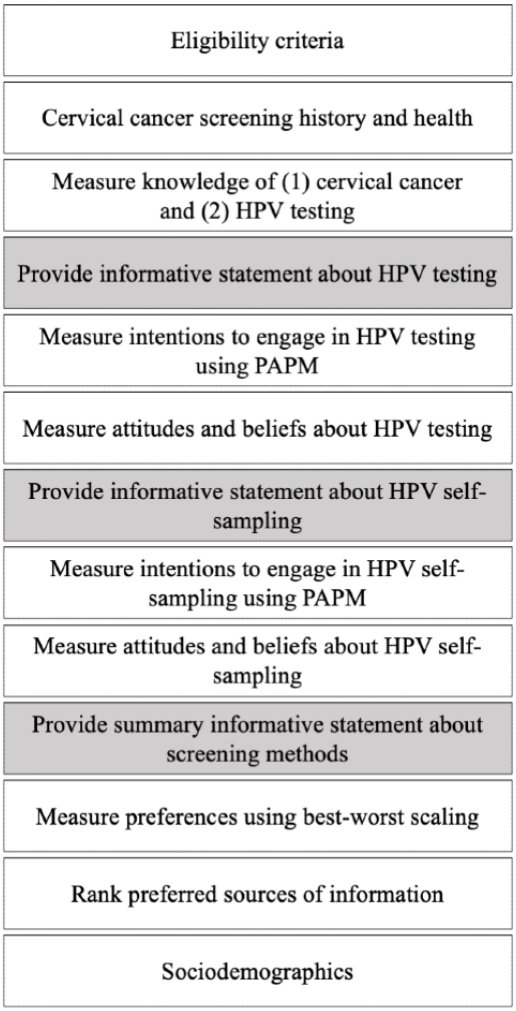

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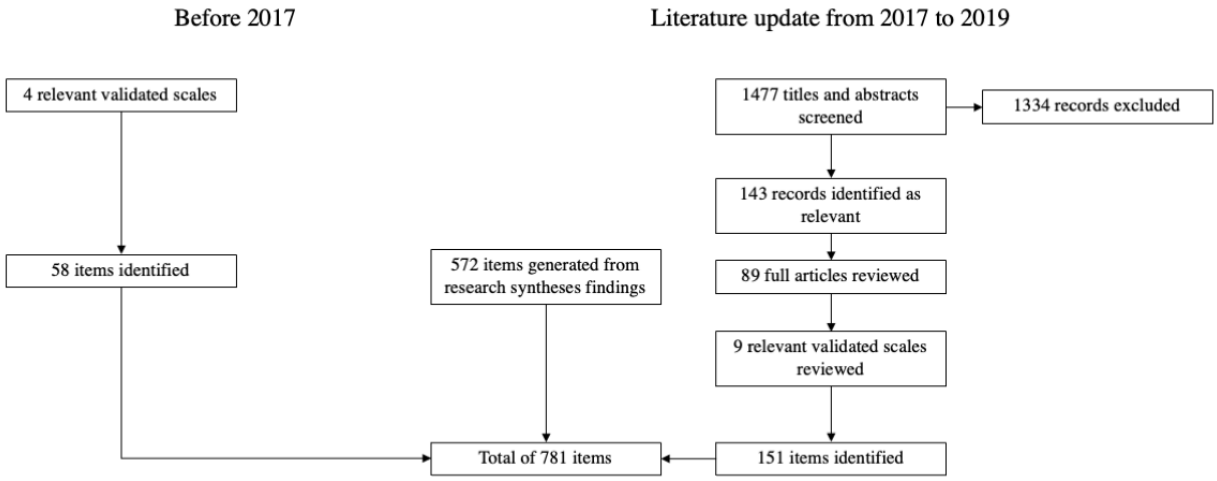
Figure 2. Flowchart of item sources.



At this stage, the focus was on the item's underlying construct and not its wording. Reasons for rejecting items included the following: (1) duplicate of a factor already retained, (2) not applicable to Canadian context (eg, "There are resources in my community for low and no cost cervical cancer screenings" as Canada has a universal health care system [45]), (3) infrequent and isolated factor (eg, "I worry that tube contents may spoil or spill during transportation to doctor" [63]), and (4) not applicable to our project's quantitative and survey methodology (eg, open-ended items such as "There are many warning signs and symptoms of cervical cancer. Please name as many as you can think of" [44]).

In total, of 781 items that were reviewed, 137 (17.5%) items were retained. Of these 137 items, 85 items were categorized for scale development: 14 for cervical cancer knowledge, 14 for HPV testing knowledge, 44 for attitudes and beliefs about HPV testing, and 13 for attitudes and beliefs about HPV self-sampling. These 85 items were reviewed and revised separately for clarity, consistency, and grade-8 reading level to account for different language and literacy levels. In addition, certain cervical cancer knowledge and HPV testing knowledge items were revised to achieve a balance of *true* and *false* items (ie, made negative or affirming by adding words such as *not*).

Assessing Preferences Using Best-Worst Scaling

To explore women's preferences for their cervical cancer screening parameters (type of test, screening interval, and age of screening initiation), we designed questionnaire items according to the best-worst scaling (BWS) methodology [64]. Using this methodology, participants' preferences were examined for different screening intervals (domain A) or various ages of screening initiation (domain B), while also considering multiple screening strategies (ie, Pap test, HPV test, HPV-Pap cotesting, and HPV self-sampling). In domain A, 3 screening intervals were included for assessment according to their applicability to HPV test–based screening implementation: 3 years (the most common interval in Canada for existing cytology-based programs [7]), 5 years (widely recommended for HPV test–based screening [20,65]), and 10 years (implemented for women aged ≥40 years in the Netherlands and considered for wider implementation [66]). In domain B, the following 3 ages of screening initiation were included: 21 years (the most common age of screening initiation in Canada for existing cytology-based programs [7]), 25 years (currently recommended age of screening initiation in several Canadian provinces and widely recommended in countries implementing HPV-based screening in the context of HPV vaccination; eg, the United Kingdom and Australia [7,20]), and 30 years (recommended age of screening initiation with primary HPV-based screening according to the United States Preventive Services Task Force guidelines [18,67]).

Informative Statements

Knowledge about HPV in the general population is generally very low [68,69], and knowledge about HPV testing and self-sampling is presumably low among Canadian women because such testing and sampling are not currently part of cervical cancer screening programs. Therefore, we sought to ensure that women had at least basic understanding of HPV testing and HPV self-sampling before examining their attitudes, beliefs, and intentions to screen with these tests. We designed 3 informative statements: one about HPV testing, one about self-sampling using HPV testing, and one comparing cervical cancer screening methods. The development of these statements was inspired by brochures from other countries where HPV-based primary screening is in the process of being implemented or already implemented (eg, the Netherlands, the United Kingdom, and Australia [70-72]). Each informative statement was at most 1 page in length and contained a mix of text, figures, and tables (refer to the example in Multimedia Appendix 1). All informative statements were included after the items that measure participants' knowledge.

Questionnaire Revisions and Translation

A draft version of the questionnaire was circulated to our team of coinvestigators and collaborators (globally based researchers

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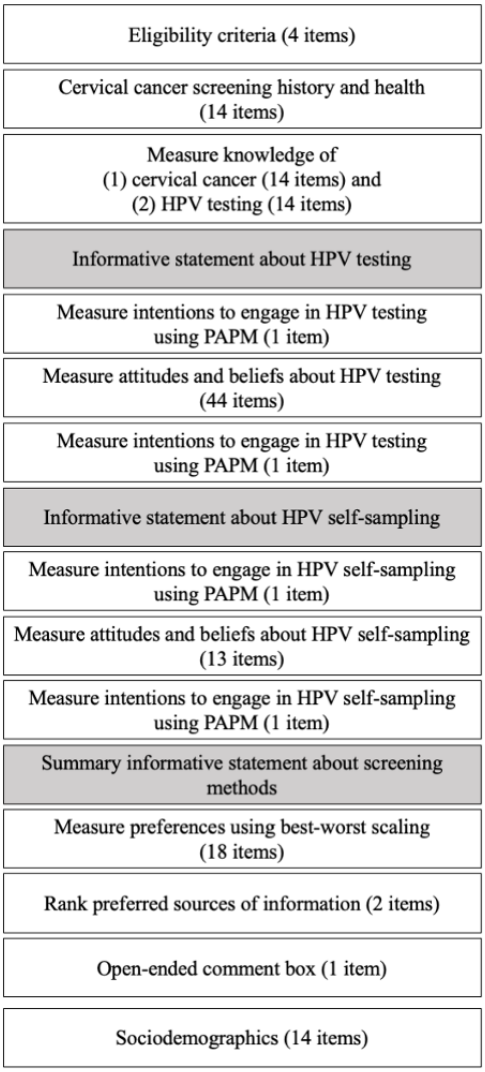
and public health decision makers with expertise in HPV research, cervical cancer screening, epidemiology, oncology, psychometrics, behavior change, and health psychology theory) for review of accuracy of content and feedback. Their suggestions were reviewed and used to refine our questionnaire further (ie, item wording, informative statement content, and questionnaire structure). Then, this version was translated into French by a specialized translation firm, Asiatis, and verified by a native French-speaking member of the research team (GGM).

Phase 1B: Questionnaire Validation

Given our objective of developing a comprehensible questionnaire, cognitive interviewing was used as a pretesting method to detect potential sources of errors in the question-answering process [73]. This method permits an assessment of the readability, understanding, and clarity of items to reveal potential differences between the intended meaning of the question from the researcher and the participants' interpretations [74]. Participants were recruited to provide verbal feedback on their understanding and experience as they completed the questionnaire over Zoom (Zoom Video Communications) with 2 members of the research team being present. Participants read the items as if they were answering the questionnaire and were instructed and prompted to *think-aloud* and provide feedback and suggestions (eg, comment if they did not understand an item or were confused and explain how they reasoned and selected their response) [75]. Each interview lasted between 1 and 2 hours. Our team reviewed the participants' comments after each interview session and made changes to the questionnaire iteratively to address the issues that arose.

The cognitive interviewing phase was completed when no new issues or feedback were raised by the participants. This process required a sample of 7 women, aged 21 to 70 years. Of the 7 interviews, 4 (57%) interviews were conducted in English and 3 (43%) were conducted in French. On the basis of the participants' feedback, changes were made to the questionnaire to improve the clarity of items, informative statements, instructions, page formatting, and overall questionnaire structure and flow. Refer to Figure 3 for the final structure and item count.

Figure 3. Study 1 questionnaire structure and item count. HPV: human papillomavirus; PAPM: Precaution Adoption Process Model.



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Phase 1C: Data Collection and Psychometric Validation

Study Design

A cross-sectional web-based survey was administered from October 2021 to November 2021 to a national sample of Canadian women, aged 21 to 70 years, in English and French. Participants completed the questionnaire developed in phases 1A and 1B The survey design and preliminary results are reported according to Checklist for Reporting Results of Internet E-Surveys (CHERRIES; Multimedia Appendix 2) [76]. An electronic consent form describing the study investigators, study goals, procedure, expected survey length, and confidentiality was provided at the start of the survey. Then, the participants were asked whether they consented to taking part in the survey. By clicking on the icon that states they agree to participate, consent was implied, whereas if they declined, the survey was terminated. The information collected during the survey was completely anonymous.

Participants

The inclusion criteria were as follows: (1) born female; (2) aged between 21 years, which is the youngest age recommended to begin screening across provincial programs, and 70 years, which is the oldest age; (3) Canadian resident; and (4) intact cervix (eg, not having undergone hysterectomy). The exclusion criterion was having been diagnosed with cervical cancer previously. An oversampling quota was used to ensure that half of the sample was currently underscreened for cervical cancer (ie, >3 years since the previous Pap test or never screened) and the other half was adequately screened (ie, <3 years since the previous Pap test). Census-based quotas were used for primary language and province and territory of residence to reinforce sample representativeness.

Overview

The following measures were administered in the order shown in Figure 3. All questions were presented on separate pages of the questionnaire. Participants were not able to go back or review their previous responses, except within each of the psychosocial item sections.

Screening History

Participants were asked when they last had a Pap test to assess their screening group: (1) within the past year, (2) within the past 1 to 3 years (adequately screened group), (3) >3 years ago, or (4) never (underscreened group). Then, the participants who reported receiving at least one previous Pap test were asked whether they had ever received an abnormal test result. In addition, given the study's timing in the fall of 2021, participants who reported receiving a Pap test >3 years ago were asked whether the COVID-19 pandemic had prevented them from receiving a Pap test, as cervical cancer screening was paused in some provinces and territories during parts of the pandemic.

Sociodemographics

A total of 4 items used dichotomous response option (yes or no) to measure identification as visible minority [77]; influence of religious or spiritual beliefs on health decisions; living in Canada for ≥10 years; and completion of a trade certificate or diploma, college degree, or university degree. Self-reported ethnic origin was measured with 1 item using the 9 response options recommended by Statistics Canada [78]. We used multiple validated response options to measure gender identity [79]. In addition, household income, employment status, province or territory of residence, and travel time between one's home and a health care office or clinic were measured.

Cervical Cancer–Related Health Behaviors and Risk Factors

Participants answered the following items: self-reported health (from very poor [1] to excellent [6]) [80], use of oral birth control pills for ≥5 years (yes or no), number of children given birth to (0 to ≥10), smoking history (current smoker, smoked in the past, or never smoked), vaccination with at least one dose of an HPV vaccine (yes or no or don't know), having a family physician (yes or no), height, weight, previous diagnosis of sexually transmitted infection (yes or no), number of lifetime sexual partners, and age of sexual debut.

Psychosocial Items for Scale Development

Participants were presented with all items selected as part of phase 1A For the knowledge items, participants responded to each item with *true*, *false*, or *I don't know*. For attitudes and beliefs items, participants responded to each statement on a 7-point Likert scale ranging from strongly disagree (1) to strongly agree (7). Item presentation was randomized within each section for each participant to mitigate order bias.

HPV Testing and Self-sampling Intentions

Using the Precaution Adoption Process Model (PAPM) [81], women selected their current decision-making stage regarding the proposed screening method (HPV testing or self-sampling using the HPV test) from five options: (1) unengaged in the decision to be screened with the HPV test or self-sampling, (2) undecided about whether to be screened with the HPV test or self-sampling, (3) decided not to be screened with the HPV test or self-sampling, (4) decided to be screened with the HPV test or self-sampling, or (5) acted (already screened with the HPV test or self-sampling). A full description of the theoretical background and use of PAPM is provided in the *Study Design* section of study 2.

BWS for Screening Preferences

Following the orthogonal main effects design recommended by Aizaki and Fogarty [64] and using the R software packages, *DoE.base* [82] and *support.BWS2* [64], a full set of questions was developed for each of our 2 domains: screening intervals (domain A) and age of screening initiation (domain B). To examine preferences in domains with 4 attributes (ie, screening methods), each of which have 3 attribute levels (ie, screening interval options [domain A] and screening initiation options [domain B]), participants must answer 9 questions that contain the same number of randomly assigned combinations of attribute levels (corresponding to the defined attributes). Therefore, participants answered 18 items; 9 related to cervical cancer screening intervals and 9 related to age of initial screening. Items within each domain were presented randomly for each participant.

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Preferences for Screening Information and Routine Screening

Using a drag-and-drop interface, participants ranked their preferred source of information from the following options: public health agency website, social media, and health care professional. A similar item was used to assess participants' preferred type of health care practitioner to administer routine HPV testing among the following: family physician, gynecologist, nurse or nurse practitioner, and physician's assistant.

Recruitment and Data Collection

Recruitment and survey programming were facilitated by Dynata, an international market research firm. Before administering the programmed questionnaire, the research team tested the survey using multiple permutations of response options to ensure its technical functionality and usability and made changes as necessary. Then, Dynata administered the survey to their large panel of Canadian residents who are recruited through *by-invitation-only* method, in which participants' identities are validated by other partnered businesses to ensure response quality. Eligible participants were invited to complete a survey about *health and wellness* through several platforms, including emails, smartphone app notifications, and Dynata's website, using a link that is unique to each potential participant. Before beginning the survey, participants' IP address and unique identifier provided to them by Dynata were used to flag potential duplicate responses. Sample recruitment was conducted over 2 weeks in October 2021 and November 2021. Participants were compensated according to Dynata's rewards and points system (eg, Amazon and Starbucks). Participants were required to complete all questions before continuing the survey to prevent missing data.

Sample Size

We calculated the minimum sample size for conducting factor analyses using the criteria recommended by Mundfrom et al [83], which include the expected ratio of variables to factors, level of communality, and agreement between the sample and population solutions (K). On the basis of ratio of variables to factors of 4 (for the 13 items reflecting attitudes and beliefs for sampling), low level of communality (ie, range 0.2-0.4), and excellent agreement between the sample and population solutions (ie, K=0.98), the minimum sample required was 500 (rounded up from 450). As our analytic plan includes conducting EFA and confirmatory factor analysis (CFA) on separate samples and considering that oversampling is needed to account for approximately 18% invalid and inattentive responses [84], the sample needed is 1220 observations, that is, (2 × 500 × 100) / 82 = 1219.

Data Cleaning

Direct and statistical data cleaning methods were used stepwise to identify potentially *inattentive* or *unmotivated* respondents in our final data set of completed questionnaire responses. In total, 2 attention check items were used in the survey: one within the items related to HPV test attitudes and beliefs scale and one in the items related to HPV self-sampling attitudes and beliefs. Following the instructed response design [84], each of these items asked participants to select a specific response choice from a Likert scale to verify attention (eg, "please select 'strongly agree,' for this question only"). Participants who responded correctly to at least one of these items were retained. Next, participants who *straight-lined* (ie, answered all items using the same response) were identified by calculating the variance in response for all the HPV testing attitudes and beliefs items. Participants who did not exhibit any variance in their responses across these items were excluded. Finally, among the remaining participants, those in the longest 2.5% and shortest 2.5% of the survey response times were excluded.

Data Analysis—Objective 1: Scale Validation

To evaluate dimensionality, we will conduct EFA and CFA separately for cervical cancer knowledge, HPV testing knowledge, and HPV testing and self-sampling attitudes and beliefs items. The final data set will be split randomly into 2 equal samples, and one sample will be used to conduct EFA and the other sample will be used to validate the factor structure using CFA. To select the optimal number of factors, we will use the parallel analysis approach and the syntax developed by O'Connor [85]. For items within each factor, we will use item response theory modeling; for binary data (knowledge items), we will use the 2-parameter logistic regression model that accounts for item difficulty and discriminant capacity; and for ordinal data (attitudes and beliefs items), we will use the graded response model that accounts for discriminant capacity and probability of selecting a certain Likert scale score (eg, strongly agree). Concurrently, we will examine how well each item measures the latent trait by plotting the item information against the latent construct ability. We aim to retain items that cover a wide range of difficulty and have high discriminant capacity and information value. To estimate the CFA model fit, we will use the fit indices and cutoff criteria recommended by Hooper et al [86]: (1) relative (normed) chi-square test ($\chi^2/_{df}$=2 to 5) by Wheaton et al [87], (2) standardized root mean square residual (<0.8), (3) root mean square error approximation (<0.06), (4) comparative fit index (≥0.95), and (5) Tucker-Lewis index (≥0.95). To evaluate internal consistency for items loading onto each factor, Cronbach α will be calculated.

BWS Preferences

To analyze BWS preference data, we will use the counting and modeling approaches described by Aizaki and Fogarty [64]. Consistent with the counting approach, for domain A (screening interval) and domain B (age of initiation), we will calculate the best-minus-worst score (higher scores reflect higher preferences) for each attribute (eg, HPV test) and attribute level (eg, 3 years [for screening interval] and 25 years [for age of initiation]). For the modeling approach, we will use conditional logistic regression to model preferences as a function of the sum of the values of attributes and attribute levels [64]. For attributes and attribute levels, we will estimate odds ratios and 95% CIs.

Results

Overview

In total, 83.49% (1027/1230) valid responses were retained for analysis following data cleaning. Data analysis is ongoing. Results of study 1, including findings from the BWS analyses and the development of cervical cancer knowledge, HPV testing

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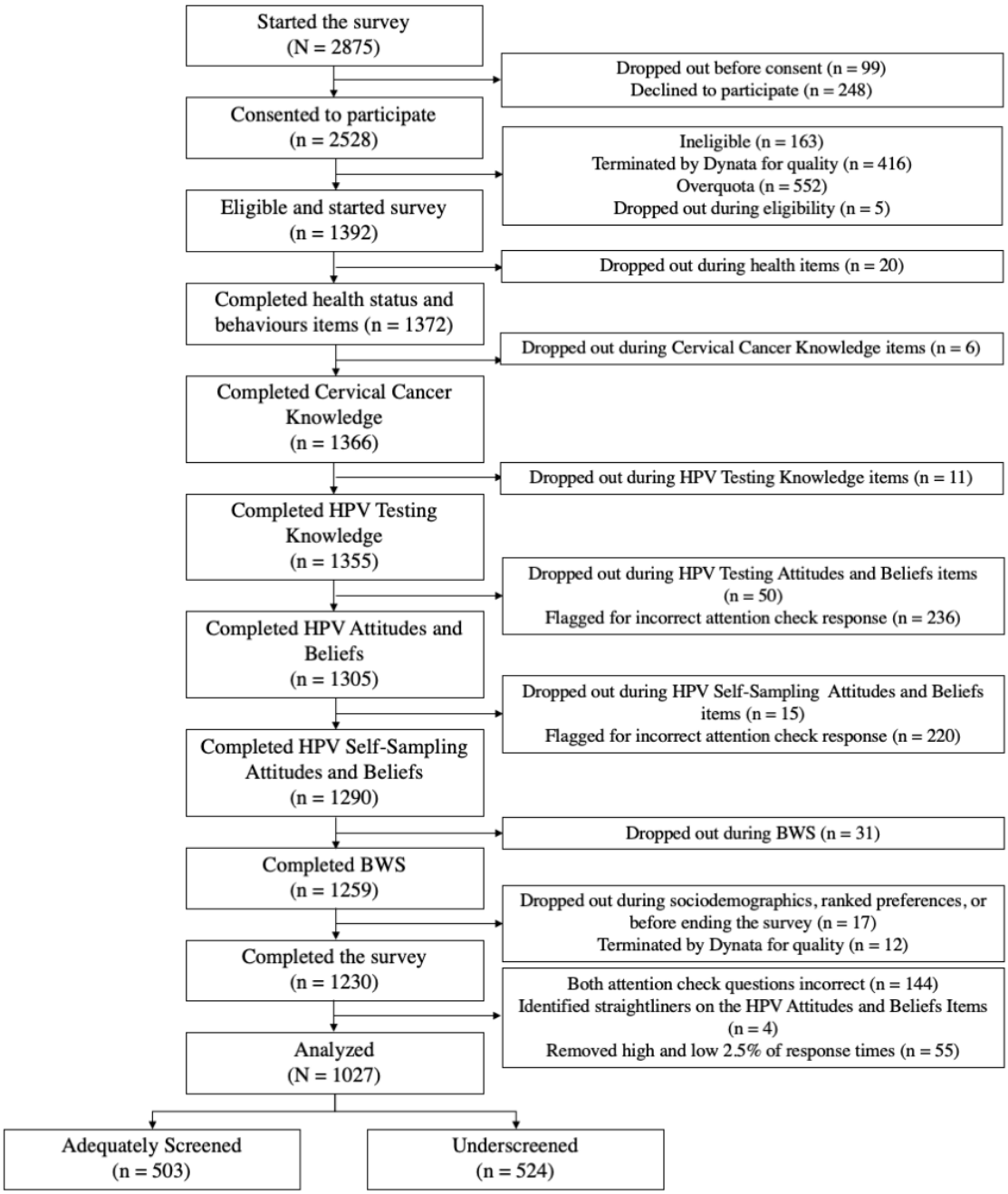
knowledge, HPV testing attitudes and beliefs, and HPV self-sampling attitudes and beliefs scales are expected to be published in the summer and fall of 2022.

Objective 2: Questionnaire Feasibility

Preliminary results suggest high level of feasibility. Through the recruitment methods of Dynata, data collection was completed within 2 weeks. As detailed in the *Data Cleaning* section, overall, data were of good quality, with the exclusion of 16.5% (203/1230) of complete responses owing to poor quality, being consistent with previous research in our laboratory and expectations for survey research [39,84,88]. The mean response time (after data cleaning) was 30.4 (SD 20.5) minutes, consistent with other surveys conducted by our research team [89]. It is possible that some participants left the survey and returned to it later, which could explain the slightly higher response time than our estimated 25 minutes. Given that the scales in study 2 will be made more concise through psychometric analyses applied to responses from this study, we expect the survey in study 2 to be shorter in length. Of the 1392 participants who were eligible and began the survey, 1230 (88.36%) participants completed the survey, with an attrition rate of 11.64% (162/1392) (refer to Figure 4 for a diagram detailing participant attrition). Attrition primarily occurred in the HPV attitudes and beliefs section (50/162, 30.86%), which is the longest section of the survey, with 44 items. We expect that the validation and shortening of this scale for study 2 will help to address this issue.

Figure 4. Study 1—participant flow diagram. BWS: best-worst scaling; HPV: human papillomavirus.



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Study 2: Expanded Population-Based Survey of Canadian Women

Methods

Study 2: Ethics Approval

Study 2 received approval from the research ethics board of the Centre intégré universitaire de santé et de services sociaux West-Central Montreal (project ID 2022-2960) in July 2021. Informed consent will follow the same procedure as that in study 1.

Study Design

A cross-sectional web-based survey will be administered in summer of 2022 to a nationally representative sample of Canadian women, aged 21 to 70 years, in English and French. The study population and inclusion criteria will be the same as those in study 1. Oversampling will be used to ensure that half of the sample is adequately screened and the other half is underscreened. Additional quotas will be used for the following factors: age, household income, and rural or urban residence (considering low cervical screening rates in rural Canada [7]) based on census data from Statistics Canada. Data collection will be conducted by Dynata, following the same procedure as that in study 2.

The questionnaire will follow the same structure and include the same sections as the survey detailed in study 1. Of the knowledge, attitudes, and beliefs items used for scale development in study 1, only those items retained after extensive psychometric analyses will be used in the study 2 questionnaire as part of the resulting shorter, validated scales. In addition, 2 previously validated measures, the extended HPV General Knowledge and HPV Vaccine Knowledge scales, will be added [69], given the relevance of HPV and HPV vaccination in cervical cancer. The measurement of the outcome variables (intentions to screen using the HPV test and self-sampling) is informed by PAPM [81], a categorical, stage-based model of health decision-making. As a binary, *yes or no* outcome limits accuracy, using a multistage model provides a more precise, nuanced understanding of women's decision-making process that acknowledges the unique barriers associated with movement between each stage toward engaging with the behavior [90].

Sample Size

We calculated the sample size based on the estimation that approximately 30% of women will be in each of the PAPM adoption stages, *unengaged*, *undecided*, and *decided to*, and 10% will be in the *decided not* stage. As multinomial logistic regression can be considered as a series of binary logistic regressions, we based our calculations on the work of Peduzzi et al [91], which recommends a minimum of 10 observations per variable and the formula, N=10k/p, where N is the minimum number of observations needed, k is the number of predictor variables, and p is the smallest proportion in the binary model, that is, N = (10 × 15) / 0.25 = 600. Therefore, the minimum sample needed to reach sufficient power is 1500 because 40% of the sample (eg, unengaged+decided not) must represent 600 observations. Given that our objective is to estimate the association between psychosocial factors and intentions of HPV testing in both underscreened women and adequately screened women, we need 3000 (ie, 1500 in each group) valid responses to perform the analyses. Considering that an oversampling of maximum of 18% is required to account for careless responses, the approximate total number of survey responses needed is 3650.

Data Analysis

Corresponding to objective 1, we will conduct univariate analyses (means and proportions) for scale items (eg, knowledge and attitudes) and bivariate analyses (2-tailed *t* tests and chi-square tests) to estimate the differences between adequately screened women and underscreened women. We will calculate the effect size using Cohen *h* and Cohen *d* for proportions and continuous variables, respectively. Corresponding to objective 2, we will estimate the associations between psychosocial factors and intentions of HPV testing and self-sampling using multinomial logistic regression and model the log odds of PAPM stages (dependent variable) as a linear combination of the independent variables (eg, HPV testing knowledge and BWS preference scores). We will report odds ratios and 95% CIs of being in a PAPM stage versus the reference category (ie, unengaged) for each independent variable. Initially, we will conduct bivariate analyses to estimate the association between the outcome and independent variables. Then, independent variables showing significant associations (P<.10) will be entered simultaneously in the final model. We selected the following indices to report model fit: (1) Cox-Snell R^2, (2) Cragg-Uhler R^2, and (3) McFadden R^2 [39,92]. We will use the Hausman-McFadden test to evaluate the final model for independence of irrelevant alternatives, which postulates that a person's choice (ie, PAPM stage) is unchanged by other available choices (ie, fewer PAPM stages) [93]. Analyses will be conducted separately for underscreened women and adequately screened women. Analyses will be conducted using SPSS (IBM Corporation), R software (R Foundation for Statistical Computing), and STATA (StataCorp).

Results

As of May 2022, data collection has not begun for study 2. Data collection is expected to begin in June 2022 or July 2022, and results are expected to be published in late 2022 and early 2023.

Discussion

Principal Findings

This study will use 2 complementary cross-sectional web-based surveys of Canadian women to develop psychometrically tested scales measuring cervical cancer knowledge, HPV testing knowledge, HPV testing attitudes and beliefs, and HPV self-sampling attitudes and beliefs and, then, include these scales in a broad survey to investigate the psychosocial correlates of women's intentions to engage in HPV-based cervical cancer screening.

Scales developed in study 1 will be informed by measures in the extant literature and further enhanced by the generation of new items based on systematic evaluation of themes in the

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psychosocial literature on HPV testing. Using the TPB and HBM to guide item selection will further ensure that the scales provide meaningful insights into the factors affecting screening behaviors. Application of advanced psychometric methods, including item response theory, which facilitates the development of parsimonious measures [94], will help to ensure that the scales are comprehensive, while being brief and easy to administer. We expect the cervical cancer knowledge scale to expand on the psychometric methods applied for similar measures such as the Cervical Cancer Awareness Measure developed by Simon et al [44] and the HPV testing knowledge scale to show increased reliability compared with the existing subscale developed by Waller et al [48]. The HPV testing and self-sampling attitudes and beliefs scales will expand on existing measures by using advanced psychometrics in an up-to-date and representative sample. Accordingly, we expect our scales to represent a new measurement standard for investigating the attitudes, beliefs, and knowledge associated with HPV-based screening. In addition, the use of BWS to estimate preferences for cervical cancer screening will enable evaluation of women's perceptions of trade-offs between different testing methods, and importantly, screening intervals and ages of initial screening. These changes have been barriers in other countries where HPV-based screening has been implemented [22,52].

Our expanded population-based survey (study 2) will provide comprehensive data to inform and support the development of Canadian HPV-based cervical cancer screening programs. Through objective 1, the specific evaluation of differences in knowledge, attitudes, and beliefs about HPV testing among women who are underscreened and those who are adequately screened will enable the development of targeted interventions to improve knowledge, address negative attitudes and beliefs, and reassure women about upcoming changes. In objective 2, analyzing the sociodemographic and psychosocial factors associated with screening intention stages will provide insight into developing interventions that consider the multiplicity of barriers to screening. Our investigation will offer a valuable response to calls to action to examine inequalities in cervical cancer screening in the interest of cervical cancer elimination [8]. Furthermore, by comparing women's knowledge, attitudes, beliefs, and preferences toward HPV-based screening with the proposed guidelines, our findings will help to inform screening recommendations and ensure successful transition from cytology to HPV-based screening in Canada.

Knowledge Dissemination Plan

To reach both research and health professional audiences, the study findings will be published in open-access, peer-reviewed scientific journals. Presentations will be made at national and international scientific meetings (eg, Canadian Association of Psychosocial Oncology, International Papillomavirus Society conference, and International Psycho-Oncology Society) and in webinars (eg, Consortium for Infectious Disease Control and International Papillomavirus Society). To reach policy makers, we will share a final research report with the Public Health Agency of Canada, CPAC, Canadian Task Force on Preventive Health Care, and provincial and territorial cancer screening program advisory boards. We will also share our results with nonprofit organizations such as the Canadian Cancer Society, the Society of Obstetricians and Gynaecologists of Canada, the College of Family Physicians of Canada, and HPV Global Action who have expressed strong interest in disseminating our results. We will produce content (eg, infographics) and engage with Canadian women on social media (Twitter, Facebook, etc). Research summaries will be drafted for dissemination to national media outlets to inform women about this public policy change and encourage discussions about HPV-based cervical cancer screening.

Strengths and Limitations

A major strength of this study is the rigorous and comprehensive process to develop psychometrically validated scales informed by theoretical frameworks. In addition, examination of the feasibility of the developed questionnaire through study 1 will ensure that the survey used in study 2 will be easy to understand and relevant to Canadian women. BWS presents an innovative approach to assess preferences that controls for biases observed in typical multiple-choice or ranking assessments of preferences. The use of PAPM to examine intentions toward HPV testing and self-sampling will provide a theoretically informed and nuanced understanding of women's decision-making compared with other studies using continuous or binary measures. Using a market research polling firm will enable time-efficient and cost-efficient recruitment and data collection. Furthermore, the web-based survey methodology will prevent the issue of missing data. Quota-based sampling will allow us to recruit a nationally representative sample based on recent census data. Attention check items and data cleaning techniques will allow us to identify and exclude unmotivated or *careless* responders, ensuring that high-quality data will be collected and analyzed.

The study design has some limitations. Relying on respondents' self-report for their screening history of having had a Pap test in the past 3 years or not is subject to recall bias. Our anonymous web-based survey design prevents us from verifying it against health records data. To minimize this limitation, women will be provided with a reminder informative statement explaining what a Pap test is and how it is performed before asking them about their screening history. Given that the COVID-19 pandemic has prevented and continues to prevent women from engaging in cervical cancer screening, this may affect women's report of their screening history and change the composition of women in our *underscreened* and *adequately screened* categories. It is not clear how this will affect our data, as the effect of the COVID-19 pandemic on screening access in Canada is not well understood in most provinces and territories [95]. To address this issue, we will include an item asking those participants who report being underscreened whether the COVID-19 pandemic had prevented them from receiving screening, and sensitivity analyses will be performed to examine the pandemic's impact on screening. In addition, the lack of investigation at 2 different time points precludes any investigation of how intentions for HPV testing and self-sampling may relate to uptake and acceptability as these testing methods are introduced. Longitudinal examinations of acceptability and intentions toward HPV-based screening will be needed as implementation occurs in Canada. Unfortunately, our study design and recruitment strategy may preclude specific analyses in gender and sexual minority groups, considering the

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low case counts observed in population-wide web surveys (eg, 0.4% gender-diverse individuals in study 1). Recognizing the unique barriers faced by these groups in screening for cervical cancer, future research should specifically investigate the perceptions of gender and sexual minority Canadians toward HPV testing and self-sampling implementation [3,14,96]. Similarly, comprehensive understanding of cervical cancer screening and HPV in the First Nations, Inuit, and Métis populations is critical [5,34]. Our study could highlight certain issues in these populations (considering 2.9% representation in study 1), but unique participatory action initiatives involving relevant nongovernmental organizations and community advocacy groups are needed to fully understand their views and address their concerns.

Conclusions

Understanding the psychosocial factors that might affect women's perceptions of and intentions to engage in HPV-based screening will be critical as Canada plans to implement changes to cervical screening programs and guidelines. Through this multistep study, we will develop several validated scales to facilitate population-based investigations of these factors by other researchers. The use of these scales to investigate a representative sample of Canadian women's perceptions of HPV-based screening will provide directly applicable knowledge to public health and health care professionals.

Acknowledgments

This study was supported by the Canadian Institutes of Health Research (CIHR) project grant (funding reference number 165905; refer to peer-reviews in Multimedia Appendix 3). OT is supported by the CIHR-Frederick Banting and Charles Best Doctoral award (award number FBD-170837) outside the submitted study. GKS is supported by the Edith Kirchmann Postdoctoral Fellowship at Princess Margaret Cancer Centre and by a CIHR 2019 fellowship award (CIHR MFE 171271) outside the submitted study. The authors thank Eduardo Franco (McGill University) for his feedback on the project's aims and design and survey content. The authors also thank Johnny Dagher (Dynata) and his colleagues for their expert help in programming and administering the survey for this study.

Data Availability

The data sets that will be generated through this study will not be published in a publicly available repository in accordance with the ethics proposal approved by the overseeing research ethics board. They will be available from the senior author (ZR) on reasonable request and upon agreement of confidentiality and data use policies provisioned by the primary institution. The full questionnaire used in the study will be available upon request to the corresponding author, and a detailed questionnaire outline for study 1, including several sample items for each section, is available in Multimedia Appendix 4.

Conflicts of Interest

GDZ has served as a consultant and advisory board member at Merck and as an advisory board member at Moderna and Pfizer. He has also received investigator-initiated research funding from Merck, which was administered through Indiana University. GKS reports obtaining consulting fees from the World Health Organization outside the submitted study. AKL is the provincial prime care lead for cancer screening at Ontario Health (Cancer Care Ontario). MS has received grants from Abbott; Becton, Dickinson and Company; Bio-Fire; Hologic; Roche; GlaxoSmithKline; and Merck. EMD has served as an advisory board member at Merck.

Multimedia Appendix 1
Example informative statement.
[PNG File , 520 KB - resprot_v11i6e38917_app1.png]

Multimedia Appendix 2
Checklist for Reporting Results of Internet E-Surveys (CHERRIES) checklist.
[PDF File (Adobe PDF File), 128 KB - resprot_v11i6e38917_app2.pdf]

Multimedia Appendix 3
Canadian Institutes of Health Research—external peer review reports.
[PDF File (Adobe PDF File), 34 KB - resprot_v11i6e38917_app3.pdf]

Multimedia Appendix 4
Study 1—detailed questionnaire outline with sample items.
[PDF File (Adobe PDF File), 715 KB - resprot_v11i6e38917_app4.pdf]

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Abbreviations

BWS: best-worst scaling
CFA: confirmatory factor analysis
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CIHR: Canadian Institutes of Health Research
CPAC: Canadian Partnership Against Cancer
EFA: exploratory factor analysis
HBM: Health Belief Model
HPV: human papillomavirus
PAPM: Precaution Adoption Process Model
TPB: Theory of Planned Behavior

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Protocol

Morbidity Patterns in Primary Care in Hong Kong: Protocol for a Practice-Based Morbidity Survey

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Abstract

Background: Up-to-date and accurate information about the health problems encountered by primary care doctors is essential to understanding the morbidity pattern of the community to better inform health care policy and practice. Morbidity surveys of doctors allow documentation of actual consultations, reflecting the patient's reason for seeking care as well as the doctor's diagnostic interpretation of the illness and management approach. Such surveys are particularly critical in the absence of a centralized primary care electronic medical record database.

Objective: With the changing sociodemographic profile of the population and implementation of health care initiatives in the past 10 years, the aim of this study is to determine the morbidity and management patterns in Hong Kong primary care during a pandemic and compare the results with the last survey conducted in 2007-2008.

Methods: This will be a prospective, practice-based survey of Hong Kong primary care doctors. Participants will be recruited by convenience and targeted sampling from both public and private sectors. Participating doctors will record the health problems and corresponding management activities for consecutive patient encounters during one designated week in each season of the year. Coding of health problems will follow the International Classification of Primary Care, Second Edition. Descriptive statistics will be used to calculate the prevalence of health problems and diseases as well as the rates of management activities (referral, investigation, prescription, preventive care). Nonlinear mixed effects models will assess the differences between the private and public sectors as well as factors associated with morbidity and management patterns in primary care.

Results: The data collection will last from March 1, 2021, to August 31, 2022. As of April 2022, 176 doctor-weeks of data have been collected.

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Conclusions: The results will provide information about the health of the community and inform the planning and allocation of health care resources.

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International Registered Report Identifier (IRRID): DERR1-10.2196/37334

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KEYWORDS

morbidity survey; primary care; general practice; family medicine

Introduction

Primary care is the setting where the majority of people will seek health care. Studies on the ecology of health care show this is the case in the United States, where 52% of patients who consulted a doctor in the past month saw a primary care doctor [1], and also in Hong Kong (84.5% of patients) [2]. Information about the health problems of patients presenting in primary care is therefore crucial to understanding the health of the general community for the planning and allocation of health care resources.

It is important to replicate morbidity surveys from time to time given changing demographic and socioeconomic profiles. In Hong Kong, the last morbidity study was carried out in 2007-2008 [3]. Within the last 10 years (2005-2015), there has been an increase in the proportion of people aged 65 years or older, level of educational attainment, individual and household income, and cross-border immigration from mainland China, while there has been a notable decline in unemployment [4]. These sociodemographic changes are reflected in the health problems and concerns of patients who present to primary care and also in the changing prevalence of various diseases over time [5,6]. Practice-based morbidity surveys conducted at 10-year intervals have been able to capture changes in the prevalence and trends of health problems presenting in primary care as observed in England and Wales (1991-2001) [6] and in Hong Kong (1994-2007) [3,7].

Superimposed on this background is the expectation that chronic disease and psychological problems will continue to be a major burden of illness globally and in Hong Kong as we move deeper into the 21st century [8]. There is increasing pressure for primary care to shoulder the care for the majority of these patients given the volume of patients and the demonstrated effectiveness and cost-effectiveness of family doctor–led primary care [9]. Local Hong Kong evidence shows that chronic disease makes up an increasing proportion of problems seen by primary care doctors, with the bulk of patients seen in public outpatient clinics [10].

Since the last morbidity study in Hong Kong in 2007-2008 [3], the Hong Kong Government has implemented some primary care initiatives in response to the increasing burden on public general outpatient clinics (GOPC) such as the GOPC Public-Private Partnership, Elderly Health Care Voucher Scheme, and the Vaccination Subsidy Scheme. These aim to encourage patients to seek care in the private sector, particularly for care of chronic diseases. Tracking morbidity and management trends would provide an indication of the impact of these initiatives on the prevalence of chronic disease and its care in both public and private primary care sectors.

Apart from the morbidity pattern, specific information on the management pattern such as prescription, investigation, referral to specialists, health promotion, and disease prevention is important for assuring the quality of primary care services and for identifying support services needed. In 2014-2015, there were an estimated 6 million primary care encounters in the public sector alone [11], which extrapolates to about 30 million primary care encounters in the combined public (20% of total encounters) and private sectors across Hong Kong [12]. The most recent morbidity study found that the Hong Kong referral rate to specialists was 2.5% in 2007-2008 [3], which means that even a small increase of 1% in referral rate would produce a huge relative increase of 40%, translating to an additional 300,000 specialist referrals. Changes in consultation trends in primary care do occur [13], with substantial potential impact on health care service needs and expenditures, and must be monitored.

With an aging population, increasing prevalence of chronic disease, and the implementation of primary care initiatives to shift some of the burden of chronic disease care from the public to the private sector, a primary care morbidity study is timely and important to document and evaluate the impact of these changes.

This study aims to determine the changes in morbidity and management patterns in Hong Kong primary care compared with the patterns identified in the morbidity study conducted in 2007-2008 [3]. Specific objectives include the following:

1. To identify and describe the patterns of morbidity in primary care
2. To determine the management patterns of primary care doctors including prescription, investigation, referral, and preventive care
3. To examine the differences in morbidity patterns in public and private health care sectors
4. To determine the doctor and practice characteristics associated with morbidity and management patterns in primary care

Methods

Study Design

This is a prospective practice-based survey of Hong Kong primary care doctors that will explore the morbidity and management patterns in primary care to inform health care service and practice.

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Subjects

The target population in this study is primary care doctors in Hong Kong. We will invite doctors practicing in different primary care settings and in different regions of Hong Kong to join the study, reflecting the range of problems that may be characteristic of demographically different settings. We will include doctors working in the public (GOPCs and Department of Health clinics) and private sectors (solo practices, university health services, nonprofit organizations, and private hospital family medicine clinics).

Sample Size Calculation

The sample size calculation is based on the first two primary objectives of our study, which are to determine the proportion of health problems/diagnoses among all clinical encounters and the proportion of various management activities in terms of prescription, investigation, referral, and preventive care. The 2007-2008 morbidity study found that respiratory conditions comprised the largest proportion of problems (36.2%) and among these, upper respiratory tract infection was the most common diagnosis (26.4%) [10]. On this basis, if we conservatively anticipate the proportion of a type of health problem/diagnosis to be 50% with a confidence interval of 95% and a maximum error of 0.5%, we will need to encounter at least 38,415 health problems over one year. This translates to about 10,000 health problems per season. In the 2007-2008 morbidity study, 109 doctors recorded 69,973 health problems over the course of the year, which meant that on average, each doctor encountered about 250 health problems in one week. Based on this estimation, 40 doctor-weeks will be required to encounter the requisite number of health problems for each season. Assuming there is a one-third dropout rate of doctors, 60 doctor-weeks per season will be required. According to a general population study on service utilization patterns in primary care, around 80% of those who visit a Western medical practitioner would attend a private clinic whereas the remaining 20% would attend publicly funded primary care services [12]. Considering this, we need 48 doctors from the private sector and 12 doctors from the public sector to participate in the study.

Recruitment of Subjects

Because there is no complete, publicly available primary care doctor register with contact information, we will undertake a targeted recruitment. We will recruit doctors in the Primary Care Research Network established during a previous study on the epidemiology of depression in primary care conducted by the Department of Family Medicine and Primary Care at The University of Hong Kong. This resulted in a network of 60 primary care doctors across 45 practices who expressed interest to participate in future research studies [14]. In addition, we will invite members of the Hong Kong College of Family Physicians, honorary teachers of the Department of Family Medicine and Primary Care at The University of Hong Kong and the Division of Family Medicine, School of Public Health at the Chinese University of Hong Kong. We will also specifically target doctors listed in the Primary Care Directory, a voluntary directory, and the doctors listed as service providers in the GOPC Public-Private Partnership Programme on the corresponding websites. Those who are interested will receive a briefing on the study by the principal investigator and/or a member of the research team and provide written informed consent if they wish to participate.

Data Collection

Data collection will take place for one week in each month of the year for 18 months starting March 2021, resulting in 18 designated weeks of data collection. This will permit evaluation of the variation in morbidity through the fifth and most serious wave of the COVID-19 pandemic in Hong Kong and across seasons, which has been a significant consideration in previous studies. Seasons may be divided into 3-month periods based on historical climatological data with spring as March-May, summer as June-August, autumn as September-November, and winter as December-February. Thus, there will be 3 weeks of data collection in each season. The study will run over 18 months to capture temporal trends as well as seasonal variation of diseases such as influenza. The first full week of each month in which there are no public holidays will be designated as the data collection week to maximize the number of working days. The week will be defined as 7 consecutive days from Sunday-Saturday as most private doctors in Hong Kong work on weekends and public GOPC are open for a half-day on Saturday. Each participating doctor will collect data on consecutive patients during any of the designated weeks of each season for a total of 6 weeks of data collected per doctor. The research team will collect all completed forms after each data collection week. All data will be checked for proper coding and be doubly entered, cleaned, and compiled into a central database for analysis.

Data Collection Forms and Tools

Background Information Form

Each doctor participating in the study will provide background information including demographics, practice characteristics, training, and involvement in government-coordinated primary care initiatives. To maintain anonymity, doctors will be allocated a unique identifier to link their background information with the patient encounter data collected.

Encounter Form

Doctors will manually record information on every patient encounter that occurs during the designated data collection week on a standard data collection form. The information on this form includes basic patient demographics (age and sex), whether he/she is a new patient, the presenting problem as stated by the patient, the diagnosis (or corresponding International Classification of Primary Care, Second Edition [ICPC-2] code) as determined by the doctor, the management activities undertaken, drugs prescribed, and preventive care interventions initiated. Doctors can complete most of the form with checkmarks or simple abbreviations and can write in the diagnosis/problem if they are not sure of the ICPC coding. Doctors in the public sector GOPC are already using ICPC coding in their usual practice and may find it routine to record diagnoses in this way. For forms completed with written diagnoses, trained research assistants will translate these to the corresponding ICPC codes.

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ICPC-2

ICPC-2 is the most widely used international classification for systematically capturing and ordering clinical information in primary care [15]. The ICPC-2 is widely used in general practice for the classification of three important elements of the health care encounter: reasons for encounters, diagnoses or problems, and processes of care.

Outcome Measures

Primary Outcomes

1. Prevalence of health problems and diseases presenting in primary care
2. Rates of management activities including referral, investigation, prescription, and preventive care intervention by primary care doctors
3. Distribution of health problems and diseases presenting in the public compared with the private primary care setting
4. Factors that affect the proportion and distribution of health problems in the public sector compared with the private sector

Secondary Outcomes

1. Prescription rates of specific classes of drugs
2. Seasonal variation in primary care morbidity pattern
3. Relationship between patient's presenting problem and doctor's diagnosis

Confounding Variables

1. Demographic information of patients
2. Practice sector
3. Nature of the health problem (acute or chronic)
4. Background characteristics of the doctor and the practice

Data Analysis

The patterns of morbidity in primary care will be presented by descriptive statistics for the prevalence of health problems and diseases, as well as the rates of management activities (referral, investigation, prescription, preventive care), weighted for the proportion of private and public primary care doctors in Hong Kong. The pattern of morbidity will be compared with the previous pattern in 2007-2008. All estimates will be accompanied by 95% CIs.

Stratified estimates in the patterns of morbidity in primary care by public and private doctors will also be reported and compared with the previous pattern in 2007-2008. The influence of the health care sector on morbidity patterns will be assessed by comparing the prevalence and rates of public and private doctors by nonlinear mixed effects analysis with logit link that accounts for potential covariance among health problems from the same doctor.

Factors associated with morbidity and management patterns in primary care will be assessed by nonlinear mixed effects model with logit link to cater for the dichotomous outcomes. Potential factors including patient demographics (age, sex), doctor background characteristics (age, qualifications, years of practice, type of practice, average number of consultations, participation in primary care initiatives), and nature of problem (acute, chronic, preventive) will be taken as covariates in the model. Both univariable and multivariable analyses will be performed. In the multivariable analysis, the presence of multicollinearity will be assessed by examining the tolerance. Factors involved in multicollinearity will only be considered one at a time.

Ethical Approval

This study has received ethical approval from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 19-806), Hong Kong East Cluster (HKECREC-2021-091), Kowloon East Cluster (REC(KC/KE)-21-0124/ER-2), Kowloon Central Cluster (REC(KC/KE)-21-0131/ER-2), Kowloon West Cluster (161-01), and New Territories East Cluster (2021.368).

Results

Data collection started March 1, 2021. As of April 2022, 176 doctor-weeks of data have been collected. The data collection will continue until August 31, 2022.

Discussion

Overview

In determining the approach for this study, we reviewed different data collection methods for morbidity and clinical practice in primary care to support the conceptualization and methodology selected. Commonly used approaches in gathering health and health service data in primary care include population surveys, retrospective analysis on medical records or registers, and practice-based morbidity surveys using patient encounter forms. However, methodological or practical considerations may limit the usefulness of any of these methods.

Population surveys such as general household surveys about individual health conditions and health service usage provide a broad-based perspective, where health problems that have not been consulted can also be identified [16]. However, the reporting relies on patient recollection [17], and the accuracy of morbidity identification largely depends on patient's knowledge. Underreporting is also expected, especially for "sensitive" diseases such as sexually transmitted infections and cancer [16], or among older adult patients [18].

Data drawn from electronic medical records or registers of patient health care information provide rich databases for evaluating disease prevalence and morbidity trends in primary care as demonstrated in various international studies [19-24]. The data obtained are mostly accurate for medically diagnosed health problems. However, in the absence of centralized computerized databases, data retrieval may be difficult and labor intensive [25]. This is the case in Hong Kong, where centralized systems capture data only for the public government GOPCs, which provide only 20% of primary care.

On the other hand, practice-based morbidity surveys are a feasible option for capturing accurate and more comprehensive data [25]. They allow documentation of actual consultations, reflecting the patient's reason for seeking care and the doctor's diagnostic interpretation of the illness, which can be standardized by validated tools [16]. Both of these features are essential in health care service planning, which must rely on

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accurate information about health problems but also consider patient need. Because of this, such surveys continue to be used on a large scale in the United States, where the Centers for Disease Control and Prevention initiated the National Ambulatory Medical Care Survey in 1973 and has been running it annually since 1989 [26]. In Australia, the Bettering the Evaluation and Care of Health program collected general practitioner–patient encounter data for 18 years until 2016. These data were used widely for policy development and to improve Australian health care delivery and patient care [27]. Practice-based morbidity studies conducted in primary care settings have proven (and continue) to be a useful and reliable methodology for documenting disease prevalence and for service planning [6,10,28-32].

An issue that we encountered in the sample size calculation was whether we could assume that the number of health problems needed to encounter in each season should be evenly distributed. Such an assumption may not necessarily be reasonable, particularly for some season-specific diseases. However, based on the raw data of the earlier Hong Kong morbidity study, the overall most commonly occurring diagnosis was upper respiratory infection (26.4% of encounters), which was also the most commonly occurring diagnosis in all 4 seasons, ranging in frequency from 32.1% in winter to 22.7% in spring. The 14 diagnoses that account for >1% of visits were the same top 14 diagnoses across all 4 seasons and there was only variation in the order of frequency in each season. This is consistent with data from a study on the seasonal variation in diagnoses in primary care based on the United States National Ambulatory Medical Care Survey [33]. The key finding was that there was little seasonal variation among the 23 most commonly occurring diagnoses (which accounted for >1% of encounters)—only the rank order of the diagnoses varied from season to season.

As our sample size calculation is based on the primary objective of the study, which is to determine the prevalence of health problems/diagnoses among all clinical encounters, the calculation is derived from the proportion of the most commonly occurring diagnosis encountered in the earlier morbidity study. Since the most commonly occurring diagnosis accounts for 22.7%-32.1% of encounters in any given season, the conservative estimate of 50% that we used in our sample size calculation is reasonable to calculate the total number of health problems needed to encounter per season.

Limitations

This study was originally planned and approved prior to the start of the COVID-19 pandemic. We delayed the implementation in the hope that the pandemic would pass quickly but as this has not happened, we will proceed with the expectation that the effect of COVID-19 will be a limitation of the study as it is affecting usual patient health care–seeking behaviors including for chronic disease [34]. We will also seize the opportunity to capture the full period of the worst (fifth) wave of the COVID-19 pandemic in Hong Kong and to examine how stringent pandemic control measures by the Hong Kong Government affect primary care consultations, and presumably the patterns after the surge has eased and things have returned back to normal.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no complete data sets were generated or analyzed at this stage of the study.

Authors' Contributions

CLKL and JYC are the co–principal investigators of the study. JPYT is the project coordinator. CLKL, JYC, DC, SYW, and ET contributed to the study design. CLKL, JYC, and ET designed the sample. DC, SYW, ET, MKWL, WK, YCL, CC, WL, TD, MW, and WL helped to coordinate the study at local sites. JYC and JPYT drafted the manuscript. All authors read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Health and Medical Research Grant (HMRF) - Research Fund Secretariat, Research Office, Food and Health Bureau of Hong Kong.
[PDF File (Adobe PDF File), 3778 KB - resprot_v11i6e37334_app1.pdf]

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Abbreviations

GOPC: general outpatient clinic
ICPC-2: International Classification of Primary Care, Second Edition

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Protocol

The Health Impact of Social Community Enterprises in Vulnerable Neighborhoods: Protocol for a Mixed Methods Study

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Abstract

Background: This 4-year research project focuses on 6 social community enterprises (SCEs) that operate in 5 neighborhoods in a Dutch city. Residents of these neighborhoods face problems such as poor average levels of physical and mental health, high unemployment rates, and weak social cohesion. SCEs offer residents social, cultural, and work-related activities and are therefore believed to help these persons develop themselves and strengthen the social ties in the community. Because of a lack of empirical evidence; however, it is unclear whether and how SCEs benefit the health and well-being of participants.

Objective: This paper outlines a protocol for an evaluation study on the impact of SCEs, aiming to determine (1) to what extent SCEs affect health and well-being of participating residents, (2) what underlying processes and mechanisms can explain such impact, and (3) what assets are available to SCEs and how they can successfully mobilize these assets.

Methods: A mixed methods multiple-case study design including repeated measurements will be conducted. Six SCEs form the cases. An integrated model of SCE health intervention will be used as the theoretical basis. First, the impact of SCEs is measured on the individual and community level, using questionnaires and in-depth interviews conducted with participants. Second, the research focuses on the underlying processes and mechanisms and the organizational and sociopolitical factors that influence the success or failure of these enterprises in affecting the health and well-being of residents. At this organizational level, in-depth interviews are completed with SCE initiators and stakeholders, such as municipal district managers. Finally, structurally documented observations are made on the organizational and sociopolitical context of the SCEs.

Results: This research project received funding from the Netherlands Organization for Health Research and Development in 2018. Data collection takes place from 2018 until 2022. Data analysis starts after the last round of data collection in 2022 and finalizes in 2024. Expected results will be published in 2023 and 2024.

Conclusions: Despite the societal relevance of SCEs, little empirical research has been performed on their functioning and impact. This research applies a variety of methods and includes the perspectives of multiple stakeholders aiming to generate new empirical evidence. The results will enable us to describe how SCE activities influence intermediate and long-term health outcomes and how the organizational and sociopolitical context of SCEs may shape opportunities or barriers for health promotion. As the number of these initiatives in the Netherlands is increasing rapidly, this research can benefit many SCEs attempting to become more effective and increase their impact. The findings of this research will be shared directly with relevant stakeholders through local and national meetings and annual reports and disseminated among other researchers through scientific publications.

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KEYWORDS

social community enterprise; health; well-being; public health; social determinants of health; health inequalities; assets-based approach; conceptual modeling

Introduction

Background

Despite many efforts, national policy in the Netherlands has not been able to affect the persistence of health inequalities. The health of people with a low socioeconomic status (SES) has always lagged far behind that of people with a high SES [1]. Life expectancy of people with a low SES is 6 to 7 years lower than that of people with a high SES, and the difference in healthy life expectancy is even greater, namely 14 years [2]. In the Netherlands, socially vulnerable groups, including those with low SES, are generally less healthy and less engaged in health-promoting activities than higher SES groups [3]. As in many countries, health in the Netherlands is also unevenly distributed across residential areas [4,5]. An effective method in reducing health inequalities may therefore lie in a process-oriented neighborhood development approach [6,7]. Social community enterprises (SCEs) offer such an approach in which residents of disadvantaged neighborhoods can participate in society, be stimulated to live healthier lives, and play an active role in their own community's development. Examples of SCEs are organizations that run a small laundry facility in the neighborhood for vulnerable families, promote work activities for new immigrants, or organize cultural and creative activities in a poor district. It is crucial for a social enterprise organization that its objectives are primarily social, and that its surpluses, arising from revenues of commercial activities, are principally reinvested to achieve these social objectives [8]. If a large proportion of the participants come from the surrounding district in which the organization is located and its activities are strongly directed toward the development of the district and its residents, that organization is considered an SCE [9].

SCEs have been linked to various beneficial outcomes, at both individual and community levels. For instance, SCEs are expected to provide a cheaper alternative to costly governmental urban development and might contribute to safety and livability of the neighborhood [10], employment opportunities for excluded groups [11], and social inclusiveness [12]. In addition, Roy et al [13] found evidence that "social enterprise activity can impact positively on mental health, self-reliance/esteem and health behaviors, reduce stigmatization, and build social capital." However, past research has delivered limited evidence of the benefits of SCEs, and empirical studies on how and to what extent they can contribute to health and well-being are rare. Research on beneficiaries, such as participating residents, is similarly scarce [13].

It remains unclear how and to what degree the activities of SCEs impact the health and well-being of residents in vulnerable districts. Therefore, as a first goal, this paper outlines a protocol for an evaluation study aimed at gaining more insights into the health outcomes of SCEs at individual and community levels, specifically investigating the extent to which SCEs affect the health and well-being of participating residents.

Besides outcomes, surprisingly little empirical research has been done on the underlying processes and mechanisms of health impact [14,15]. Thus, it remains unclear how involvement in the activities of SCEs might lead to improved health outcomes. It is known that many SCEs organize social as well as commercial activities on a neighborhood level. What this research aims to clarify is how participating in these activities might strengthen people's health. Possibly important factors here are an increase in self-esteem, the prospective of having weekly social activities such as a weekly lunch or walking exercise, or a sense of belonging and ownership.

SCEs seem to share some common features with social care farms and green citizen initiatives, such as an orientation toward empowerment, strengthening of assets, and a focus on communities [16-18]. Care farms combine agricultural production with health, social, and educational services, like the provision of day care, supported workplaces, and residential places for clients with a variety of disabilities [19-21]. Green citizen initiatives constitute urban-based services such as community and institutional gardens or city farms. In particular, social care farms entail a shift in care in recent decades characterized by the terms deinstitutionalization, socialization, and normalization and a shift from institutional to community care. Studies based on the experiences of social care farms and green citizen initiatives indicate that, for a variety of citizens with specific needs, the key to improving the quality of life of participants in SCEs lies in meaningful and activating activities, a safe and welcoming community, and an informal context that is close to normal life [16,22]. Thus, it is important to understand the interplay that takes place between participation in SCE activities and health development and to create insight into the processes and mechanisms that underlie it. Therefore, the second goal of the evaluation study is to gain more insights into the processes and mechanisms that are at work in these SCEs and that determine the impact of the residents' participation on outcomes of health and well-being.

Whether an SCE has impact on the health and well-being of residents is also determined by the organizational and sociopolitical context in which these initiatives operate [13]. One crucial condition is that this context can create opportunities for the SCE initiatives to thrive and strengthen the assets of individuals and communities [12]. Context concerns factors such as the capabilities of initiators; their organizational form; legal setup; number of activities and projects; management style of the organization; district in which SCEs operate and communities that are linked to them; networks of boards; funding from government officials and commercial, social, or cultural organizations; and collaboration with such institutions. For example, De Bruin et al [23] state that care farming organizations, which combine commercial and social activities in a similar way to SCEs, require an empathic, creative,

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innovative staff that knows how to align meaningful activities with personal needs, support a sense of mastery, and facilitate engagement of participants.

These factors might be decisive for the extent to which SCEs can succeed at improving the well-being of residents and the livability of districts. This success has to do with their position in relation to other stakeholders in the context of the market, and of the local, regional, and national government. One crucial contextual factor might be the capacity of these initiatives to create collaboration with governments, nongovernmental organizations, and commercial parties that can provide the necessary conditions for sustaining and expanding their activities [12]. Another crucial consideration is whether efforts from the SCE in building collaboration with other stakeholders will also provide participants with opportunities to strengthen their assets. In that sense, it is relevant to investigate to what extent the SCEs use organizational strengths such as the capabilities of initiators and efforts of volunteers to successfully create conditions in their environment that lead to improved health and well-being of residents and communities. Hence, a third goal of the evaluation research is to explain how the potential of SCEs in strengthening individual and community assets is determined by organizational and contextual factors.

Theoretical Framework

The theoretical basis of the evaluation research can be found in an asset-based model of health and 2 conceptual models, namely the social enterprise intervention model by Roy et al [13] and the empirically informed conceptual model by Macauley et al [24]. On the basis of these models, we have constructed an expanded model that functions as the theoretical framework of this research.

Asset-Based Model of Health

The asset-based model of health emphasizes the capabilities of persons and opportunities for collaboration in communities and organizations to sustain and promote health [25,26]. The approach is based on the salutogenic model of health [27], which means that by focusing on assets instead of problems or deficiencies, it is possible to identify factors and mechanisms that allow people to move toward the health end of the spectrum between ill health and health. The fundamental premise is that individuals will do better in the long run if they are supported to identify, recognize, and use the strengths and resources available in themselves and their environment [28,29]. On a community level, asset approaches can help people to discern and use those skills, resources, knowledge, and connections within communities that can promote health and support well-being [30]. For instance, social enterprises can be effective in providing employment opportunities and creating more enterprising communities [11]. By strengthening residents' assets, SCEs can contribute to social cohesion and improve their quality of life, health, and well-being [12]. Moreover, low-income residents involved in these community initiatives can accrue 4 different nonfinancial assets (ie, social, cultural, human, and political capital) that can improve their health and well-being [25,31]. This is an iterative process in which residents' improved health and well-being further support the acquisition and development of new assets.

According to Benenson and Stagg [31], SCEs may call on the assets that are already available in the community as well as enable the development of new assets on both individual and community levels. The activities of the SCEs aim to strengthen the capacities of residents to participate in society—for example, by offering skill lessons for getting a job or by developing additional social relationships to reduce loneliness. On a community level, these enterprises may seek to support community health by creating a green and safe physical environment and by increasing social cohesion. We expect that increased availability and use of individual and community assets will support residents and communities in dealing with the challenges they face, thus strengthening their health and well-being. For example, by sharing experiences on health issues in familiar settings, participants may strengthen their health literacy.

Integrated Model of SCE Health Intervention

The theoretical framework is further based on the integration of 2 conceptual models developed to strengthen our understanding of how SCEs can contribute to health outcomes. Both aim to describe how activities by SCEs can impact intermediate and long-term health outcomes. The first is the model by Roy et al [13], and the second is the model by Macauley et al [24]. To fit our research questions, several adaptations have been made to these models to create an integrated model (see Figure 1).

The model by Roy et al [13] puts forward a chain of causality containing the different steps through which intermediate and long-term health outcomes are generated. These steps involve the (1) internal and external factors determining the social mission of a social enterprise, (2) intervention, (3) intermediate effects, and (4) long-term outcome. The assets include emotional well-being, social networks and relationships, good work, and social functioning. The long-term outcomes revolve primarily around social capital, connectedness, and sense of coherence, leading to improved health and well-being. The elements describing the factors that determine the social mission of the SCEs are necessary to answer our second research question on processes and mechanisms and our third question on assets. From this model, we have reframed the factors determining the social mission as the organizational and sociopolitical context.

In their model, Macauley et al [24] elaborate in more detail on the long-term health outcomes on which SCEs might have an impact. In this model, these are improved sense of meaning and control; economic impact; access to services; enhanced confidence and self-esteem; employment, employability, and meaningful work; enhanced social networks; and positive spaces and environments. In line with the assets model by Morgan and Ziglio [26], the health outcomes of the model by Macauley et al [24] can take place on 3 levels: individual, community, and system. Thus, the model describes the impact exerted on the different levels by processes (ie, activities that, intentionally or not, may lead to positive health outcomes) and mechanisms which form chains of causality leading to better situations of health and well-being.

As a final adaptation, we have strengthened the aspect of communities and the sociopolitical context of the district and

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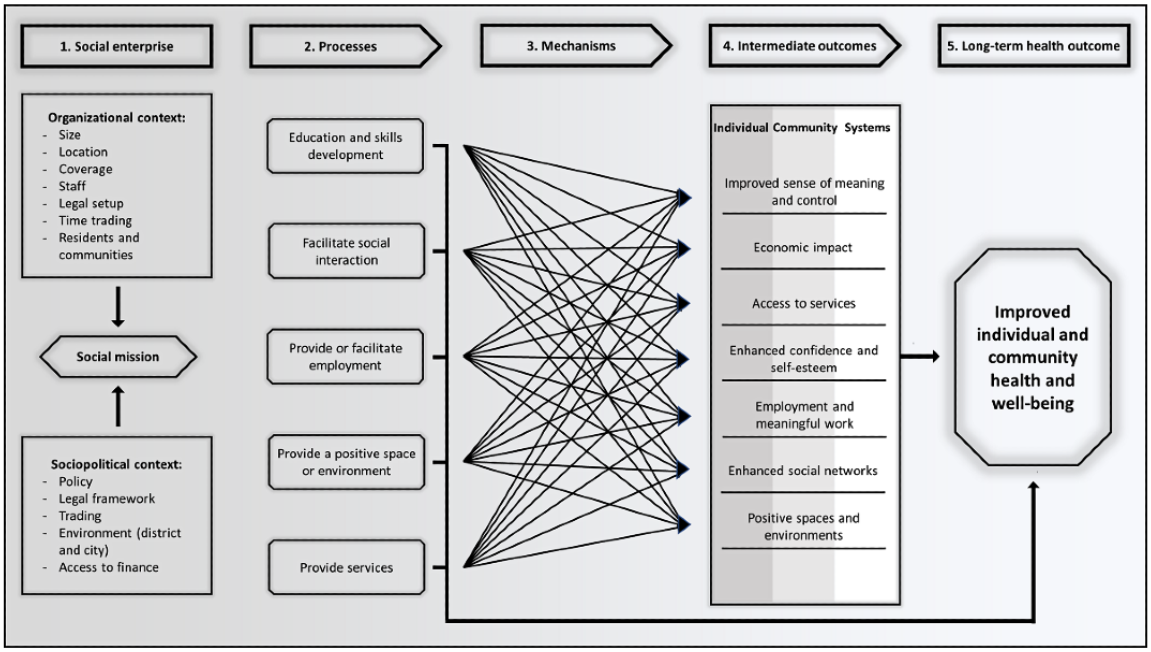
the city in our model (see under social enterprise, Figure 1). This also relates to a wider development in the Netherlands: the emergence of a stronger district-oriented approach by local government in the last decade, which has had an especially notable impact on the opportunities for neighborhood initiatives within the sociopolitical context in Dutch municipalities, and the rise of community-oriented social enterprises [32]. For example, SCEs that are embedded within specific districts might have the advantage that they can stimulate participation of residents in such communities more than organizations oriented on the level of an entire city. One of the reasons for a potentially higher impact is that these individuals might be more motivated by the fact that their efforts benefit the neighborhoods in which they themselves live. The integrated model combining the relevant analytical elements for our research is presented in Figure 1.

To conclude, the study outlined in this protocol aims to contribute knowledge on the potential of SCEs to impact health and well-being and reduce health inequalities. The following research questions were formulated:

- What is the impact of SCEs on health outcomes at individual and community levels?
- What underlying processes and mechanisms can explain the possible health impact of SCEs?
- What assets are available to SCEs through their organization and their context, and how can SCEs successfully mobilize these assets?

Figure 1. Integrated model of the social community enterprise health intervention based on Roy et al [13] and Macaulay et al [24].



Methods

Design

This research applies a mixed methods multiple-case study design including repeated cross-sectional measurements. The cases to be studied are 6 SCEs located across 5 vulnerable neighborhoods in a medium-sized Dutch city. We will use questionnaires, interviews, and observations as research instruments.

Setting

Before the start of this study, interviews will be held with the 6 selected SCEs to ensure that they conform to the definition stated earlier. All SCEs focus to a large degree on improving the district they are located in. They all operate in districts that face a combination of serious problems such as low average levels of physical and mental health, high levels of unemployment, low levels of participation and education, low levels of social cohesion and livability, and perceptions of deterioration and lack of safety of the neighborhood. Every community enterprise in our study aims to reduce these problems: that goal is the fundamental reason for the existence of the enterprise. A core principle these SCEs share is that they are convinced that the social problems should be dealt with through the participation and self-management of the district's residents. The community enterprises take the residents' assets as a starting point and develop activities from there onward. Other fundamental principles include taking an entrepreneurial attitude by the initiators and promoting such an attitude among their participants (eg, by creating a cooperative of small businesses).

The selected SCEs differ, however, in context, in the demographic profile of the districts and participants, in the differences in target groups, in the main problems of the residents and the districts, and in the type of entrepreneurs and activities. Some of these initiatives attract only vulnerable residents such as unemployed persons and asylum seekers, while others organize activities that are directed at all residents and attract persons with both low and high SES. Examples of activities are cultural activities for people to meet each other, activities that improve the neighborhood such as greening of public spaces and garden maintenance, and strictly commercial activities such as managing parking lots or a small bicycle shop. Depending on the type of activities, these SCEs attract from a

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dozen to a hundred persons on a weekly basis. The diversity of these social enterprises allows for a cross-case comparison demonstrating which processes and mechanisms apply to which contexts, and which types of asset building lead to which effects.

Data Collection

Health Impact on Individual and Community Levels

To evaluate the impact of the 6 SCEs on health and well-being, quantitative data will be collected from participants in the activities of the selected SCEs during the duration of the project. Data collection, including administering questionnaires and holding interviews, will take place at the locations of the SCEs. The anonymity of the participants will be safeguarded by several measures such as the use of separate rooms where residents can be interviewed and complete the questionnaires in private. The procedure for the selection and recruitment of the participants will be coordinated in advance with the initiators. In our study, participants of the SCEs will be recruited randomly by the researchers, except for those residents who the initiators believe might find participation too burdensome. Both participants and the initiators from the SCEs will be notified beforehand about the aim of the questionnaire, the main topics, and the anonymous way in which the information will be used, and their consent will be requested. Residents who start an activity in year 1 of our research will receive follow-up questionnaires for 3 years; residents who start in year 2 are followed for 2 years, and so on. This approach is expected to result in a sample of 270 participants across the 6 community enterprises (ie, 45 participants per neighborhood). Considerable effort will be put into encouraging residents who stop participating in the activities of the community enterprises to continue completing the questionnaires until the end of the project.

The outcome measures concern the intermediate health outcomes as presented in the integrated model (see Figure 1). On an individual level, these are sense of meaning and control; confidence and self-esteem; employment, employability, and meaningful work; and physical health. Physical health will be added as an outcome to the model, as the initiatives directly and indirectly influence health literacy by offering healthy lunches and social participation in sports activities. On the community level, the outcome measures are economic impact, access to services, social networks, and social cohesion. Several existing or validated instruments will be used as input for the questionnaire (see Table 1). Examples are the University of California, Los Angeles Loneliness Scale to measure social connectedness and the Dutch General Self-Efficacy Scale and Dutch Rosenberg Self-Esteem Scale to measure confidence and self-esteem. Table 1 describes which outcome measures are part of the questionnaire and the original instruments from which the questions were derived.

The questionnaires will be administered on paper or online. SPSS (version 25.0, IBM Corp) will be used for descriptive statistics for every measurement; the follow-up measurements will examine developments of participants. The data will be analyzed using multilevel regression models in SPSS and SAS (SAS Institute Inc) statistical software.

Table 1. References related to the questionnaire outcome measures.

Outcome measure	Original instrument
Educational level	• Municipal Report Livability and Safety in the Neighborhood 2017 [33] • GGD[a] Monitor Gelderland-Midden [34]
Social connectedness	• UCLA[b] Loneliness Scale–CBS[c] [35]
Living environment	• Municipal Report Livability and Safety in the Neighborhood 2017 [33]
Sense of meaning and control	• Adjusted version of the Daily Meaning Scale [36]
Confidence and self-esteem	• Dutch General Self-efficacy Scale–Short form [37-39] • Dutch Rosenberg Self-Esteem Scale [40]
Resilience	• GGD Monitor Gelderland-Midden [41]
Overall health	• GGD Monitor Gelderland-Midden [34] • PROMIS[d] Scale v1.2–Global Physical Health G03 [42,43]
Economic impact	• GGD Monitor Gelderland-Midden [34]
Self-perceived impact of participation at the SCE[e]	• The Work and Meaning Inventory [44]

[a]GGD: Municipal Health Services (Gemeentelijke Gezondheidsdienst).

[b]UCLA: University of California, Los Angeles.

[c]CBS: Central Bureau for Statistics (Centraal Bureau voor de Statistiek).

[d]PROMIS: Patient-Reported Outcomes Measurement Information System.

[e]SCE: social community enterprise.

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Underlying Processes and Mechanisms on the Individual Level

To understand the underlying processes and mechanisms on the individual level, interviews will be held with 2 groups. To gain a better understanding of the assets that are mobilized through community enterprises' activities, in-depth qualitative interviews will be performed with participants in those activities. Each year, 4 to 5 participants per SCE will be invited to take part, resulting in a total sample of 16 to 20 participants over 4 years for each neighborhood. The interviews will be held with people who have been involved in the activities for a longer period of time and who are also participating in the questionnaire research. The interviews will be conducted by members of the research team. Each interview will follow a predefined semistructured format. This will ensure that the retrospective interviews focus on understanding which individual and community assets are mobilized through the participation in the activities and how the mobilized assets lead to better health.

Participants and the initiators from the SCEs will be notified beforehand about the aim of the interview, the main topics, and the anonymous way in which the data will be used. At the start of the interviews, permission will be requested to record the conversation. All recordings will be transcribed, and both audio files and transcriptions will be stored at a secure site. The transcripts will be analyzed by thematic coding and content analysis using Atlas ti.8 (Scientific Software Development GmbH). This analysis will be directed at unravelling the mechanisms of change on an individual level. Quotes that reveal essential elements of the processes, mechanisms, and outcomes at stake will be selected to illustrate our findings. Furthermore, semistructured in-depth interviews with the initiators of the SCEs, district managers, and social district team employees will be conducted each year.

Underlying Processes and Mechanisms at the Organizational Level

Information at the organizational level will be collected by interviewing initiators of SCEs, social district team employees, and the district managers of the municipality. At least 3 persons per initiative per year will be interviewed, which will add up to a minimum of 45 interviews. Semistructured in-depth interviews will be scheduled during the first, second, and fourth year of the project, at time points to be determined, to be able to document changes in the approach of the community enterprises. The interviews will focus on the community and organizational assets mobilized through the SCEs. In addition, they will inquire about the constraining and facilitating factors in the collaboration between the community enterprises and other stakeholders, such as the local government. Besides that, the competencies and activities of the initiators, as well as their expectations, wishes, and experiences, will be explored. The interview questions will concern (1) changes in their approach and activities, (2) the participation and involvement of residents, (3) the assets of participants as individuals and groups, and (4) the initiatives themselves. The data from these interviews will allow us to identify the factors that play a role in the success of SCEs and the implementation of their activities in local policies. With these insights, the approaches of the enterprises and the policies of the municipality can be improved.

During the 4 years of the research project, observations per initiative will be made on the mechanisms of change on the organizational level through participatory research (ie, making notes during informal happenings) and from informal communication (eg, email conversation, phone calls) with the initiators. Using analytical schemes, structured observations will be collected in which we will describe the approach of the staff of the initiatives and their concrete actions and opinions, interactions with participants and stakeholders and their actions and opinions, and the processes and mechanisms described earlier. Comparisons between the SCEs and their organizational and political settings will be made. These insights will provide us with an improved understanding of success or failure of SCEs and their different approaches.

Data Triangulation and Analysis

By applying a variety of research methods, this study aims to assure the validity of this research and make it possible to examine different dimensions of the phenomenon of SCEs. Data from the questionnaires and interviews with participants, initiatives, and stakeholders will be combined with our own observations. This data will provide insights into the context, processes, and mechanisms at work that form potential pathways along which assets are strengthened and participants at SCEs can gain improved health. In particular, the insights into mechanisms that explain how participants' behavior is determined by their involvement in these community enterprises will make it possible to evaluate the complex components of approaches that target health improvement in such settings. In this way, elements such as the relationship with the initiator or the involvement in a local community can be identified as determining factors. By focusing not on projects but on the processes and mechanisms that form different pathways in varying contexts, our study can gain insights that are applicable to other settings.

This study will use data extracted from stakeholders to incorporate different perspectives on improvement of health into our analysis. Via methods such as interviews, questionnaires, and observations, insights can be questioned and tested to see if they support or contradict patterns derived from the separate research instruments. Information from the interviews with participants, initiators, and stakeholders can lead to the identification of mechanisms. The collected quantitative data can then be used to question and test these identified mechanisms.

Ethical Approval

Participants and initiators from the SCEs will be notified beforehand about the aim of the questionnaire, the main topics, and the anonymous way in which the information will be used. All participants will be asked to provide permission via a written consent form. It will be made clear to participants that participation is voluntary and withdrawal from the study is possible at any time for any reason. We will monitor the number of persons who do not want to take part in this study and will record their reasons for not participating. The data collected

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will be treated confidentially and pseudonymously, which means that identifiable elements will be collected separately and will be encoded. This will ensure that the data cannot be traced back to any of the participants. The data set will be encrypted and stored in a repository with restricted access. This research will be conducted in compliance with the ethical rules for social science research. We have acquired approval for this study from the Wageningen Social Sciences Ethics Committee (CoC number 09215846).

Results

This research project received funding from The Netherlands Organization for Health Research and Development in 2018. Data collection takes place from 2018 until 2022. Data analysis will start after the last round of data collection in 2022 and will be finalized in 2024. Expected results are to be published in 2023 and 2024.

Discussion

Scientific Relevance

Despite the societal relevance of SCEs, little empirical research has been performed on their functioning and impact [14,15,45]. As Roy et al [13] suggested, this protocol article describes an evaluation study whose aim is "to better understand and evidence causal mechanisms and to explore the impact of social enterprise activity, and wider civil society actors, upon a range of intermediate and long-term public health outcomes." The findings of this research can generate new empirical evidence on the health impact of SCEs and relevant processes, mechanisms, and organizational and sociopolitical contexts. With our results, we will be able to describe in more detail how the activities of SCEs can impact intermediate and long-term health outcomes and clarify the interplay between participation and health through the activities at these initiatives. More specifically, our research can contribute to the substantiation and further refinement of the conceptual model, as we already aimed to do in the integrated model of SCE health intervention presented in Figure 1.

Societal Relevance

Many policy makers deal with questions regarding the added health value of community enterprises for vulnerable residents and deprived communities [14,45]. In turn, many SCEs struggle when trying to clarify the impact they can have on residents and communities. As the number of community enterprises in the Netherlands is increasing rapidly, this research can be beneficial for many initiatives attempting to become more effective and increase their impact among residents in deprived neighborhoods by strengthening the assets of their organizations, participants, and districts. Next to improving SCEs, our research can provide more traditional welfare city-based organizations with insights on how to promote health via the context of district-based communities.

Strengths and Limitations

This study will follow 6 initiatives extensively during a prolonged period. These 6 SCEs can be described as diverse, yet they share a number of common principles. Therefore, during the research period, the research team will be able to study a wide range of settings and situations, providing the opportunity to study the impact of different approaches on health and well-being outcomes. We will follow the 6 initiatives throughout a period of 4 years. After each year, we will offer SCE professionals a report of the research results so that they can learn directly from the study. The SCEs will benefit from this research by learning from these insights and sharing their experiences, approaches, and methods with each other. In addition, in the third and fourth year of the research period, preliminary results will be shared on local, regional, and national levels with other SCEs and local and regional governments. Another strong point of this research is its mixed methods design. When different methods for measuring the same processes and mechanisms result in the same outcomes, this is extra support for our findings.

This study faces several challenges. First, to collect the data as described (ie, interviews, questionnaires and observations), this research will be dependent on the cooperation of many parties, namely the participants, initiators, and stakeholders such as the district managers and social district employees. This is a challenge that we aim to overcome by investing strongly in the relationships with the initiators and other stakeholders, even before the start of the research project. Regular meetings will be scheduled with the initiators during the project to maintain trusting and constructive relationships that provide a support base for this research.

A second challenge is that the number of respondents that can be recruited is dependent on possible growth or downsizing of the selected initiatives during the research period. At least 3 initiatives are limited in size and have been established recently. Hence, we must take into account that during the research period these initiatives might collapse, leaving us with limited collected data. In addition, an initiative may change its approach drastically; for example, it might cease to aim its activities at the neighborhood or at residents with low SES. We have taken this risk into account by selecting more initiatives than strictly necessary, which will make it possible to reach the required number of participants for this research even if one of the initiatives withdraws from the project.

Last, as many other factors can determine possible positive effects on the health of the participants of the SCEs, this research cannot deliver hard evidence for any causal relations between their health and their participation in activities at the SCEs. Likewise, this research will not entail control groups in other districts among different types of organizations. However, by using in-depth interviews, structured questionnaires, and observations, this research can apply data triangulation, which will make it possible to gain more insights into the causal relationships that determine the health outcomes at SCEs.

In addition to its internal validity, this research will also need to be externally valid. The fact that this research is limited to one municipality will restrict the extent to which the conclusions can be generalized to other situations. This problem will be partly overcome by the use of multiple, diverse cases. Finding comparable processes and mechanisms in these different settings

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will help to provide a basis for generalizing the results to comparable situations for SCEs in other sociopolitical contexts [46].

Valorization and Dissemination Plan

National and local governments can benefit from this research, as we provide insights into beneficial forms of collaboration between initiatives and government. In this way, this study can provide input to improve policy. In response to the inequalities mentioned above, it is Dutch policy to promote community-based health-enhancing programs that improve the health and well-being of socially vulnerable groups [47]. These programs emphasize intersectoral collaboration and build on concepts like supportive environments, community participation, and community ownership [3]. In line with this, there is a growing interest within national and local governments in involving residents in district-oriented entrepreneurial activities. The Dutch government has published a white paper that emphasizes its aim of supporting residents in taking up societal issues [48]. One way for residents to do so is to participate in an SCE.

Insights into the mechanisms of how SCEs possibly improve residents' health and well-being can make local policy and programs more effective. To promote our research results and recommendations for SCEs and local governments, we will organize local and national meetings and workshops at which SCEs and similar initiatives can exchange thoughts and findings with policy makers and other stakeholders. Furthermore, we will collaborate with expert organizations, such as the Provincial Alliance on Livability, Pharos (Dutch center for expertise on health inequalities) and Movisie (Dutch knowledge institute for social issues). Their role in this collaboration is twofold: to deliver expertise and offer us opportunities to discuss our results with other SCEs and local decision makers and policy advisors in the Netherlands.

The results of this research will be shared with other academics through publication in international open-access peer-reviewed journals. The quantitative data of this research project will be made available on request via the restricted access functionality in Data Archiving and Networked Services–Electronic Archiving System (DANS-EASY) after an embargo period to allow publication of results (maximum 2 years, conforms with DANS-EASY embargo period). The qualitative data are not open access but will be available on request.

Acknowledgments

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Authors' Contributions

LV, JH, and EH designed the study. EH took the lead in the writing of the manuscript. All authors have read and approved the final manuscript and contributed to the drafting and revision of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Review 1 decision project 531001317 by the Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw, The Netherlands Organisation for Health Research and Development) - Preventieprogramma 5 (Prevention Program 5).
[PDF File (Adobe PDF File), 60 KB - resprot_v11i6e37966_app1.pdf]

Multimedia Appendix 2
Review 2 decision project 531001317 by the Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw, The Netherlands Organisation for Health Research and Development) - Preventieprogramma 5 (Prevention Program 5).
[PDF File (Adobe PDF File), 58 KB - resprot_v11i6e37966_app2.pdf]

Multimedia Appendix 3
Review 3 decision project 531001317 by the Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie (ZonMw, The Netherlands Organisation for Health Research and Development) - Preventieprogramma 5 (Prevention Program 5).
[PDF File (Adobe PDF File), 56 KB - resprot_v11i6e37966_app3.pdf]

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Abbreviations

DANS-EASY: Data Archiving and Networked Services–Electronic Archiving System
SCE: social community enterprise
SES: socioeconomic status

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Protocol

Relationship Quality and Health Among Black Same-Sex Male Couples: Protocol for a Symbolic Netnography Study

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Abstract

Background: Across a range of studies, health scientists have found that being in a romantic relationship can have positive and negative influences on one's health. A couple's health outcomes are often influenced by relationship quality—or how they perceive the positive or negative character of their relationship. These findings have important implications for how scientists and interventionists may leverage romantic relationships facilitating good health among couples. However, in general, couples research has not included Black same-sex male couples in large enough numbers to make previous studies' findings relevant to them. This represents a gap in the scientific literature and, more importantly, a missed opportunity to understand how romantic relationships influence health for a group that must navigate distinct, multilevel health and social inequities.

Objective: This study aims to (1) decode and understand the ways in which Black same-sex male couples express their romantic relationships in virtual contexts via symbolic indicators, (2) determine how Black same-sex male couples describe the quality of their romantic relationships, and (3) explore how Black same-sex male couples make meaning of their relationship quality and its impact on their relational and individual health.

Methods: We will use joint dyadic interviews embedded within a symbolic netnography research design to accomplish our aims. We will use grounded theory to analyze our qualitative data. We will then triangulate our findings to determine how well they answer our research questions.

Results: This study received ethical approval on October 8, 2020 and we began data collection in November 2020. Results are expected to be available no later than December 31, 2022.

Conclusions: This study will apply novel symbolic netnographic qualitative methods to further our understanding of Black same-sex male couples' romantic relationships and how they contribute to their health. The findings will be used to develop programs to improve Black same-sex male couples' health in community and virtual settings.

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KEYWORDS

symbolic netnography; qualitative; relationship health; Afrocentric psychology; same-sex couples; Black sexual minority men; interdependence theory; methods

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Introduction

Background

Several psychological and public health studies have found that being in a romantic relationship can have positive and negative influences on the individual health of each partner and the couple as a unit [1-4]. In general, romantic partners mutually influence each other's health [5], and each romantic partner's health tends to become more similar over time [6]. These health outcomes are influenced by many factors, several of which are related to relationship quality. Relationship quality has been defined as one's subjective judgment of the positive or negative character of one's relationship [7]. Relationship quality encompasses a range of positive feelings and emotions, such as feelings of love, trust, care, affection, and commitment [8]. Social support for one's relationship has also been found to be a positive influence on relationship quality [9,10].

However, in general, couples research has not included Black same-sex male couples (BSMCs) in large enough numbers to make the available findings relevant to them [11]. This represents a gap in the scientific literature and, more importantly, a missed opportunity to understand how romantic relationships influence health for a group that must navigate distinct, multilevel health and social inequities. The few studies specifically about BSMCs have seldom focused on relationship quality and the factors that influence it outside of the context of HIV prevention [12-14]. For example, we know little about these couples' relationship intimacy, physical affection, and couple-level sexual orientation disclosure [9,15]. However, these factors may be assets that could be leveraged to promote relationship quality, mitigate health inequities, and promote holistic (ie, biopsychosocial-spiritual) health among BSMCs. Overall, there are several relational determinants that could affect these couples' relationship quality and health that are understudied or have not yet been identified.

Researchers who investigate these understudied and yet-to-be-identified factors affecting BSMCs' relationship quality and health will benefit from utilizing culturally specific frameworks that are relevant to future couples-based health interventions and policies for this group [16]. Qualitative methods are an appropriate starting point in developing and refining these culturally specific frameworks [17]. Qualitative methods will allow researchers to understand BSMCs in their own words. Researchers may also learn how these couples characterize and articulate their relationship quality and make meaning of its relationship to their health. We elected to use qualitative methods for these reasons. Specifically, we will use symbolic netnography and joint dyadic interviewing to gain an in-depth understanding of the couples' relationship quality and health, as well as to refine our culturally specific theoretical framework, described below, to explain how these factors influence each other.

Symbolic netnography is a qualitative research methodology that seeks to understand a group's cultural experiences as presented via social media [18]. Unlike media analysis, which examines portions of media content, symbolic netnography examines greater portions of communication, information, and culturally representative content that are mediated by technological platforms and applications. Symbolic netnography's cultural centering involves elucidating cultural elements found in social media communication, such as language, identities, values, and visual imagery (ie, photos, videos, and emoticons). Further, researchers are participant-observers, because they need to have an embedded cultural understanding of the phenomenon; otherwise, their interpretations become more descriptive than explanatory.

Theoretical Framework

The philosophical assumptions that underpin the present study are informed by an integrated Afrocentric interdependence theoretical framework that merges Optimal Conceptual Theory applied to sexual and gender minorities (OCT-SGM) [19,20], interdependence theory [21], and Wilson and colleagues' model [22] for Black men's positive mental health. Specifically, OCT-SGM is an Afrocentric theory that assumes the following [23]:

> *(a) Life happens in a spiritual context and...human beings are the physical manifestation of spirit (i.e., extrasensory energy that connects all life-forms); (b) good health is achieved through perceptual and behavioral alignment with the spiritual nature of life, (c) the relationships between the interlocking systems of oppression at the societal level interact with sexual and gender minorities (SGMs) intersecting identities at the individual level to confer privilege (e.g., socioeconomic resources) and disadvantage (e.g., intersectional stressors) that vary across time and context, and (d) SGM people's spiritual alignment and responses to varying levels of privilege and disadvantage mutually influence each other.*

From this perspective, spiritual alignment is fluid and can fluctuate from high to low. OCT-SGM is a holistic theory that can help us begin to understand how spirituality influences BSMCs. It should be noted that the spirituality discussed here is culturally specific to Black sexual-minority men and has been defined as follows [23]:

> *(a) [A] relationship with something greater than themselves, (b) part of themselves, (c) a guiding force in their lives, and (d) multidimensional in nature. The culturally-specific aspects of their spirituality were identified as being (a) an energetic union of masculine and feminine energy within their physical body, (b) connected to their ancestors, (c) an integration of the divine and the sensual, and (d) the use of spirituality to combat intersectional oppression.*

This definition of spirituality was developed from qualitative work conducted exclusively with Black sexual-minority men to understand their particular ways of making meaning of the sacred. It is important to note that scholars have conceptualized spirituality as a distinct construct from religion. Religion has been defined as "a shared system of beliefs, mythology, and rituals with a god or gods" [24]. There has been very little research related to the role of spirituality in same-sex couples' lives. Most of that research has been conducted with predominately white samples [25]. The limited research on this

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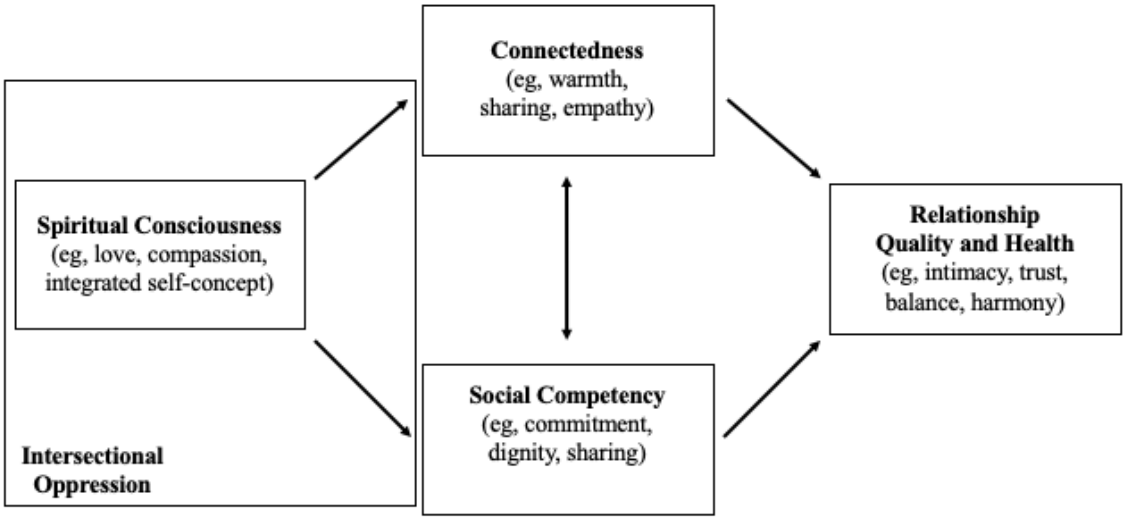
topic has found that religious same-sex couples believe that their religious and spiritual values add sacred meaning to their relationships [26]. Additionally, some couples have reported that they are subjected to the homonegative attitudes of others who use religious doctrine to justify their prejudice. These findings provide couple-level data but have very little relevance for BSMCs. The research studies they are based upon are not inclusive of these couples or grounded in their cultural realities. Our culturally specific framework of OCT-SGM may be applied at the couple level by examining it alongside interdependence theory.

Interdependence theory purports that partners in a couple mutually influence each other and make subjective judgments about those influences related to whether they confer rewards or costs to each individual partner and the couple as a whole [21]. The aim of interdependence theory is to "explain how two partners influence each other, how this shapes couples' interactions, and how these interactions determine the development of relationships" [21]. Interdependence theory helps make sense of how couples' individual and dyadic experience of their relationships helps to maintain them or lead to their termination.

Wilson and Williams [27] and Wilson and colleagues [22] proposed that positive mental health outcomes for Black men were tied to their ability to engage and enact consciousness, connection, and competency in their interpersonal relationships. Consciousness refers to one's level of spiritual consciousness (ie, spiritual alignment). Connection refers to one's relationships with one's spiritual nature, the spiritual nature of others, and the expression of the sacred in one's actions with others. Competency is one's ability to develop, choose, and effectively implement social, cognitive, behavioral, and affective skills to create and maintain equitable relationships and health. Taken together, positive mental health for Black men is directly related to the quality of their relationships.

Our integrated Afrocentric interdependence theoretical framework (Figure 1) proposes that BSMCs' health, as individual partners and as a unit, is determined by their ability to maintain perceptual consciousness and behavioral alignment with the spiritual nature of life as they navigate varying levels of privilege and disadvantage due to interlocking systems of oppression. These experiences of intersectional oppression have the potential to dampen spiritual consciousness and negatively affect the romantic relationship. These experiences may also help BSMCs rely more on their spiritual consciousness to make meaning of their experiences, both positive and negative, within and outside of the couple, as opportunities to enhance healthy relationship factors. High spiritual consciousness allows BSMCs to cultivate and share cultural strengths (eg, racial pride and adaptability) and develop integrated holistic self-concepts as Black sexual-minority men that contribute to self-love and compassion. This spiritual consciousness affects their ability to achieve substantive connection to themselves and their romantic partners and cultivate warmth, sharing, and empathy in their relationships. Spiritual consciousness also helps these couples cultivate perceptual and social environments that are conducive to developing social, cognitive, behavioral, and affective skills to deepen commitment, dignity, and sharing within their relationships. These factors (ie, spiritual consciousness, connectedness, and social competency) are interrelated, and when well-developed contribute to high relationship quality and good health [27].

Figure 1. Integrated Afrocentric interdependence theoretical framework.



We acknowledge that our integrated Afrocentric interdependence theoretical framework is highly conceptual at this point. This is purposeful, as we have attempted to explain the relationships between culturally specific psychosocial-spiritual elements of BSMCs' health. This level of innovation is necessary for two specific reasons. First, there is simply not enough currently available empirical work on these topics with this particular population. Second, it is imperative that we ground our understanding of BSMCs outside of Eurocentric epistemologies. We intentionally center the Afrocentric paradigm to counter Eurocentric ways of knowing and epistemologies of ignorance that highlight deficit and pathology-related foci and thereby sustain health inequities in their (explicit and implicit) perpetuation of oppressive ideologies [12,28]. Our theoretical framework provides a starting place to understand BSMCs' health in a way that is culturally grounded

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and holistic. The proposed study will serve as an opportunity to empirically refine our theoretical framework.

Study Aims

The aims of this study are to (1) decode and understand the ways in which BSMCs express their romantic relationships in virtual contexts via symbolic indicators, (2) determine how the couples describe the quality of their romantic relationships, and (3) explore how the couples make meaning of their relationship quality and its impact on their relational and individual health.

Methods

Ethical Approval

This study received ethical approval and oversight from the Rowan University Institutional Review Board on October 8, 2020 (IRB-FY2021-7).

Setting and Participants

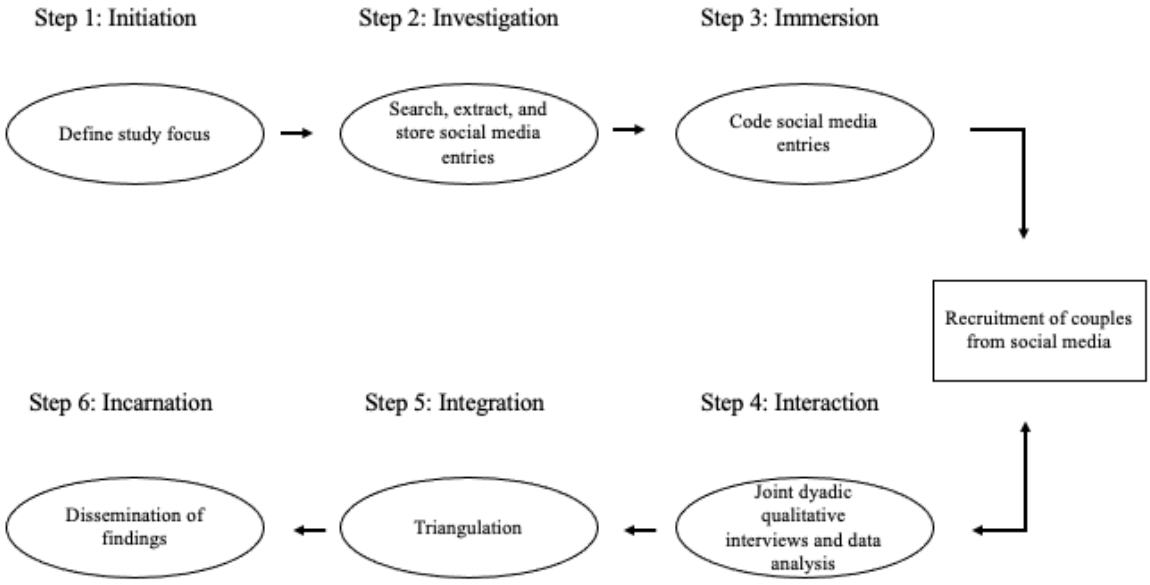
All study procedures will be remote and take place on online platforms (ie, Facebook, Instagram, Twitter, and Zoom videoconferencing). Only BSMCs will be recruited for this study. Both partners in the couple must self-report (1) being at least 18 years old; (2) having been assigned male sex at birth; (3) identifying as a Black (meaning of African descent) American man; (4) currently being in a committed (at least 3 months long) romantic relationship with each other [9], in which "committed" is taken to mean both partners consider their partner above anyone else and the relationship has been sexual [29]; (5) having access to a reliable high-speed internet service that allows for videoconferencing; (6) being able to proficiently speak and comprehend English; (7) being willing to participate in both the initial interview and the follow-up member checking interview; and (8) being able to provide informed consent. Each partner must also provide (via picture or video) a negative test result for HIV from within the last 6 months. Both partners are required to agree to participate in both interviews together at the same time.

Couples will be excluded if (1) at least one partner presents with severe intoxication at the time of screening or the interview; (2) at least one partner presents with active psychosis at the time of screening or the interview; (3) at least one partner reports current, ongoing intimate partner violence within the relationship; or (4) the couple breaks up between the first and second interviews. Couples who meet all inclusion criteria and have been determined eligible but meet exclusion criteria 1 or 2 will be offered the chance to complete their interviews at a later time (no more than 2 weeks later), when intoxication or mental health symptoms do not interfere with their cognitive and behavioral abilities. Couples who meet exclusion criteria 3 or 4 will be deemed ineligible for further participation in the study.

Study Design

This study utilizes two different qualitative methods, symbolic netnography and joint dyadic interviewing, to achieve its aims. The findings from symbolic netnography inform the data collection procedures for the joint dyadic interviews, which are embedded within the netnography design. Findings from both qualitative data collection methods will be integrated using Farmer and colleagues' triangulation protocol [30] to explore convergence and divergence between them. An overview of the study procedures is depicted in Figure 2.

Figure 2. Overview of netnography study procedures.



Symbolic netnography is a form of qualitative research that analyzes a specific group's cultural experiences as reflected in their online (eg, social media) presentations and interactions [18]. Such analyses are used as building blocks to understand people's behaviors, meaning-making strategies, values, and decision-making processes. This form of inquiry offers an opportunity to understand participants in contexts they control and in their own terms across presentation modalities (eg, pictures, text, sound, and video). This is especially important for BSMCs given the decreasing availability of physical social spaces (eg, bars and clubs) exclusively for Black sexual-minority men. Gentrification has contributed to venue owners who are

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Black sexual-minority men not being able to afford their rents [31]. Additionally, the unforeseen social realities of a post–COVID-19 world have complicated Black sexual-minority men's ability to gather in culturally affirming physical spaces [32].

Joint dyadic qualitative methodology assumes that a dyad's reality is coconstructed and thus utilizes qualitative interviewing with both members of a dyad [33]. In our study, couples will be interviewed together at the same time so that we can gain an understanding of how they create a joint picture and shared narrative of their relationship and its meaning. The joint dyadic qualitative interviewing is nested within the symbolic netnography. Overall, this methodology will ensure that the knowledge we discover is couples-based and directly applicable to couples-level health.

Symbolic Netnography

The symbolic netnography follows the six steps outlined by Kozinets [18]. These guidelines include: initiation, investigation, immersion, interaction, integration, and incarnation.

Initiation

This step encompasses the specification of the study's focus. The focus of this study is BSMCs' online presentations of their romantic relationships and the symbolic indicators that provide information about the quality of those relationships. Specifically, we are interested in the following symbolic indicators: terms of endearment, relationship commitment, physical affection, social performance of the romantic relationship, expressions of care, and love languages [34] (eg, verbal and nonverbal communication of care for one's romantic partner via such acts as providing words of affirmation, gifts, and physical touch). We will also examine how social support for the couple is expressed on social media.

Investigation

At the investigation step, we will search social media databases and select BSMCs' entries that present images, text, audio, and video displaying symbolic indicators of their romantic relationships. We have chosen Facebook, Instagram, and Twitter as the social media sites that comprise the landscape of this study. These sites were chosen due to high rates of use among Black sexual-minority men [35,36]. We will use an initial list of 29 hashtags to conduct our search for BSMCs' entries. These hashtags were developed through individual interviews with a convenience sample of 20 Black sexual-minority men who were active on social media. Examples of hashtag search terms include #blackgayweddings, #blackm4m, and #blackmenlovingblackmen. We will also utilize new hashtags that we discover in the process of our initial search to conduct subsequent searches. We expect to find a large number of entries and will use theoretical sampling (ie, sampling for entries that reflect concepts related to our integrated Afrocentric interdependence theoretical framework, such as intimacy, commitment, spiritual consciousness, and Black cultural pride) to select which entries will be included in the final dataset. We will read, watch, and listen to the information presented in the entries. Social media entries will be included if they (1) are composed of images, text, audio, or video; (2) are in the English language; (3) depict a BSMC; and (4) are created by the couple and not a profile or page that highlights other couples only. Social media entries will be excluded if they are (1) videos uploaded by government, professional, educational, or news organizations; (2) entries about someone else's romantic relationship; or (3) entries with product or commercial endorsements.

We will continue to archive entries until saturation (ie, no new information is discovered) is reached for each concept. Entries will be saved via screen captures. We will redact screen names from all entries and store them in a separate, secure dataset (described below). All entries will be given an ID number that corresponds to the screen name in the separate database. The deidentified entries will be stored in an NVivo database in a password-protected folder on the principal investigator's secure drive.

Immersion

In this stage, we will review the social media entries in the NVivo database and record our reflections (via memos) about our impressions of each entry. For example, for each entry we will reflect on (1) emotions that surfaced when coding the entry, (2) who this couple is, and (3) personal biases and assumptions about the entry. This reflection process will help us cultivate "high quality...'deep' data" [18] that illustrates the couples' cultural experiences of their romantic relationships. These reflections will be compiled in an immersion journal. Next, we will analyze the social media entries via coding. We have created a coding guideline protocol that we will use to assess the symbolic indicators of relationship qualities (ie, terms of endearment, relationship commitment, physical affection, social performance of the romantic relationship, expressions of care, and love languages). This coding protocol was informed by our integrated Afrocentric interdependence theoretical framework. We will use the coded social media entries to inform refinement of our integrated Afrocentric interdependence theoretical framework to better explain BSMCs' romantic relationship quality and expressions.

We will also create a separate dataset with the social media entries' screen names and the emergent theoretical concepts associated with each entry. The screen name dataset will serve as a directory (ie, participant pool). The concepts in the emergent theory will guide theoretical sampling from the screen name dataset. We will invite couples from the screen name dataset to participate in joint dyadic qualitative interviews until we reach saturation on each theoretical concept. In this way, the process is iterative. Based on previous research, we expect to reach theoretical saturation by 20 interviews. However, if new concepts continue to emerge, we will continue to invite couples for interviews and analyze their data until saturation is reached.

Interaction

Research assistants will send private messages to contacts via the social media site. The research team will create 3 social media accounts, 1 for each social media platform: Twitter, Instagram, and Facebook. All accounts will be linked to the study email address that we will register with Gmail. All usernames will be transparent and include the following term:

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"#blackgaylove Research Team." When contacting potential participants from the screen name dataset, we will immediately identify ourselves as researchers who are recruiting for a research study. If a potential participant declines, we will not contact them again. If a potential participant does not respond immediately, we will reinitiate contact in 7 days. If a potential participant does not respond after the second contact attempt, we will not contact them again. We do not anticipate any major disruptions into the social media culture, as messages will be private and thus can be easily ignored. We will not contact a potential participant more than twice in the recruitment process to avoid coercion and minimize frustration.

Initial contact on social media will be guided by the following script: "Hello, my name is [research team member's name]. I am a part of the #blackgaylove Research Team. We're a team headed by two Black gay men and we're interviewing Black gay male couples about their relationship qualities. Would you be interested in learning more about this study? If eligible, you and your partner can earn $60 each for your time."

The partner who responds initially (the index partner [IP]) will be asked for his email address and phone number. Then he will be asked to share the other partner's (the nominated partner [NP]) contact information. A member of the research team will then contact the IP and NP via email and invite them to be screened for the study. After both the IP and NP of each couple have communicated interest in being screened for the study, a research team member will contact each partner separately to assess eligibility and obtain informed consent. Each partner will be asked to provide consent separately to encourage him to ask questions about the research process candidly and fully and to ensure that one partner does not coerce the other into enrolling.

After each partner has been screened, deemed eligible, and provided informed consent, this will be documented in the contact database, where all participant contact information is stored. At this time, each partner will be given an ID number that will be used to identify his data. This will be used in lieu of names as a measure to ensure confidentiality. Partners will then be emailed jointly (ie, the email will be addressed to both partners) with a Calendly link where they will sign up for a two-hour time slot. They will also be emailed a link to a short demographic questionnaire, accessed via Qualtrics, that they will complete before their interview. At the time of the interview, a member of the research team will assess the identity of each partner and ensure that both are present. At this time, they will also be asked to provide visual proof of a negative test result for HIV (via picture or video) from within the last 6 months. After this evaluation, the interview will be conducted and recorded via a Health Insurance Portability and Accountability Act (HIPAA)-compliant version of Zoom. All recordings will be stored locally on the research team members' computers and not stored in the Zoom cloud. Consistent with our prior work, each partner in the couple will receive $30 for their completion of each interview for a total of $60 each.

Participants in this study will be expected to complete 2 dyadic qualitative interviews. The first interview will last for no longer than 2 hours. The second interview, which will take place on a separate day, is expected to last no longer than an hour and a half. The second interview will be conducted after each couple's first interview has been transcribed and analyzed.

Joint Dyadic Qualitative Interviews

We will use the critical incident technique (CIT), which is an investigative tool to uncover existing realities or truths so they can be measured and predicted. CIT prompts participants to recall a specific, concrete incident in which the phenomenon under study was activated in their consciousness and influenced their experience of the world around them [37]. The technique gives participants freedom in describing the experience and assumes that participants will share incidents that have high priority and that have been most impactful for them. Couples will be asked to tell a series of stories about incidents when they demonstrated (1) love for each other; (2) they cared for each other; (3) how committed they were to each other; and (4) a public display of their romantic relationship. They will also be asked about social support for their romantic relationship that they have received from others, as well as how their romantic relationship has influenced their self-conception, health, and their lives overall.

Integration

After joint dyadic qualitative interviews are completed and analyzed, we will integrate the data from the 2 qualitative methods using Farmer et al's [30] triangulation protocol, which includes creating a convergence/divergence matrix to assess similarities and differences among datasets (ie, social media data and interview transcripts) and findings. We will assess coverage of codes across datasets. Then, we will conduct peer debriefing and member checking to ensure credibility and trustworthiness of the data. Member checking will be conducted by inviting participants who completed the dyadic qualitative interviews to participate in a brief follow-up interview. Specifically, we will call them and ask them to reaffirm consent to a second interview. After obtaining and documenting verbal consent, we will email each member of the couple a list of the research team's findings and ask them to review them. No more than 7 days later, we will call them via Zoom and ask them (1) whether the findings make sense to them, (2) how well their experiences are adequately represented by the findings, and (3) whether they believe some findings should be modified and how should they be modified.

Peer debriefing will include eliciting feedback from 5 academic colleagues (to be determined) at Rowan University. These colleagues will be experienced qualitative researchers who are not in the Psychology Department at Rowan University (the first author's home department) and who are unfamiliar with this study. The colleagues will be emailed the findings and transcripts and asked to assess them for over- and under-emphasized points, errors, and bias. These colleagues will be asked to respond via email to the first author with written feedback within 14 days of receipt of the findings and transcripts. All feedback will be reviewed by the research team and used to inform subsequent interpretations of the data.

Incarnation

This step involves disseminating the netnography findings in traditional outlets (eg, peer-reviewed journals and conference

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abstracts) and nontraditional outlets (eg, social media, organizational websites, and listservs). For example, in addition to publishing peer-reviewed articles, we will also create infographics describing our findings. We will share them on Instagram, Twitter, and Facebook. Social media entry data will not be shared (unless participants give explicit permission) to ensure participant privacy. Joint dyadic interview data will be reported as quotes attributed to participants' pseudonyms to protect confidentiality.

Data Analysis

Guided by Corbin and Strauss's recommendations [17], data will be analyzed using a grounded theory approach, which provides systematic methods and strategies for inductively analyzing data aimed toward theory development, and in this study, toward theory refinement. We will review a small set of transcripts (n=6) to develop a codebook. By employing grounded theory methods, transcripts will be parsed into meaningful units of information using line-by-line analysis, constant comparative analysis, and open coding [17]. We will use memos to describe code properties and dimensions and organize them into a codebook. The codebook will include the name of each code, the definition of each code, and an excerpted quote that illustrates each code. Research assistants will use the codebook to code the remaining transcripts and utilize memos to document emergent codes and discrepancies in coding. Memos will be used to keep track of analysis decisions and insights as well as to record the coder's emotions, impressions, and responses during the research process. After the initial coding of all transcripts is complete, κ statistics [38] will be used to compare results between coders. Inconsistent codes and any other discrepancies will be discussed and revisions will be made until coders obtain 90% agreement. Data collection and analysis will occur simultaneously, as is customary with grounded theory methodology. After all coding of interviews is complete, we will then code memos using the process described above.

We will refine our integrated Afrocentric interdependence theoretical framework using our codes as the building blocks. Specifically, we will compare codes across participants for similarities and differences. We will integrate similar codes into larger categories. Then, we will organize these larger categories into a core category—"a concept that is sufficiently broad and abstract that summarizes in a few words the main ideas expressed in the study" [17]. Next, we will integrate all the attributes and dimensions of the other categories into the core category. Finally, we will use memoing to develop the main descriptive story of our refined theory and construct an integrative diagram to depict it visually.

Our use of a grounded theory approach in conjunction with a directive theoretical framework and codebook may seem counterintuitive to some readers. However, these strategies are not mutually exclusive and align well with Corbin and Strauss' [17] recommendations for theory development and refinement. The authors wrote: "Though a theory that comes from data is grounded, the final 'theory,' or how concepts fit together, is constructed by the researcher...depending upon the perspective of the researcher and where he or she decides to put the emphasis" [17]. Thus, our use of a grounded theory approach allows us to refine our integrated Afrocentric interdependence theoretical framework—which informs our conceptual perspective—with empirical data that emerges from analysis of the netnography and joint dyadic interview data.

Results

Data collection began for this study in November 2020 and results are expected to be available no later than December 31, 2022.

Discussion

Principal Findings

This is a protocol for a study that seeks to (1) decode and understand the ways in which BSMCs express their romantic relationships in virtual contexts via symbolic indicators; (2) determine how the couples describe the quality of their romantic relationships; and (3) explore how the couples make meaning of their relationship quality and its impact on their relational and individual health. We expect 3 research products to be developed from this study. The first is a netnography dataset that will be analyzed to understand the couples' expression of their romantic relationships online. The second is a secure database of social media screen names of BSMCs that will facilitate recruitment of such couples in this study and possibly future studies. The third is a refined integrated Afrocentric interdependence theory that describes and explains BSMCs' romantic relationship quality and health. This theory will be used by the research team to design future couples-based health research that focuses on the distinct lived experiences and health concerns of the couples. The theory may also provide an innovative and culturally specific framework to guide other researchers who are interested in working with BSMCs in a culturally informed manner.

Potential Limitations and Alternatives

This study poses no physical risk and only minimal risk of psychological stress or harm. To protect participants, they will be provided a list of names and telephone numbers of several nationally available mental health hotlines and mental health organizations to discuss any distress they may experience. The referrals are free of charge and any follow-up fees for services beyond the first consultation will be the responsibility of the participant. Participants will be told that they can decline to answer any questions and encouraged to discontinue their participation at any time if they feel inordinate psychological or physical distress. Participants will also be informed that they have the right to withdraw their data at any time, by requesting, in writing, that it be removed from the dataset. Retaining participants between interviews is also a concern that we will address by collecting detailed contact information and providing reminders (ie, calls, emails, and text messages) to increase attendance for both interviews [39].

If a couple breaks up between the initial joint dyadic and member checking interviews, each partner will be invited to complete a break-up assessment—this has been used in our prior work [39]. The break-up assessment will query and document when the couple broke up and whether participation

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in the study contributed to the break-up. Then, we will provide free-of-charge referrals to psychological services (eg, hotlines and contact information for low-cost therapists). After completing the break-up assessment, the couple will be unenrolled from the study and study staff will no longer contact them. In our prior work, there was 20% attrition due to break-ups over a 9-month period. Given that our study period is much shorter (ie, 1 month), we anticipate a significantly lower break-up rate.

Finally, we recognize that our sample will be restricted to those with an active relevant social media presence. Our protocol does not reach couples who are not active on social media or whose social media presence does not present a public display of their romantic relationships (but who nonetheless would have perspectives to offer). However, our study serves as an important starting point for assessing romantic relationship quality among BSMCs, in a space that they control, to inform future couples-based health interventions and policy.

Conclusion

This study will apply novel symbolic netnographic qualitative methods to add to an understanding of BSMCs' romantic relationships and how they contribute to their health. Through a symbolic netnographic exploration of the couples' romantic relationships, this study will access a largely underexplored source of intersecting racial and sexual minority cultural data and symbolic relationship indicators that will be collected and analyzed in a naturalistic and holistic manner—in the social context of the couples' online presence. Further, contextualizing the couples' online data and relationship indicators in this way treats the social act of being in a BSMC as a crucial unit of analysis that can render a rich portrayal of their online social presence and interactions as more explanatory (rather than being merely descriptive) of how their relationship quality plays a part in their health as individuals and as couples. Moreover, the findings from this research project will be used to develop programs to improve BSMCs' health in community and virtual settings. It may also be used to influence policy that advocates for Black sexual-minority men's health.

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Conflicts of Interest

None declared.

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Abbreviations

BSMC: Black same-sex male couple
CIT: critical incident technique
IP: index partner
NP: nominated partner
OCT-SGM: Optimal Conceptual Theory applied to sexual and gender minorities
SGM: sexual and gender minority

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Protocol

The Surveillance of Physical Activity, Sedentary Behavior, and Sleep: Protocol for the Development and Feasibility Evaluation of a Novel Measurement System

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Abstract

Background: There is increasing recognition of the need for more comprehensive surveillance data, including information on physical activity of all intensities, sedentary behavior, and sleep. However, meeting this need poses significant challenges for current surveillance systems, which are mainly reliant on self-report.

Objective: The primary objective of this project is to develop and evaluate the feasibility of a sensor-based system for use in the surveillance of physical activity, sedentary behavior, and sleep (SurPASS) at a national level in Denmark.

Methods: The SurPASS project involves an international, multidisciplinary team of researchers collaborating with an industrial partner. The SurPASS system consists of (1) a thigh-worn accelerometer with Bluetooth connectivity, (2) a smartphone app, (3) an integrated back end, facilitating the automated upload, analysis, storage, and provision of individualized feedback in a manner compliant with European Union regulations on data privacy, and (4) an administrator web interface (web application) to monitor progress. The system development and evaluation will be performed in 3 phases. These phases will include gathering user input and specifications (phase 1), the iterative development, evaluation, and refinement of the system (phase 2), and the feasibility evaluation (phase 3).

Results: The project started in September 2020 and completed phase 2 in February 2022. Phase 3 began in March 2022 and results will be made available in 2023.

Conclusions: If feasible, the SurPASS system could be a catalyst toward large-scale, sensor-based surveillance of physical activity, sedentary behavior, and sleep. It could also be adapted for cohort and interventional research, thus contributing to the generation of evidence for both interventions and public health policies and recommendations.

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KEYWORDS

accelerometer; thigh-worn; sensor-based; system acceptability; surveillance; physical activity; physical health; physical; sedentary; sedentary behavior; sleep; surPASS; public health

Introduction

The surveillance of physical activity, at a population level, is being met with new demands [1]. Surveillance data should now ideally capture physical activities of all intensities across 24 hours, sedentary behavior, and sleep [1]. These data are very difficult to collect accurately using the traditional self-reported measures widely implemented in physical activity surveillance, primarily because habitual activities and sleep are difficult to recall, and therefore, the estimates reported are often incorrect [2].

In an attempt to overcome the limitations of self-reported measures, sensor-based measurements have been implemented in a few select cases of physical activity surveillance [3-7] and in an increasing number of large cohort studies [8-10]. Although the goals of surveillance and cohort research are inherently different—cohort research informs physical activity guidelines, whereas surveillance monitors adherence to guidelines—the challenges they face in implementing sensor-based measurements are similar. These measurements were only possible at considerable expense, with long delays in producing useful data, and with a considerable burden to all users, both those conducting the data collection and those participating in the studies. Burden can be defined as the direct and indirect financial and resource costs of interacting with the system, including the cost of equipment and expert staff, the time required to recruit participants and coordinate a meeting in person, and the time taken to analyze data and produce useful results. Under this definition, the unacceptable burden of traditional sensor-based methodologies can be summarized quite concisely. The sensors are too expensive, recruitment and data collection require a center and involve considerable logistics for participants and staff, and data analysis requires expert personnel. This burden typically results in a lot of time passing before summary reports and findings based on the collected data reach policy makers. Therefore, we need to develop a methodology for implementing sensor-based measurements of physical activity, sedentary behavior, and sleep, which is lower in burden for all users, in line with the World Health Organization's global strategy on digital health [11].

To date, we have been largely limited by the available technology. However, recent technological advances could enable the development of new systems for the measurement of physical activity, sedentary behavior, and sleep. Technological advances include a new generation of easily attachable, relatively cheap, discrete sensors capable of secure data transfer via Bluetooth connectivity; new smartphone apps for the integration of sensor and participant input, cloud storage, and automated analysis capacity; and web-based applications for the real-time tracking of data collection progression. These technologies potentially give us the ability to rapidly and automatically analyze data and provide useful, timely feedback to all users in a manner compliant with current data privacy regulations. Additionally, such technologies will increase the potential for collecting and harmonizing data within and across countries in the future, if adapted as a standardized methodology for accelerometry data collection. Thus, exploiting these new technological developments will be the first step toward improving the way we collect accelerometry data at scale.

The surveillance of physical activity, sedentary behavior, and sleep project team (SurPASS) envisions incorporating this new generation of technical solutions and infrastructure in the development of a system for sensor-based surveillance that can be used globally. We see the current protocol as the first step, where we document a method for the development and evaluation of a sensor-based system for surveillance among working age adults at a national level, in Denmark. In this protocol, we will address three aims:

1. Defining the user specifications of such a system.
2. Developing a system through a process of iterative evaluation and redesign.
3. Evaluating the feasibility of this system in a national surveillance program.

Methods

Overview

In this section, we describe the components for the SurPASS system, the establishment of user groups, and a plan for system development and a feasibility evaluation. The project team consists of an international group of multidisciplinary researchers and an industrial partner based in Copenhagen, Denmark (SENS Innovation ApS). SENS Innovation ApS will provide sensors, patches, and technical expertise. The target population of this first step toward achieving the SurPASS project team's vision is adults of working age in Denmark. In describing our method, we define users as any person who uses the system for some purpose. Exclusion criteria for users include already receiving a pension, being on maternity/paternity or sick leave, and anyone who suffers from an allergy to adhesive plasters.

Ethics Approval

The scientific ethics committee for the Capital Region of Denmark (journal number: 20030293) approved the SurPASS project, which will be conducted in accordance with the Declaration of Helsinki. All participants will be asked to provide informed consent before participation.

SurPASS System Components

A Wearable Sensor

An easily attachable Conformité Européenne–approved triaxial accelerometer (SENSmotionPlus, SENS Innovation ApS) will be used in the development of the SurPASS system. The

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SENSmotionPlus is a discrete, lightweight accelerometer (47 mm length × 22 mm breadth × 4.5 mm thickness; 7 grams), which is waterproof and has a memory capacity of approximately 4 days when sampling at 25 Hz. However, integrated Bluetooth data-transfer technology (2.4 GHz low-energy transfer) enables data transfer when in Bluetooth range of a user's smartphone, thus ensuring that the memory capacity will not be exceeded. The sensor has primarily been used in clinical settings to date [12] and has yet to be tested in free-living settings. A validation plan for the use of SENSmotionPlus in free-living settings is presented later.

A Smartphone App

A smartphone app will be developed to provide instructions to users regarding sensor attachment and calibration, while allowing the user to register work and sleep time. Data from the sensor will be transferred through the app to a cloud-based back end. Individualized feedback on daily activity types and durations will then be made available for participants through the smartphone app. The app is compatible with both Android and iOS operating systems.

A Back-end Infrastructure

A secure, back-end infrastructure developed by SENS Innovation will be adapted to meet the requirements of SurPASS. This back-end infrastructure is compliant with the General Data Protection Regulation (GDPR). It will also facilitate functions such as automated data cleaning, storage, and the integration of processing software.

A Processing Software

A new software flow will be created based around the validated MATLAB-Acti4 software [13]. Acti4 has been developed and validated for use with thigh-worn accelerometer data [13,14]. However, the current Acti4 flow requires considerable time for file conversion, manual data cleaning, and processing. This software flow needs to be easier to use, more automated, and capable of meeting the requirements of the back-end infrastructure developed by SENS Innovation. Most critically, the software must maintain the validated Acti4 definitions of physical activity types and postures (eg, sitting, standing, lying down, walking, running, cycling), which are defined for any epoch length >1 second [13]. In addition, it should be capable of differentiating lying down from sitting using a single accelerometer [15].

A Web-Based Application for Administrators

A web-based application will be developed to cover all core administrative tasks such as participant registration, monitoring the status of sensors, tracking when notifications need to be sent to participants, and facilitating downloading raw and processed data that can be used for alternative analysis methods and further research.

Conceptual Framework

We will develop the system and evaluate its implementation according to the user-centered design framework [16] (UCD) and a 3-phase plan outlined in Figure 1. UCD refers to an iterative design process, where design decisions are based largely on users' needs and specifications [16]. Under this framework, the "user" is defined as any person that "uses" the system for some purpose [16]. We plan to establish 3 groups of prospective users to aid us throughout the development and evaluation process. The first group (group 1) will consist of leading experts in the field of physical activity measurement, who will ensure the high scientific quality of the project evaluation, share practical experience regarding sensor-based data collection, and outline their needs as potential users of the system. These experts will be chosen within Denmark and internationally, based on their experience with sensor-based measurements of physical activity and sedentary behavior. The second group (group 2) will consist of local surveillance authority representatives and union representatives (ie, employer and employee unions), who are considered as critical stakeholders for implementation in the Danish social context, largely because the SurPASS system will necessitate measurement during working hours and thus present ethical concerns. The inclusion of these stakeholders is vital for ensuring the social acceptability of the SurPASS system in Denmark. The third group (group 3) will consist of members of the general public. Each group will provide their input on SurPASS system components (eg, smartphone app and the personalized feedback). All groups will be established using existing networks at the National Research Centre for the Working Environment, Copenhagen, Denmark.

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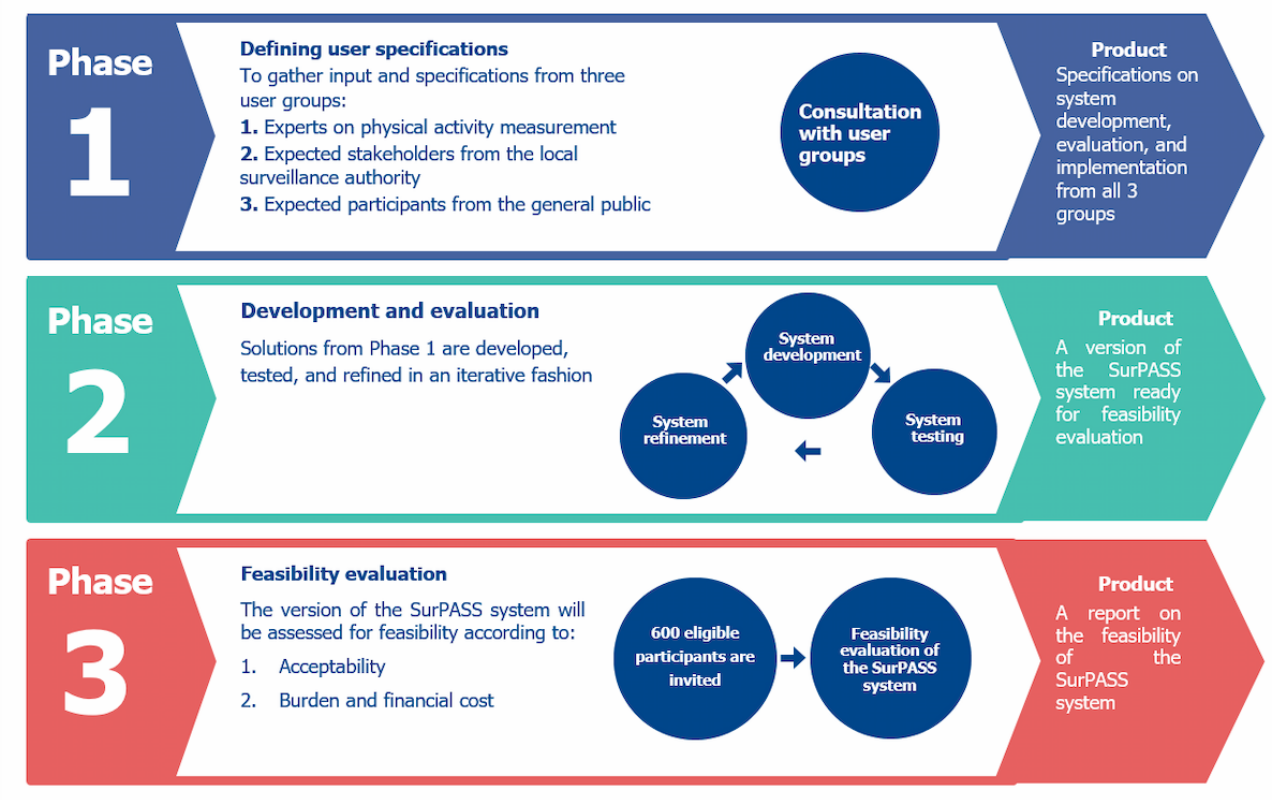
Figure 1. The 3-phase development and evaluation plan for the SurPASS system. Phase 1 is aimed at defining user specifications and outlining a system implementation plan; phase 2 is aimed at developing, evaluating, and refining the SurPASS system based on this plan; and phase 3 is aimed at evaluating the feasibility of the refined system. SurPASS: surveillance of physical activity, sedentary behavior, and sleep.



Study Phases

Phase 1: Defining User Specifications

User input from the 3 user groups will inform the system specifications. As a starting point, the SurPASS team will develop wireframes (ie, initial outlines) of the SurPASS system's components to present to user groups for input and feedback (Figure 2). Input and specifications from groups 1 and 2 will be gathered through stakeholder meetings. The initial meeting will be centered around the question, "What would be the requirements for developing and implementing a valid, low-cost, large-scale measurement system with low demands on all users?" Five subsequent biannual meetings will be aimed at seeking expert guidance and input, while also serving as a forum for updates on the project's progress. Input and specifications from group 3 will be gathered through online video consultations following a "think-aloud" format. Two SurPASS team members will take notes while the initial nonfunctional wireframe outlines of system components are presented on the screen to members of group 3. They will be asked to think aloud, giving their opinion on the appearance and functionality of each component (eg, smartphone app, sensor attachment instructions) as they interact with it. The notes taken during these sessions will be coded and translated into concrete solutions for system improvements by the SurPASS team. Coding will be done according to the severity of the issue concerning the app functionality (ie, green=no issues, blue=a minor problem, yellow=a serious problem, red=a critical problem).

The product of phase 1 will be the collated input and specifications from all user groups. This information will be used to develop the system components and to outline how the system should be implemented. Phase 1 must produce functional system components, which can then be evaluated and refined in phase 2 (eg, an interactive smartphone app).

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Figure 2. An example of a wireframe outline of a system component. Users will be asked to "think aloud" regarding the appearance and functionality of each component.

Phase 2: Development and Evaluation

Development will begin, using translated solutions from phase 1 as a starting point. These solutions will be evaluated and then further developed. Members of group 3 (the general public) will be involved in the evaluation in phase 2.

Iteration 1: Web Consultation

A functional browser-based interactive wireframe of the smartphone app—designed based on the specifications in phase 1—will be presented to 3-5 members of group 3 during online web consultations in a similar setting to phase 1. Here, emphasis will be placed more on the component functionality as the level of interactivity increases. Again, color-coded (ie, green, blue, yellow, red) notes will be translated into concrete changes in app design, leading to a beta version of a smartphone app available for public download. This beta version will be used in the evaluation during iteration 2.

Iteration 2: Evaluating System Acceptability

Using the beta smartphone app, we will evaluate the SurPASS system according to the System Acceptability framework outlined in usability engineering [17]. We will test aspects of acceptability, including system usability using the System Usability Scale [18], the utility of the sensor and the smartphone app, and the practical acceptability of the system processes including the information provided on participation, attachment, personalized feedback, and the experience of participation.

The evaluation will be conducted according to the procedure summarized in Figure 3. Briefly, a further 10-12 new members of group 3 will be asked to attach and wear a sensor over 7 consecutive days, while logging their work and sleep time in the beta smartphone app. Through online video meetings on days 1 and 7, members of the SurPASS team will observe and rate the use of provided instructions, the success of remote attachment, and the experience and expectations of participation, including users' responses to personalized feedback. The same process of think-aloud consultations and the color-coding method will be used in the consultation on day 1. In the consultation on day 7, a semistructured interview will be conducted. We chose a 7-day measurement window to capture a full working week and 2 weekend days. There is little consensus on the most representative time window; most studies around the world have chosen a 7-day measurement window for sensor-based measurements. The work of Bergman and Hagströmer [19] suggests that the size of the sample, not the length of the measurement window, is most important for reducing the standard error of the mean. The SurPASS team will use this information to refine the SurPASS system for use in the prefeasibility pilot in iteration 3.

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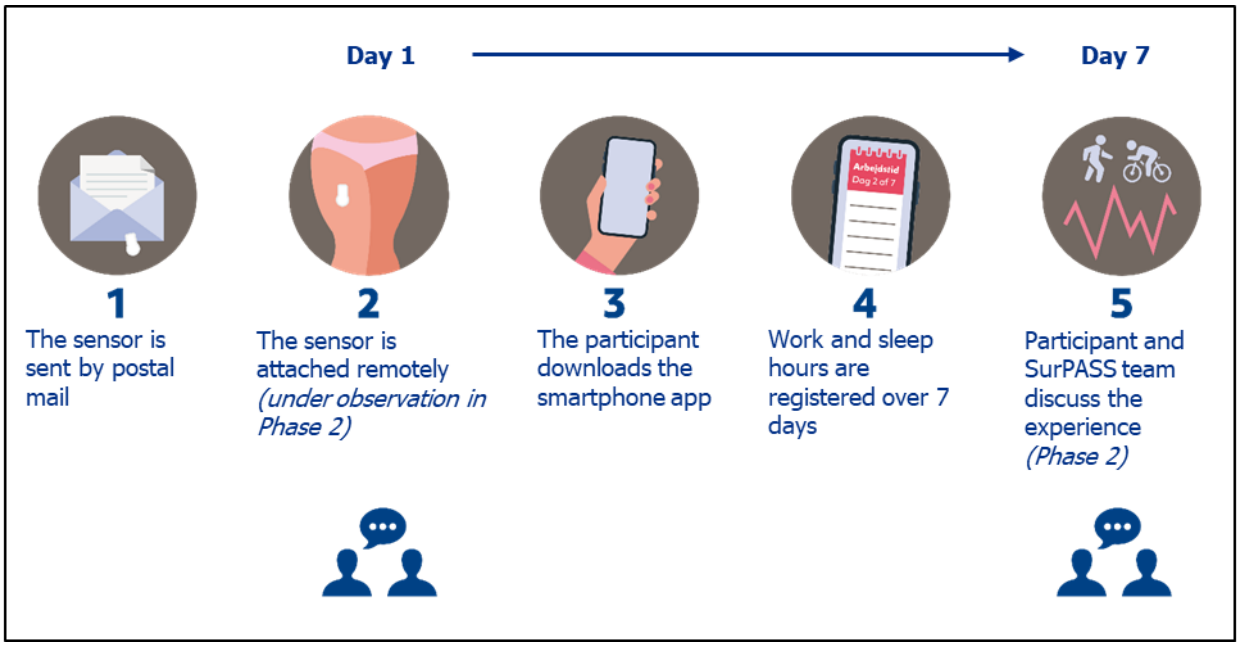
Figure 3. The planned procedure for system acceptability testing in iteration 2 of phase 2. Users from group 3 will receive a package containing a sensor and attachment material via postal mail. During an online video consultation with SurPASS team members, users will attach and initiate the sensors to begin the measurement of physical activity, sedentary behavior, and sleep. On day 7, a second web consultation will be held to discuss the participants' experience.

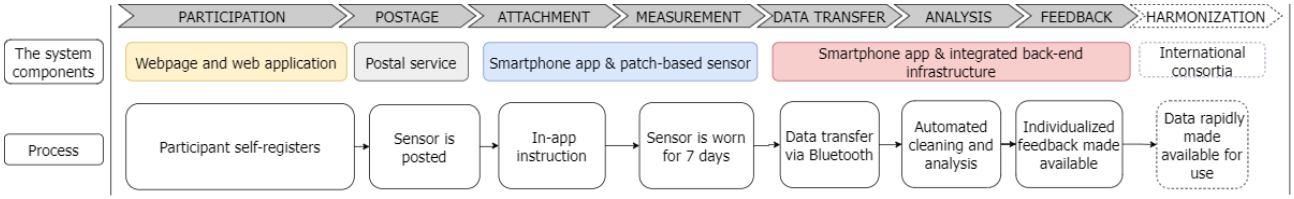


Iteration 3: Pilot Evaluation

A pilot evaluation will be conducted to test all processes of the SurPASS system, developed and refined in iteration 2, to ensure that the system is ready for the feasibility evaluation in phase 3. A procedure following the full system implementation outline (Figure 4) will be conducted among a further 30-50 new members of group 3. A semistructured interview will be conducted after the 7-day test period, to explore the participants' experience of interacting with the system. The results of the pilot evaluation will be used to solve any unforeseen issues in the system implementation outline (Figure 4) before the feasibility evaluation in phase 3. Any changes in the procedure will be reported accordingly.

By the end of phase 2, we expect to have tested components of the system on between 50-100 members of group 3.

Figure 4. The SurPASS system implementation outline, including the required system components and processes. The participant registers, receives a package, attaches and wears a sensor for 7 days, and registers sleep and work time. Data are then automatically transferred to the cloud for analysis and storage. At the end of the measurement, feedback on the participant's daily activities is rapidly produced for all users.



Phase 3: Feasibility Evaluation

The feasibility of the SurPASS system will be assessed based on acceptability and user burden. Acceptability is defined as both the *practical*—the success of critical processes in the system (eg, postage of sensors)—and the *social*—the willingness of participants to interact with the system (eg, recruitment) and their level of satisfaction with their experience. Based on the rules of thumb presented in a recent guidance on using pilot studies to inform the design of intervention trials with continuous outcomes, a sample size of approximately 200-250 participants will be required for our evaluation [20]. Since previous large-scale, sensor-based data collection studies in a European context reported recruitment rates of between 31% and 68% [7,9], we estimated that approximately 600 participants should be contacted. Prospective users (ie, members of the general public) will be recruited through the established recruitment cycle of a local surveillance authority in Denmark. A feasibility evaluation will be conducted by applying methods from the updated framework for evaluating complex interventions, including an evaluability analysis of feasibility outcome measures [21] and a traffic light system based on predefined criteria [22]. Under the traffic light system, red indicates an unacceptable performance on a feasibility outcome measure, amber indicates a potentially acceptable outcome if amendments are made, and green indicates an acceptable performance. The criteria for the traffic light system will be defined through an evaluability assessment [22] with groups 2 and 3.

All data will be collected and stored in compliance with GDPR. Participants will be anonymized by assigning identification numbers upon registration to the study. These identification numbers will then be transmitted to a data manager who will

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assign new variable names, returning a data set to researchers in a pseudorandomized version. While stored on the patch-based accelerometer, data will be encrypted according to the industrial standard AES-128. Transfer to cloud storage will be end-to-end encrypted, using a service provided by Amazon Web Services (AWS GDPR Data Processing Addendum). The stored data will be encrypted according to the industrial standard AES-256. Moreover, the data hosted by AWS and collected within the European Union (EU) will remain within EU territories and will not be accessed outside the EU. Data in the AWS database will only be accessed via a web application with access restricted to the SurPASS team. The web application will require a special login via an industry standard secure "https" connection.

Sensor Validation

Validation will be achieved by comparing the time spent on various physical activities and sedentary behaviors as measured using SENSmotionPlus against those measured by the Axivity AX3 (Axivity Ltd) and ActivPAL Micro4 (PAL Technologies) accelerometers in controlled and semicontrolled settings on the same participants. Video recording will be used as the gold-standard observation. This data will be analyzed using the SurPASS software flow that will be created around the MATLAB-Acti4 software [13].

Results

The project started in September 2020. Phase 2 was completed in February 2022 and phase 3 began in March of 2022. Findings will be published in 2023. The proposed system implementation in phase 3 is outlined below (Figure 4).

1. Participants will first register to participate via an online registration system.
2. When registration is completed, the sensor and instructions on using the system will be placed in a package and sent to the participant via postal mail.
3. Once the participant receives the package, they will download the smartphone app and follow the in-app instructions regarding the attachment of the sensor.
4. Once attached and connected to the app via Bluetooth, the sensor will record thigh movements for 7 days, uploading data regularly.
5. Data will be transferred to the back-end infrastructure, and will undergo cleaning, batch processing, and storage.
6. At the end of the measurement period, the participant will enter their last day of diary information before receiving feedback on their physical activity, sedentary behavior, and sleep during the measurement period.

Discussion

This protocol describes the developmental process that is the first step toward the next generation of surveillance tools for physical activity, sedentary behavior, and sleep. In designing the protocol, we have attempted to meet a number of new demands faced by traditional sensor-based measurement methodologies at a large scale, namely, a secure, sensor-based system that is easy to use for all users, while ensuring the rapid collection of accurate and useful data. In the process of producing the system implementation outline (Figure 4), we identified 3 key areas of risk.

First, we identified the risk of low recruitment and representative participation. Previously, sensor-based measurement on a large scale, whether it be for surveillance or cohort purposes, has struggled to recruit representative samples of sufficient size [23]. Through the early establishment and engagement of user groups, this risk can be mitigated, particularly by designing a system that overcomes barriers to use and fulfills user needs and desires. As this risk is context-dependent (eg, country, culture, institutions), future administrative users (groups 1 and 2) will need to consider how to ensure sufficient participation in the context where the system is implemented, and to adapt their approach accordingly.

Second, we identified the risks of remote sensor attachment, poor sensor utility, and poor adherence. Our system implementation outline relies on (1) the participant being able to attach the sensor easily, (2) the sensor being appropriate for free-living measurement, and (3) a high participant motivation to adhere to the procedure over several days. We plan to seek early input from the participant group (group 3) on the ease of comprehension of attachment instructions, and have repeated data collection throughout phases 1-3 to improve this aspect. Further, we will use phase 2 to provide an indication of the utility of the sensor in free-living settings and to maximize the usability of the system, which can encourage better adherence.

Third, with such a complex technological system, there will always be a risk of technological failure. The system implementation outline relies heavily on technical infrastructure for data transfer (from the sensor through the app to the cloud storage), automated analysis, and the provision of feedback. If any of these steps fail, we would risk losing data. We plan to integrate existing tried-and-tested technical infrastructure to mitigate this risk.

The strength of this protocol is the continuous inclusion of stakeholders throughout the development and evaluation of the system. Further, the development and evaluation of the system will be conducted in iterative cycles, allowing for continual improvement and incorporation of user input. A limitation of the current protocol is that the evaluation of the system will be limited to the social and cultural context that it is tested in. Each of the challenges and risks highlighted above will vary in degree depending on where in the world the system is tested and the culture of that place. Thus, the evaluation of whether the system is feasible or not will only be applicable in a Danish context until tested elsewhere. Future projects could consider including methods such as ecological momentary assessment to better understand the influence of context [24]. We have also opted to implement a single thigh-worn sensor. This placement has some limitations and the use of a single sensor does not allow for the capture of important physical activities such as awkward postures (ie, those deviating considerably from neutral positions)—for example, elevating arms above shoulder level and bending of back, kneeling, and squatting. Finally, in this step, we focus only on adults of working age, limiting our findings to this population.

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The SurPASS system developed in this project will be just the first step toward achieving the SurPASS team's vision. Further evaluation will undoubtedly be required to consider and improve on any transparency, accessibility, scalability, replicability, interoperability, privacy, security, and confidentiality issues that may arise as the system is adapted and challenged in new contexts (eg, low- to middle-income countries). In this first step, we consider the privacy, security, confidentiality, and transparency issues within the Danish context through the development of data usage and licensing agreements, as well as provide indications of future scalability through cost analysis. If the SurPASS system were feasible, it would represent a huge leap forward in the process of developing surveillance tools to meet the new demands on physical activity surveillance. The SurPASS system could facilitate the production of more accurate and useful data, which can be rapidly provided to key stakeholders once the validity of the sensor has been fully established. We believe that by developing a system that is low in burden, the prevalence of sensor-based measurement will increase, perhaps reaching population groups that are seriously underrepresented currently (eg, low- to middle-income countries, lower socioeconomic status settings). A higher prevalence of sensor-based measurements would also lead to increased public awareness regarding the importance of daily physical activity, sedentary behavior, and sleep (eg, through the rapid provision of accurate feedback). However, feedback to users is something that will need to be continually optimized as we gather better user information on how feedback is perceived to ensure it is relevant for users. Finally, many of the challenges encountered in the surveillance of physical activity are also faced by cohort and interventional studies, particularly burden and cost. The SurPASS system could be adapted for cohort and intervention research, further expanding the capacity of research programs and consortia [25,26] to provide high-quality evidence to inform policy and practice. The SurPASS project started in September 2020 and is currently in phase 2. The first results of the development and evaluation will be available in 2022, with the results of the feasibility evaluation made available in 2023.

The protocol presented describes a system that, if feasible, could act as a catalyst toward large-scale, sensor-based surveillance, thus taking the first step toward advancing physical activity, sedentary behavior, and sleep research and elevating evidence-informed policy and practice.

Acknowledgments

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Authors' Contributions

All authors contributed to planning and designing the protocol and finalizing the manuscript. PC drafted the initial manuscript and revised the protocol based on coauthor contributions. All authors have reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AWS: Amazon Web Services
EU: European Union
GDPR: General Data Protection Regulation
SurPASS: surveillance of physical activity, sedentary behavior, and sleep
UCD: user-centered design

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Protocol

Culturally Safe eHealth Interventions With Aboriginal and Torres Strait Islander People: Protocol for a Best Practice Framework

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Abstract

Background: There is growing global evidence on the adoption and effectiveness of eHealth (including mobile health and telehealth) by First Nation peoples including Aboriginal and Torres Strait Islander people. Although there are frameworks to guide eHealth development, implementation, and evaluation, it is unknown whether they adequately encapsulate the health, cultural, and community-related priorities of Aboriginal and Torres Strait Islander people.

Objective: The aim of this research program is to prepare a best practice framework that will guide the co-design, implementation, and evaluation of culturally safe eHealth interventions within existing models of health care for Aboriginal and Torres Strait Islander people. The framework will be a synthesis of evidence that represents best practices in eHealth, as determined by Aboriginal and Torres Strait Islander people.

Methods: Research activities to develop the best practice framework will occur in stepped but overlapping qualitative research phases with governance from an existing multiagency research collaboration (the Collaboration). The research protocol has been informed by key research frameworks such as the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and Developers of Health Research Reporting Guidelines. The seven phases of research will include the following: systematic literature review, scoping review, theme development, theme consultation, Delphi processes for expert reviews, and dissemination.

Results: Members of the Collaboration conceived this research program in August 2020, and a draft was produced in June 2021 with subsequent funding obtained in July 2021. The Collaboration approved the protocol in December 2021. Results for several research phases of the best practice framework development are expected by January 2023, commencing with the systematic literature review and the scoping review.

Conclusions: The research program outlined in this protocol is a timely response to the growing number of eHealth interventions with Aboriginal and Torres Strait Islander people. A best practice framework is needed to guide the rigorous development and evaluation of eHealth innovations to promote genuine co-design and ensure cultural safety and clinical effectiveness for Aboriginal and Torres Strait Islander people.

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KEYWORDS

eHealth; mHealth; telehealth; Aboriginal; Indigenous; First Nations; best practice; Australia; development; framework; Torres Strait Islander; co-design; culturally safe; culturally sensitive; evaluation; health care model

Introduction

eHealth Interventions

eHealth broadly refers to the delivery and management of health care using a range of information and communication technologies that connect consumers with health professionals (see Multimedia Appendix 1) [1-3]. The term eHealth is used throughout this paper to encompass modalities that involve interaction between health professionals and consumers, including telehealth, mobile health (mHealth), videoconferencing, smart technology platforms, and remote monitoring.

eHealth's strength lies in its ability to connect consumers and health care professionals, who are often separated geographically. However, geographical separation is not the sole driver for the adoption of eHealth. Since early 2020, the global impact of COVID-19 has fast-tracked innovation in health service delivery and highlighted eHealth as a critical resource not only to reduce exposure to and the spread of infectious disease but to enable continuity of health care more broadly [4-6]. Many consumers and caregivers experience the value of eHealth when social, cognitive, or mental health conditions pose additional challenges to accessing health services. eHealth is enabling mental health care [5,7] and support for a range of chronic illnesses such as diabetes and heart disease within clinical [8-10] and in-home settings [11,12]. Comparable or superior clinical effectiveness of eHealth has been established for some modalities such as telehealth [8,13], with emerging evidence for others including mHealth platforms and text messaging [9,14,15]. Furthermore, digital health innovations may facilitate health access for culturally diverse populations despite systemic barriers including narrow conceptualizations of health, English as the dominant language, racism, and discrimination [10,16,17].

eHealth with Aboriginal and Torres Strait Islander People

There is growing global evidence on the adoption of digital technologies by First Nation peoples [10,18-20]. Australian research has shown eHealth can address access challenges associated with health care for Aboriginal and Torres Strait Islander people. For example, telehealth services can help avoid the distress of separation from Country and kin by reducing the need for in-person travel to primary or tertiary care appointments that may involve navigation of unfamiliar environments [18,21]. Additionally, eHealth may reduce costs associated with patient travel, operating costs for the service provider [22], and enable the expansion of services offered by Aboriginal and Torres Strait Islander primary care and community organizations [18,23]. Research also notes that eHealth interventions can increase family involvement in health care [24] and that family inclusion can enhance engagement with eHealth [3]. Effective and engaging mental health interventions such as *AIMhi Stay Strong*, and *iBobbly* demonstrate the relevance of eHealth and significance of co-design processes with Aboriginal and Torres Strait Islander people [20]. Both these mobile apps have undergone further research and development following the positive outcomes of pilot testing [25-27]. A recent app development and feasibility trial regarding social and emotional well-being with Aboriginal and Torres Strait Islander women reported mixed results for adoption, engagement, and user feedback [28].

Implementation and Evaluation of eHealth

eHealth frameworks guide the development of platforms and lift the rigor of implementation, evaluation, and reporting. Foundational works by Eng et al [29] on the "Evaluation of Interactive Health Communication" have been complemented by other key guides including the CONSORT (Consolidated Standards of Reporting Trials) statement [30], the Mobile health evidence and Reporting Assessment (MeRA) [31], Mobile Application Rating System [32], the Centre for eHealth Research and Development roadmap [33], Model for Assessment of Telemedicine [34], and ongoing work in digital health implementation by Greenhalgh et al [35,36]. Application of these frameworks increases the potential impact and relevance of eHealth, including its contribution to addressing health inequalities [33,37].

Culturally Safe eHealth With Aboriginal and Torres Strait Islander People

The frameworks, however, may not accurately reflect the values and priorities of the culturally diverse populations for which they may be intended. For example, Aboriginal and Torres Strait Islander people conceptualize health and well-being as dynamic, holistic, and interconnected, in contrast to the dominant biomedical approach [38-40] on which the majority of health interventions are based. Extensive eHealth research conducted by Maar et al [41] with First Nations communities of Canada has emphasized the need for respect and commitment to community priorities, worldviews, and culture throughout the research process. Therefore, it is critical to acknowledge that western-derived frameworks are not directly transferrable to Aboriginal and Torres Strait Islander health settings and such research must be embedded with culturally respectful approaches [41-43].

A culturally safe framework for eHealth evaluation is also significant because of the persistent health inequities between Aboriginal and Torres Strait Islander people and non-Indigenous people. Complex interactions between racism, marginalization, and rapid social and economic change continue to perpetuate gross inequities in health service provision, health outcomes, as well as health and well-being for Aboriginal and Torres Strait Islander people in Australia [44-46]. Furthermore, although eHealth adoption and evidence of its effectiveness are

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increasing, there remains a global "digital divide" (or "digital poverty"), where persons who may benefit most from eHealth face persistent and complex barriers to access these services [47]. These barriers include socioeconomic challenges, increasing age, chronic illness, education including health literacy, ethnicity, remoteness, and digital literacy [3,19,48-51]. Such factors are crucial considerations in the co-design, trial, implementation, and evaluation of eHealth interventions.

Therefore, it is unknown whether existing eHealth implementation or evaluation frameworks adequately encapsulate the health, cultural, and community-related priorities of Aboriginal and Torres Strait Islander people.

Although scientific reviews [10,19,20] and recommendations for application of eHealth in diverse cultures have been published [3,41,50], there is currently no comprehensive research, implementation, and evaluation guide. Consequently, eHealth interventions with Aboriginal and Torres Strait Islander people have routinely been brief, single studies that lack authentic alignment with co-design principles [52] and yield low-grade evidence for health outcomes. The World Health Organization observes this as a weakness of the broader global eHealth movement, which has "…driven a proliferation of short-lived implementations and an overwhelming diversity of digital tools, with a limited understanding of their impact on health systems and people's well-being" [37]. Consensus from public health research has also noted the critical lack of quality standards and evidence-based content for most health-based apps, particularly those stating clinical benefits [53-55]. Sustainable and relevant eHealth interventions are needed where genuine co-design incorporates multidisciplinary expertise, end-user perspectives, and addresses the health priorities of Aboriginal and Torres Strait Islander communities in line with foundational research principles [42,43].

The overall aim of this research program is to prepare a best practice framework that will guide the co-design, implementation, and evaluation of culturally safe eHealth interventions within existing models of health care for Aboriginal and Torres Strait Islander people. A best practice framework can be described as a synthesis of key elements that will ensure best practices in real-world settings, beyond empirical studies [56]. Therefore, the proposed framework will be a synthesis of evidence that represents the best practices in eHealth, as determined by Aboriginal and Torres Strait Islander people.

Methods

Research Partners

It is imperative that holistic and cultural values of health and well-being are upheld in eHealth research with Aboriginal and Torres Strait Islander people. The Collaboration acknowledges the expertise and leadership of Aboriginal and Torres Strait Islander Community Controlled Health Organisations (ATSICCHOs) in the delivery of primary care across Australia [57,58]. ATSICCHO models of care with Aboriginal and Torres Strait Islander people are centered on connections to culture, Country, and kin [59-61]. Research partnerships with ATSICCHOs and other community-controlled organizations in Queensland and the Northern Territory have been developed through ongoing relationships and consultations by the Collaboration members. Participants from the partnering organizations for the research activities outlined in this protocol will include stakeholders, hereby used to refer to doctors, Aboriginal and Torres Strait Islander health workers, nurses, administration staff, research personnel, board members, clients, and other community members.

Ethical Considerations

Certain phases of the research outlined in this protocol, such as the recruitment of experts for the Delphi processes, will require ethical approval from a Human Research Ethics Committee (HREC). As the Collaboration has ongoing partnerships with ATSICCHOs and other community-controlled organizations, other phases involving feasibility studies will have their own HREC approval and research protocol.

Theoretical Frameworks and Design

The scientific research questions (RQs) guiding this program of research are as follows:

RQ1: What is the scientific evidence for determining what is important to Aboriginal and Torres Strait Islander people in the adoption, engagement, and evaluation of eHealth interventions within an Aboriginal and Torres Strait Islander health context?

RQ2: What existing frameworks and practice guidelines should be used to inform eHealth interventions with Aboriginal and Torres Strait Islander people? (ie, drawing on Aboriginal and Torres Strait Islander knowledge and accepted guidelines)

RQ3: What principles and values are important to Aboriginal and Torres Strait Islander stakeholders (consumers, facilitators, etc) when co-designing and using eHealth?

RQ4: How can the above outcomes be integrated to inform a set of principles for best practices (facilitation and reporting) in eHealth interventions within the Aboriginal and Torres Strait Islander health context?

The structure of this protocol was informed by SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [62]. Although intended for clinical trials, this checklist provides research transparency and ensures that key research elements are addressed. Data collection processes and development of the best practice framework will occur in stepped but overlapping qualitative research phases (see Figure 1) informed by the work of Moher et al [63]. Each research phase draws on additional frameworks such as PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [64], Delphi approaches [65-67], and scoping frameworks [68-70]. Additional reference has been made to relevant scientific publications regarding the development of practice guidelines [71-76] and health research protocols [74,77,78] throughout the development of this protocol. Further details of each of the 7 research phases are outlined as follows.

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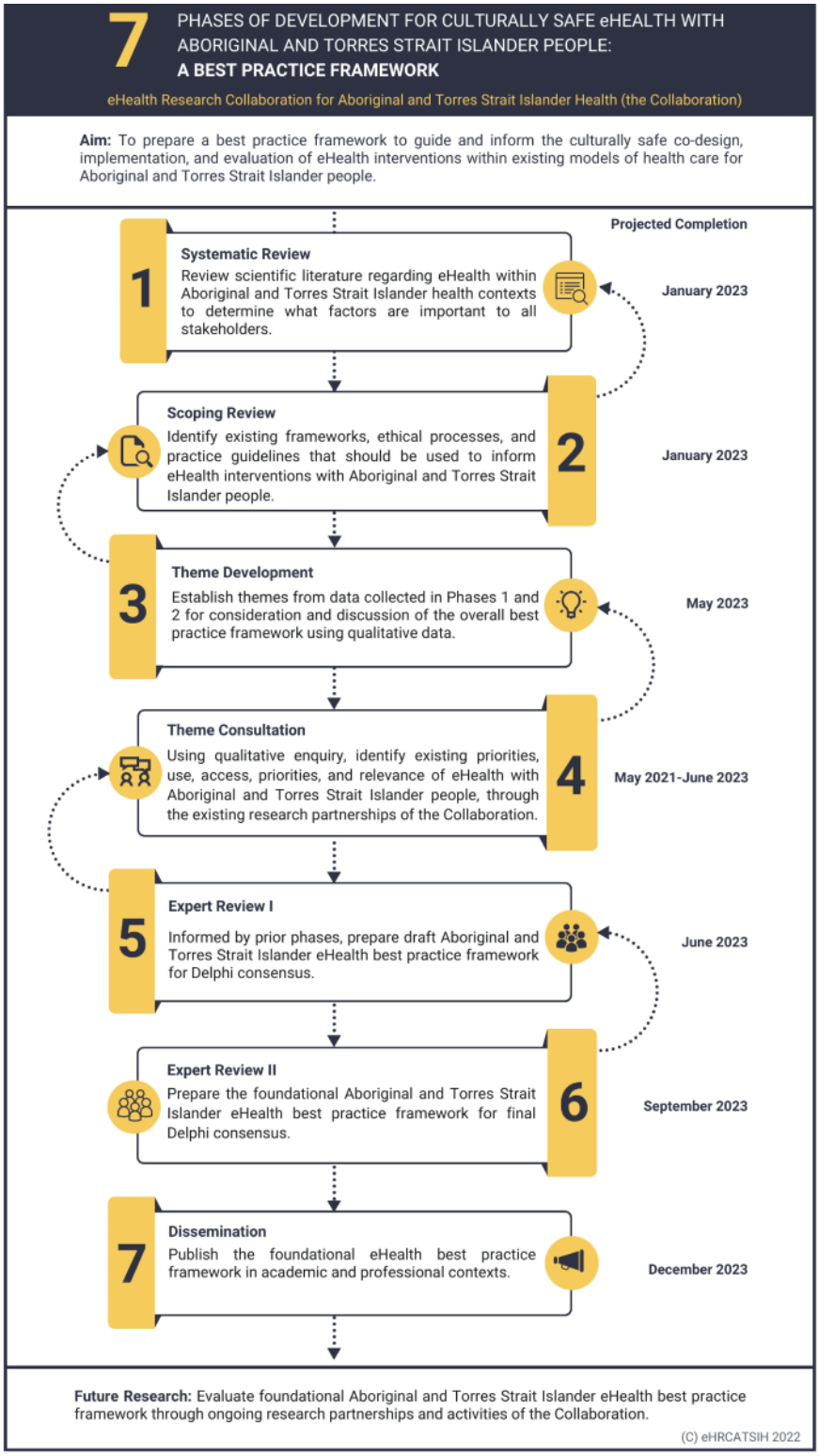
Figure 1. Developmental phases of the eHealth best practice framework.



Phase 1: Systematic Literature Review

Study Aim

The aim of this systematic literature review will be to identify the characteristics of eHealth facilitation, implementation, and adoption with the goal of determining what factors are important to Aboriginal and Torres Strait Islander people and determine gaps in the literature. This study will address RQ1. A full protocol for this systematic review will be registered with the International Prospective Register of Systematic Reviews and follow the PRISMA guidelines for reporting a systematic literature review [64].

Searches, and Inclusion and Exclusion Criteria

Recommendations by the Lowitja Institute [79] and university librarians will refine the search terms and strings to capture all iterations of eHealth interventions with Aboriginal and Torres Strait Islander people. eHealth search terms will be based on

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keywords including eHealth, telehealth, telemedicine, remote monitoring, mHealth, Internet of Things, and smart technology. Electronic database searches will be conducted on Cochrane, Embase, CINAHL, PubMed, Scopus, Web of Science, and PsycINFO, and they will be limited to full-text papers in English, with no limit regarding the publication date. Participants of the intervention studies of all ages will be either Aboriginal and Torres Strait Islander people or health staff (either Aboriginal and Torres Strait Islander or non-Indigenous) who work with Aboriginal and Torres Strait Islander people; if the participants are culturally diverse, the outcomes specific to Aboriginal and Torres Strait Islander people are reported. As per the aim of this systematic review and the scope of the overall research protocol, studies that relate to eHealth interventions with other First Nations populations will be excluded. Studies will be focused on an eHealth intervention (as defined in the Introduction) and report on one or more of the following outcomes: adoption, implementation, integration, use (usage data), user perspectives (eg, feedback, knowledge, level of support, barriers, enablers, accessibility, and acceptability). Experimental, quasi-experimental, and qualitative studies from peer-reviewed scientific journals will be included. However, due to the potentially high yield of search results, separation of the experimental/quasi-experimental from qualitative studies may occur, with 2 systematic literature reviews produced. Database searches, screening, and data extraction will be conducted by 2 researchers.

Quality Assessment

Risk of bias and methodological quality for the experimental and quasi-experimental studies will be evaluated by at least 2 authors using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [80] and Level of Evidence tool [81].

Analysis and Reporting

A descriptive approach will be used for data synthesis due to the mix of study designs and research approaches expected across eHealth interventions. Descriptive analysis will consider the intervention(s) (modality, exposure, etc), health challenge(s) addressed, clinical outcomes, use outcomes, user-feedback outcomes, and characteristics of the intervention process that are important to Aboriginal and Torres Strait Islander people. These embedded factors will be identified through thematic analysis. For example, stakeholders within an eHealth intervention may highlight "access to technology" or "co-design" as significant factors in the application of digital health with Aboriginal and Torres Strait Islander people.

Findings of the systematic literature review(s) will inform subsequent phases of the research program for development of the best practice framework. Outcomes will also be disseminated in a scientific journal paper and at a relevant conference. Phase 1 is projected to be completed by January 2023.

Phase 2: Scoping Review

Aim and Rationale

The aim of the scoping review is to identify what existing frameworks, ethical processes, and practice guidelines, particularly grounded with Aboriginal and Torres Strait Islander peoples' knowledge, should be used to inform eHealth interventions with Aboriginal and Torres Strait Islander people, and to identify gaps in the scientific and gray literature. For example, a known gap in the literature is that the MeRA checklist has not been validated with Aboriginal and Torres Strait Islander populations. A central component of this review is to identify resources, solutions, and processes enriched with the voices, priorities, and wisdom of Aboriginal and Torres Strait Islander people. Therefore, the review seeks to identify the available frameworks, guidelines, and practice principles across the eHealth field, as well as those guiding health implementation and evaluation with Aboriginal and Torres Strait Islander people more broadly. Examples of these include the national ethical guidelines [42,82,83] and bespoke reference documents such as the South Australian Aboriginal Health Research Accord [84]. Although a scoping process was conducted earlier by the authors, this full scoping review will ensure that all literature has been captured systematically. This study will address RQ2.

Scoping Design

Broadly speaking, the research team envisages the scoping process to follow standard practices, as outlined in the updated JBI iterations [70,85] of the original work by Arksey and O'Malley and Levac et al [68,69]. The scoping review research stages will achieve in-depth and broad scoping results that will identify all relevant literature, regardless of study design. Importantly, this will include a parallel process of iterative consultation with experts to source additional practice insights. A full protocol for the scoping review will be date-stamped on the Open Science Framework.

Searches, and Inclusion and Exclusion Criteria

Electronic searches will be conducted on the Cochrane, Embase, CINAHL, PubMed, Scopus, Web of Science, and PsycINFO databases. Search terms and strings will be finalized using recommendations by the Lowitja Institute and university librarians to capture iterations of health interventions involving Aboriginal and Torres Strait Islander people. The following keywords will form the basis of the search: framework, practice guide, best practice, principles, and recommendations. Experimental, quasi-experimental, and qualitative papers will be sought in English, with no limit on the date of publication. Gray literature will be researched to identify existing resources in health care, health organizations, and health entities, via health, nongovernment, and government websites.

Searches and screening will be conducted by 2 researchers with discussion for resolving differences. Manual searches of reference lists (both scientific and gray literature) will be conducted to identify unique results or resources. Websites and other internet-based resources will be identified and screened using a tabulated spreadsheet. A final list of full-text papers and their citations that meet the inclusion criteria will be downloaded and saved.

Data Extraction and Synthesis

Relevant data from the retained papers and resources will be tabulated in a spreadsheet. The data items of relevance will include Aboriginal and Torres Strait Islander collaborative

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groups and entities, the region of Australia, health focus, characteristics of interventions, frameworks/guidelines/best practices, rationale/feedback/discussion regarding the application of frameworks, and participant feedback specific to the frameworks/research approaches.

A descriptive approach will be used for data synthesis due to the expected mix of study designs and gray literature results. Descriptive analysis will consider the identified frameworks, best practices, and guidelines, as well as their application to the setting and the health intervention (including eHealth). Thematic analysis will highlight the themes and inclusions that researchers and participants nominate or reflect as critical to culturally safe health interventions. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) will be used for quality reporting of the scoping study.

Dissemination

Findings of the scoping review will inform subsequent phases of the research program for development of the best practice framework. Outcomes will also be disseminated in a scientific journal paper and at a relevant conference. The projected completion of Phase 2 is January 2023.

Phase 3: Theme Development

Informed by the findings of Phases 1 and 2, broad themes for consideration will be drafted and used to prompt and support deliberation and discussion of the overall best practice framework using qualitative data collection methods. Appraisal of the data from Phases 1 and 2 will be conducted by members of the Collaboration with HREC approval if warranted. Members of the Collaboration are mentioned in the Acknowledgements. Criteria for themes will be established in Phases 1 and 2 using the empirical evidence available, as well as the professional judgement and considering the context of the relevant research activities underway within the Collaboration. Phase 3 is expected to be completed in May 2023.

Phase 4: Theme Consultation

Study Aim and Rationale

The aim of this qualitative research is to identify the perceptions and experiences of stakeholders about the use, access priorities, and relevance of eHealth with Aboriginal and Torres Strait Islander people and to generate overall themes. The qualitative research activities will be embedded within existing eHealth research studies by members of the Collaboration. This pragmatic data will complement the themes derived from the literature in Phases 1 to 3.

Study Design and Data Collection

Semistructured interviews and focus groups will be used to explore the perceptions and experiences of stakeholders within the research partnerships and activities of the Collaboration. Specific inclusion/exclusion criteria and recruitment strategies will be outlined in each of the eHealth study protocols with HREC approval and published in due course. For example, a mixed method feasibility trial is currently being conducted for an mHealth platform to manage hypertension and other cardiovascular risk factors with stakeholders from 2 ATSICCHOs in Queensland (Mahoney and Goodman, 2021; HREC/2021/QCH/61500). Qualitative enquiry conducted within the mHealth platform feasibility study includes a core set of questions about eHealth that will be replicated in other feasibility studies led by the Collaboration. The overall line of enquiry for the qualitative activities will be published in due course. Although themes from Phase 3 will be available to support the qualitative process, the methods for data collection and analysis will be phenomenologically informed, whereby the phenomena of eHealth and user needs are explored, described, and interpreted as they relate to the individuals and their own experiences. A phenomenological approach is regularly used in qualitative health research to understand health care user and service provider experiences because it prioritizes the voices and narratives of the participants as opposed to the interviewer and line of questioning [86]. This approach is particularly important as we aim to understand if there are culturally specific needs and values related to eHealth implementation and adoption.

Analysis and Synthesis of Findings

Interviews and focus groups will be audio-recorded and transcribed in preparation for thematic analysis. Although there are synergies across the Collaboration's research activities and feasibility trials, study investigators will conduct their respective data collection and analyses independently. Resulting themes and research outcomes will be cross-referenced across studies in cooperation with other study investigators, only after the conclusion of the data collection and analysis to prevent crossover of research findings. Scientific dissemination of the broader research design, study participants, interventions, outcomes, and conclusions for each eHealth feasibility study will be coordinated by study investigators. Specifics relevant to the reporting of the resulting best practice framework will be documented accordingly. Phase 4 is projected to be completed in June 2023.

Phase 5: Expert Review I

The concepts and overall themes defined up to this point (Phases 1 to 4) will be put forth in a draft document with a ranking scale as part of a Delphi exercise. The Delphi consensus method is a systematic process where items can be refined based on expert opinion and consensus [65,67]. Members of the Collaboration will participate in the first review of the concepts that will form the first draft of the best practice framework. In subsequent Delphi rounds, members of the Collaboration will recruit subject matter experts, key research personnel, and partners from ATSICCHOs and community-controlled organizations with expertise in Aboriginal and Torres Strait Islander health. Ethical approval from the relevant HREC will be outlined in research protocols (with inclusion/exclusion details) and obtained prior to data collection. Delphi participants will be invited to review the draft concepts and to indicate which ones should be prioritized or removed. This review process will be informed by Polit and Beck's method [65], with each item ranked from 1 (Do not use) to 4 (Definitely keep). Scoring will be determined by summing the percentages of agreement between the panels; items that have a score greater than 79% will be included and those with scores less than 69% will be removed; those with

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in-between scores will be iteratively reviewed until a consensus is achieved (or for a maximum of 3 rounds). The accepted concepts will then be formatted into a document for further evaluation. Phase 5 is expected to be completed in June 2023.

Phase 6: Expert Review II

Pragmatic feedback and discussion from Phase 5 will be used by the Collaboration to revise the set of principles that make up the framework using constant comparison to ensure that revisions are in line with Phases 1 to 4. A subsequent and final modified-Delphi exercise will be conducted with a broader, national panel of research experts and Aboriginal and Torres Strait Islander health professionals identified by the Collaboration. Ethical approval from the relevant HREC will be outlined in research protocols (with inclusion/exclusion details) and obtained prior to data collection. This final research phase will produce the foundational best practice framework for culturally safe eHealth interventions with Aboriginal and Torres Strait Islander people. Phase 6 is anticipated to be completed in September 2023.

Phase 7: Dissemination

The foundational best practice framework will be disseminated in a scientific journal paper, together with an internal report to document the stages of research, evidence, feedback, authorship, and collaborations. Phase 7 is expected to be completed in December 2023.

Results

Scoping work by members of the Collaboration with Aboriginal and Torres Strait Islander partners in 2019-2020 established interest and capacity for eHealth research projects including mHealth for hypertension management [87], Internet of Things to support independent living [88] and for housing suitability with climate change impacts [13]. Several of these feasibility projects commenced in 2020-2021 and qualitative data collection with research partners has commenced.

Conceptual discussion by the Collaboration for a best practice framework and the associated research program occurred in August 2020. A draft of the research program was produced in June 2021 with subsequent funding obtained in July 2021. The Collaboration approved the protocol draft in December 2021.

Results for several research phases of the best practice framework development are expected by January 2023, commencing with the systematic literature review and the scoping review. The projected completion times of subsequent phases are outlined in Figure 1, with the overall research program expected to be completed in December 2023.

Discussion

Key Anticipated Findings

The overall aim of this research program is to produce a best practice framework that will guide the co-design, implementation, and evaluation of culturally safe eHealth interventions with Aboriginal and Torres Strait Islander people. The development of the eHealth best practice framework will draw on evidence of best practices sourced from scientific and gray literature, health and community stakeholders, and key experts to reflect the values and priorities of Aboriginal and Torres Strait Islander people.

Maar et al [41] proposed a set of “wise practices” for cultural safety in eHealth with First Nations communities in 2019. The practices were developed from extensive qualitative data collected throughout a 5-year randomized clinical trial for managing hypertension with eHealth. Although the recommendations add significant value to the field, they are derived from works involving First Nations communities from Canada, and therefore cannot be directly applied to eHealth with Aboriginal and Torres Strait Islander people in the Australian setting.

Previous work involving Aboriginal and Torres Strait Islander people in the emerging digital health space have provided anecdotes regarding the important inclusions for such work. For example, favorable reports of user engagement, positive health outcomes, and the relevance of mHealth to support Aboriginal and Torres Strait Islander communities were attributed to the significance of co-design, embedded knowledge of Aboriginal and Torres Strait Islander people within projects, and consideration of local contexts rather than using a “one size fits all” approach [20]. However, more complete understanding and consensus are required on what is important to Aboriginal and Torres Strait Islander people when conducting eHealth interventions. Currently, no benchmark exists regarding the cultural safety within such studies and how eHealth can be effectively integrated within the existing models of care and leadership of ATSICCHOs. This integration is critical for maximum relevance and effectiveness in ensuring the well-being of Aboriginal and Torres Strait Islander people and for contributing to closing the gap in health disparities. This protocol has outlined a program of research designed by the Collaboration that seeks to meet this need.

Literature regarding the development of other guidelines within Aboriginal and Torres Strait Islander health settings offers insight into this research program. Although the approach of each research group to the development of guidelines varied given the differing health foci, there were parallels of significance [71,73-75]. Authentic consideration of culturally respectful research approaches with Aboriginal and Torres Strait Islander people was foundational. Research teams also highlighted the value of multiple sources for a quality evidence base, including literature, theory, and inputs from multiple stakeholder groups [71,73-75]. Reaching consensus from group-based activities was reported as a plausible challenge. Research teams worked through this by having further discussions with individual stakeholders and groups during subsequent rounds of consultation [73] or by recommending a discretionary approach in certain facets of applying the practice guidelines [71]. The challenge of capturing the diversity of all possible stakeholders considering remoteness, language, and literacy levels was acknowledged by authors [75].

Strengths

This research program has several strengths. First, the protocol draws on a number of sources as an evidence base to shape the

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final framework. Beyond the thorough reviews of literature, best practice evidence will be gained from the expertise of Aboriginal and Torres Strait Islander leaders and health professionals, and insights provided by the Aboriginal and Torres Strait Islander people who are participants in eHealth research studies [56]. Second, the previous and ongoing eHealth research activities of the Collaboration across diverse settings provides governance for the research, along with an extensive network of research experts in the fields of eHealth and Aboriginal and Torres Strait Islander health. Both these strengths will ensure that the resulting best practice framework will not result from a single research team with a narrow frame of reference. Finally, the best practice phases are scheduled to occur over several years. This timeline will enhance the iterative process of data collection, theming, and stakeholder consultations with flexibility in the delivery of outputs.

Limitations

The limitations of this research may involve either a dearth or an excess of evidence in the scoping and systematic reviews. This will be managed with guidance from the Collaboration as needed. The feasibility of conducting the consultation phases of this research may also be a challenge. Although the Collaboration has an excellent network of experts, a flexible approach will be necessary in light of the recent challenges related to travel and in-person sessions. For example, Delphi consensus sessions may need to be hybrid, including internet-based and in-person sessions.

Following dissemination, it will be important for the Collaboration to conduct ongoing promotion, evaluation, and adaptation processes of the best practice framework, as emphasized by Moher et al [63]. Application of the framework in future eHealth trials in partnership with ATSICCHOs and other Aboriginal and Torres Strait Islander stakeholders will generate evidence for its validity. Maintenance of a relevant and rigorous framework will be necessary as technology continues to evolve.

Conclusions

This protocol has outlined the phases of a research program to prepare a best practice framework that will guide and inform the co-design, implementation, and evaluation of culturally safe eHealth interventions within existing models of health care for Aboriginal and Torres Strait Islander people. Data collected throughout the phases will be sourced from scientific literature, stakeholders, and the expertise of Aboriginal and Torres Strait Islander health sector, providing rigor and validity to the resulting framework.

It is timely that principles are generated to guide the overall eHealth research process, drawing on the excellence of Aboriginal and Torres Strait Islander primary health care models in real-world settings. The iterative and collaborative approach of this research program will also ensure that Aboriginal and Torres Strait Islander people determine the cultural safety and research relevance. Future research to validate the framework and monitor its relevance will be important.

Acknowledgments

This project will use governance from an existing multiagency research partnership, the eHealth Research Collaboration for Aboriginal and Torres Strait Islander Health (the Collaboration). The Collaboration was established in 2019 and is led by Indigenous researchers and scientists who guide the ethos of research activities and responsibilities. This approach facilitates co-creation and co-design methodologies where the voices, values, and priorities of Aboriginal and Torres Strait Islander communities and people are upheld. The Collaboration's aim is to promote an evidence base for technology in health care specific to the interests and needs of Aboriginal and Torres Strait Islander people through the facilitation of eHealth research (with respect to consultation, co-design, trial, and evaluation) and the co-development of technologies. As such, the Collaboration will act as a Scientific Reference Group with input to the conduct and dissemination of the research activities. This research program is supported by an internal Commonwealth Scientific and Industrial Research Organisation (ACORN) grant. A member of the Collaboration is supported by the Queensland Children's Hospital via a philanthropic grant from Woolworths.

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Authors' Contributions

GRC, KB, and RM conceptualized the program of research and designed the protocol. GRC prepared the manuscript with significant input from KB. RM and members of the Collaboration provided additional input and critical review of the manuscript. All authors and the Collaboration members have read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Information and communication technologies in health care: definitions, health scenarios, and example products.
[DOCX File , 23 KB - resprot_v11i6e34904_app1.docx]

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Abbreviations

ATSICCHO: Aboriginal and Torres Strait Islander Community Controlled Health Organization
CONSORT: Consolidated Standards of Reporting Trials
HREC: Human Research Ethics Committee
mHealth: mobile health
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
RQ: research question
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Development of a Patient-Centered Preference Tool for Patients With Hematologic Malignancies: Protocol for a Mixed Methods Study

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Abstract

Background: The approval of novel therapies for patients diagnosed with hematologic malignancies have improved survival outcomes but increased the challenge of aligning chemotherapy choices with patient preferences. We previously developed paper versions of a discrete choice experiment (DCE) and a best-worst scaling (BWS) instrument to quantify the treatment outcome preferences of patients with hematologic malignancies to inform shared decision making.

Objective: We aim to develop an electronic health care tool (EHT) to guide clinical decision making that uses either a BWS or DCE instrument to capture patient preferences. The primary objective of this study is to use both qualitative and quantitative methods to evaluate the perceived usability, cognitive workload (CWL), and performance of electronic prototypes that include the DCE and BWS instrument.

Methods: This mixed methods study includes iterative co-design methods that will involve healthy volunteers, patient-caregiver pairs, and health care workers to evaluate the perceived usability, CWL, and performance of tasks within distinct prototypes. Think-aloud sessions and semistructured interviews will be conducted to collect qualitative data to develop an affinity diagram for thematic analysis. Validated assessments (Post-Study System Usability Questionnaire [PSSUQ] and the National Aeronautical and Space Administration's Task Load Index [NASA-TLX]) will be used to evaluate the usability and CWL required to complete tasks within the prototypes. Performance assessments of the DCE and BWS will include the evaluation of tasks using the Single Easy Questionnaire (SEQ), time to complete using the prototype, and the number of errors. Additional qualitative assessments will be conducted to gather participants' feedback on visualizations used in the Personalized Treatment Preferences Dashboard that provides a representation of user results after completing the choice tasks within the prototype.

Results: Ethical approval was obtained in June 2021 from the Institutional Review Board of the University of North Carolina at Chapel Hill. The DCE and BWS instruments were developed and incorporated into the PRIME (*P*reference *R*eporting to *I*mprove *M*anagement and *E*xperience) prototype in early 2021 and prototypes were completed by June 2021. Heuristic evaluations were conducted in phase 1 and completed by July 2021. Recruitment of healthy volunteers began in August 2021 and concluded in September 2021. In December 2021, our findings from phase 2 were accepted for publication. Phase 3 recruitment began in January 2022 and is expected to conclude in September 2022. The data analysis from phase 3 is expected to be completed by November 2022.

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Conclusions: Our findings will help differentiate the usability, CWL, and performance of the DCE and BWS within the prototypes. These findings will contribute to the optimization of the prototypes, leading to the development of an EHT that helps facilitate shared decision making. This evaluation will inform the development of EHTs to be used clinically with patients and health care workers.

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KEYWORDS

co-design; informed decision making; mHealth; electronic health care tools; shared decision making; patient engagement; hematologic malignancies

Introduction

Background

Hematologic malignancies include both indolent and highly aggressive blood cancers such as leukemia, lymphoma, and multiple myeloma. Outcomes for patients are heterogeneous based on disease and functional factors. The last decade has brought an unprecedented increase of Food and Drug Administration (FDA)–approved chemotherapeutic agents for patients with hematologic malignancies [1-6]. These approvals have expanded treatment options yet increased the complexity of treatment decisions. One primary role of clinicians is to elicit patients' preferences to personalize treatment recommendations [7]. The standard shared decision-making process, however, is currently unreliable to accurately elicit patient preferences, frequently resulting in patient-provider preference-discordance [8-15]. Developing strategies to improve shared decision making is a key priority in advancing patient-centered care in oncology [16].

Novel stated preference methods including best-worst scaling (BWS) instruments and discrete choice experiments (DCEs) have recently been developed that can accurately quantify patient preferences [17,18]. BWS instruments have been used to prioritize the values of stakeholders [19]. Object case BWS instruments (henceforth simply referred to as BWS instruments) are thought to have less cognitive burden on respondents compared with other preference elicitation instruments [20]. Profile case DCEs (henceforth simply referred to as DCEs) are the most frequently employed type of DCE in health care. DCEs require participants to make choices between pairs of hypothetical treatments with different outcomes and have been particularly useful at rigorously quantifying the trade-off preferences of patients for treatments and informing patient-focused drug development [7]. Through a multistage process involving stakeholder engagement with patients, caregivers, and the FDA, we developed a BWS instrument and a DCE for patients with acute myeloid leukemia (AML) [19,21-23]. Using the BWS, we elicited the treatment preferences of 832 patients with AML and demonstrated that patients had the strongest concerns about outcomes in psychosocial and physical domains [19]. Using the DCE, we elicited specific treatment outcome preferences of 294 patients with AML and demonstrated substantial differences among preferences [22]. Some patients preferred to maximize their overall chance of long-term survival and were willing to endure a high burden of side effects or a lengthy hospitalization for this opportunity; others preferred to minimize treatment effects to maintain their quality of life.

DCEs and BWS instruments have been developed on paper and electronically [24]. To the best of our knowledge, comparative assessments of the usability, cognitive workload (CWL), and performance between DCEs and BWS instruments when developed as electronic health care tools (EHTs) have not been performed. This evaluation is important because use of EHTs has been shown to result in improved health outcomes, including increasing knowledge, improvement in risk perception, and improvement in communication between patients and health care workers [25]. In addition, involving older adults (>60 years of age) diagnosed with hematologic malignancies in the design process can positively impact their learning, sense of participation, and improve the development of the EHTs to better reflect the needs of the intended population [26].

Prior Work

A paper version of the prototype was initially developed through a process involving multiple stakeholders including patients, advocacy groups, and researchers. This prototype was based on a DCE and developed specifically to elicit attribute preferences for treatment outcomes of patients with AML [22,23]. The DCE was piloted and then used in a national survey of patients with AML, who found it to be acceptable and feasible [27], and has been used prospectively in patients in an ongoing feasibility and acceptability trial with the UNC (University of North Carolina) Lineberger Comprehensive Cancer Center.

BWS is a simpler form of a DCE that does not involve changing levels of attributes. A BWS survey was developed by the principal investigator (DRR) of this study to capture the preferences of patients with AML and was used in a previous study, sampling 832 patients, illustrating that patients had the strongest concerns about treatment outcomes in psychosocial and physical domains [19,21].

Both the DCE and the BWS are algorithm based and were developed to quantify patient preferences based on a series of choice tasks, within which the number of attributes as well as the number of levels within each attribute determines the number of choice tasks required to assess preferences, as each attribute within each level has to be displayed a prespecified number of times to be validated [28].

Objective

We aim to use mixed methods with an iterative co-design approach to develop an EHT that incorporates the concepts,

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tacit knowledge, and lived experiences of all stakeholders [29,30]. Use of a co-design process will not only contribute to the empowerment of stakeholders but also lead to the development of an EHT that helps patients and health care workers arrive at a therapy decision that is aligned with patient preferences. Our primary objective is to evaluate the perceived usability, CWL, and performance of the DCE and BWS within the prototypes.

Methods

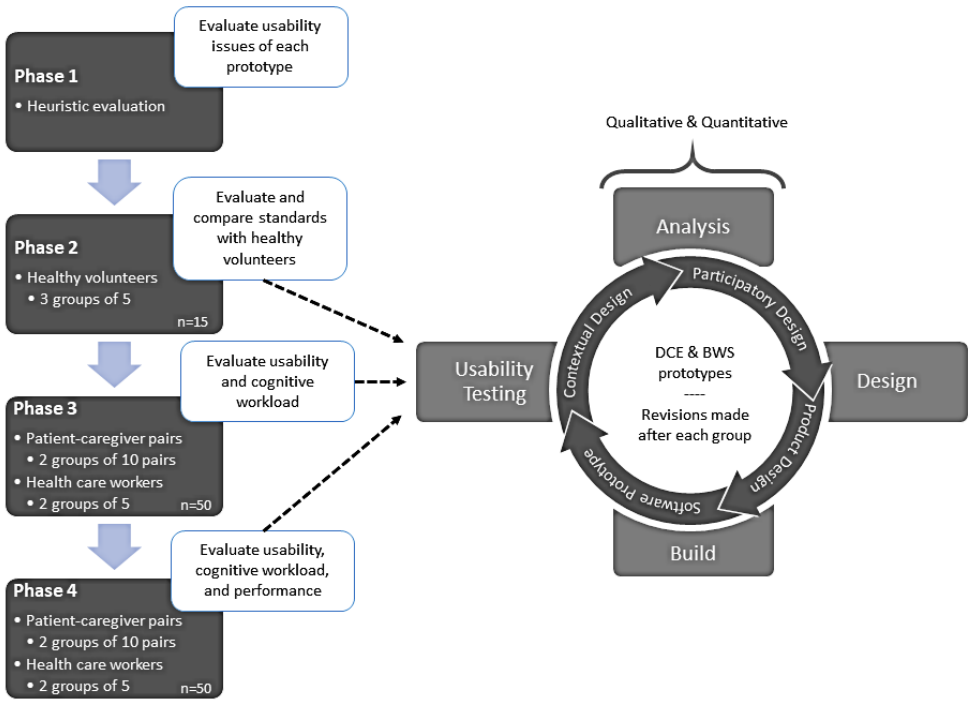
Study Design and Methodology

Overview

We will use a mixed methods research approach utilizing an iterative co-design approach. In phase 1 we will first conduct heuristic evaluations on each prototype to identify and improve existing usability issues. Usability testing will then be conducted in 3 stages: (1) with healthy volunteers to establish standards for validating the results of the target population; (2) with patients and caregivers to obtain subjective and objective feedback based on both their tacit knowledge and their novel experience using each prototype; and (3) with health care workers using qualitative assessments to gain insight into their overall impression of the tool as well as whether they would recommend this to patients and caregivers. Within phases 2-4, participants will evaluate visualizations on a Personalized Treatment Preferences Dashboard, which shows a visualization of the results a user would see upon completion of the choice tasks within the prototype. We will evaluate the prototypes and visualizations using qualitative assessments (think-aloud sessions and semistructured interviews) to develop an affinity diagram for thematic analysis, and quantitative assessments using validated questionnaires to evaluate the perceived usability of and the CWL required to perform tasks within the prototypes. This study will be conducted in iterative development stages, in which feedback from participants will be analyzed and incorporated into the design that will then be presented to subsequent groups, as depicted in Figure 1.

The involvement processes utilized in this study will be classified by the participatory co-design framework originally developed by Leinonen [31] and further refined, representing 4 distinct groupings: contextual inquiry, participatory design, product design, and software prototype as hypothesis (functional prototype) [32], as depicted in Multimedia Appendix 1. Evidence gathered from this study will be used to develop a functional prototype that effectively elicits and displays preferences, leading to more informed treatment decisions.

Figure 1. Study design workflow. BWS: best-worst scaling; DCE: discrete choice experiment.



DCE and BWS Choice Tasks

We used the established paper form of both the DCE and BWS to develop 2 medium-fidelity prototypes using Adobe XD version 40.0.22. All participants will access the prototypes through a study-provided iPad (8th generation). Each prototype is referred to as PRIME (*P*reference *R*eporting to *I*mprove *M*anagement and *E*xperience) but has distinct choice tasks as described below.

In the DCE, participants will go through a series of 10 hypothetical choice tasks, in which the same 5 attributes are presented (event-free survival, complete remission, time in hospital, short-term side effects, and long-term side effects) at different levels for each attribute within each task. For each choice task, participants will view differing profiles, consisting of attribute levels for "drug A" versus "drug B," and will be asked to evaluate the benefits and risks for each, then select which drug they prefer, as depicted in Figure 2.

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In the BWS, participants will go through a series of 10 choice tasks, in which the same 5 attributes are presented (event-free survival, complete remission, time in hospital, short-term side effects, and long-term side effects), but the levels of each attribute vary within each task. For each choice task, participants will view 5 outcomes and will be asked to choose 1 outcome that is the most important and 1 outcome that is the least important to them, as depicted in Figure 3.

To ensure the same number of choice tasks are displayed to users when measuring performance (time to complete) between the DCE and BWS, a tenth task was added to the BWS. The tenth task will repeat choice task 2 and will not be used in quantifying patient preferences. However, as choice task 2 and choice task 10 are identical, this will provide evidence regarding the consistency with which respondents select answers within the prototype.

Figure 2. DCE choice tasks. DCE: discrete choice experiment; PRIME: *P*reference *R*eporting to *I*mprove *M*anagement and *E*xperience.

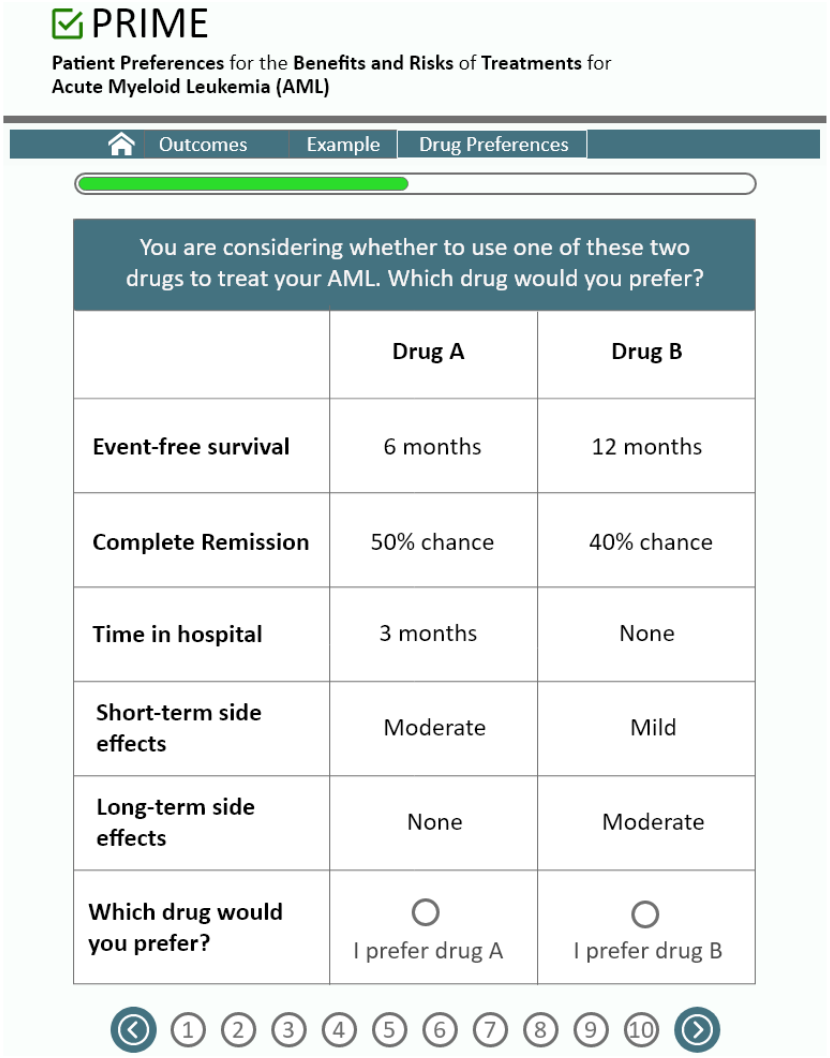

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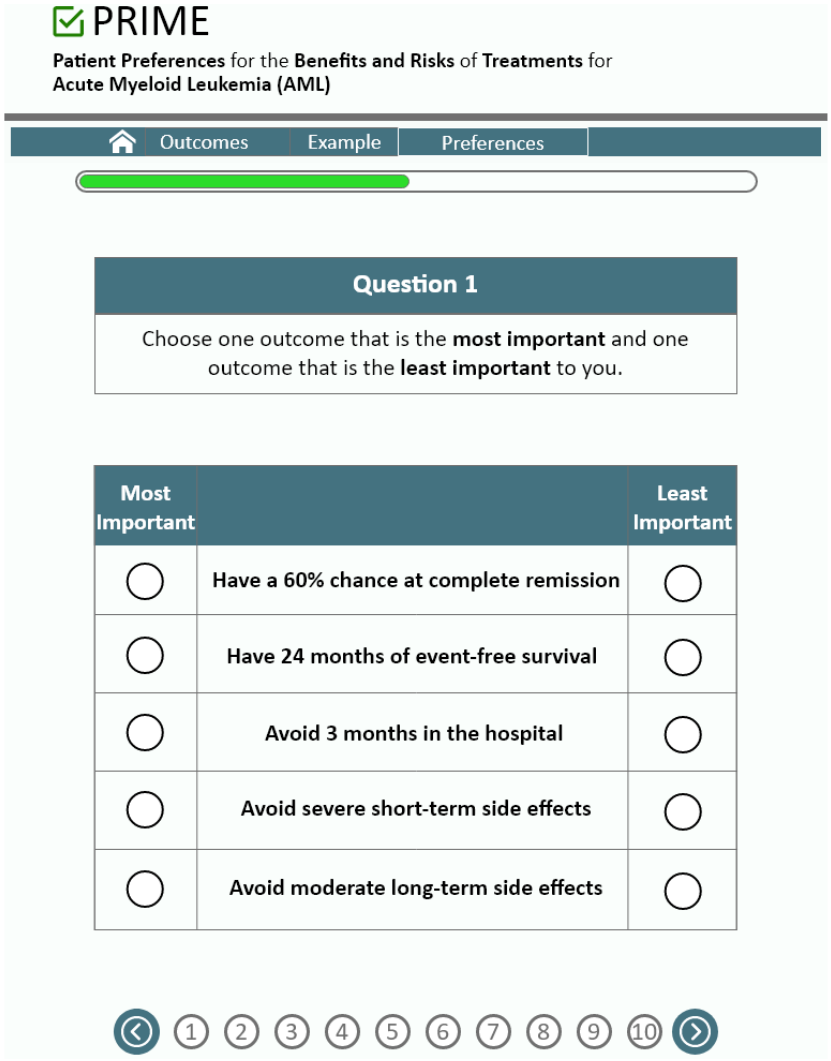
Figure 3. BWS choice tasks. BWS: best-worst scaling; PRIME: *P*reference *R*eporting to *I*mprove *M*anagement and *E*xperience.



Visualization: Personalized Treatment Preferences Dashboard

Data from both the DCE and BWS prototypes will be used to generate a graphical representation of results based on the patients' selected preferences. There is currently no standard of practice for generating visualizations of patient preferences. Therefore, we will elicit feedback on multiple visualizations in this study. Visualizations will be static representations and will not reflect the specific preferences of individual participants. To ensure the information presented is comprehensive and understandable, we have separated this from each prototype to solicit feedback specific to the visualization. Semistructured interviews will be conducted to obtain feedback on each visualization to improve participant understanding.

The first visualization (Figure 4) is a color-coded bar chart that displays the patients' values in increasing levels of importance. The second visualization (Figure 5) uses a gauge to display the benefit-risk profile from a range of "less aggressive" to "more aggressive" with an arrow pointing to the patient's specific level of aggressiveness in comparison to similar patients.

The third visualization (Figure 6) is a line graph that displays how the patient's preferences have changed over time.

The fourth visualization is a narrative visualization utilizing anthropomorphic icons to represent the patient relative to the population, as depicted in Figure 7. This visualization was informed by Segel and Heer's [33] Narrative Visualization Framework and Munzner's [34] Nested Model for Visualization Design. Specifically, Segel and Heer's organization structure, consisting of 3 divisions, namely, (1) genre, (2) visual narrative tactics, and (3) narrative structure tactics, was utilized to gain a broader perspective on best techniques for visualizing preferences. Prior studies have demonstrated that risk recall is significantly higher using narrative visualization compared with other icon types when used in risk perception visualizations [35].

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Figure 4. Bar chart.

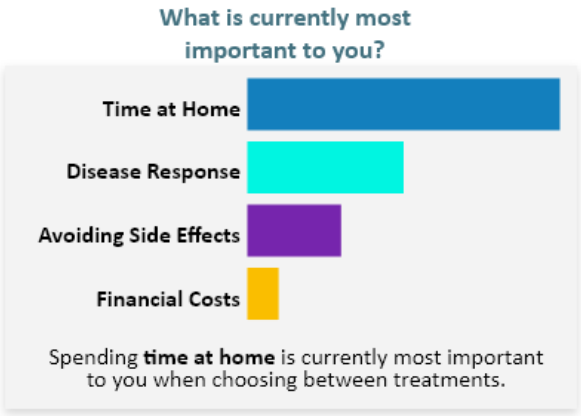

Figure 5. Gauge chart. AML: acute myeloid leukemia.

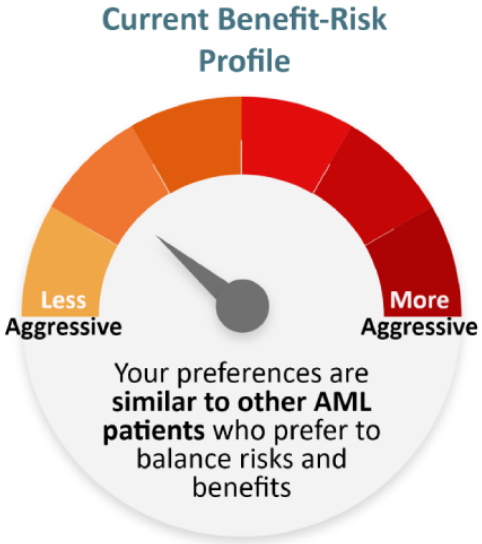

Figure 6. Preferences over time line graph.

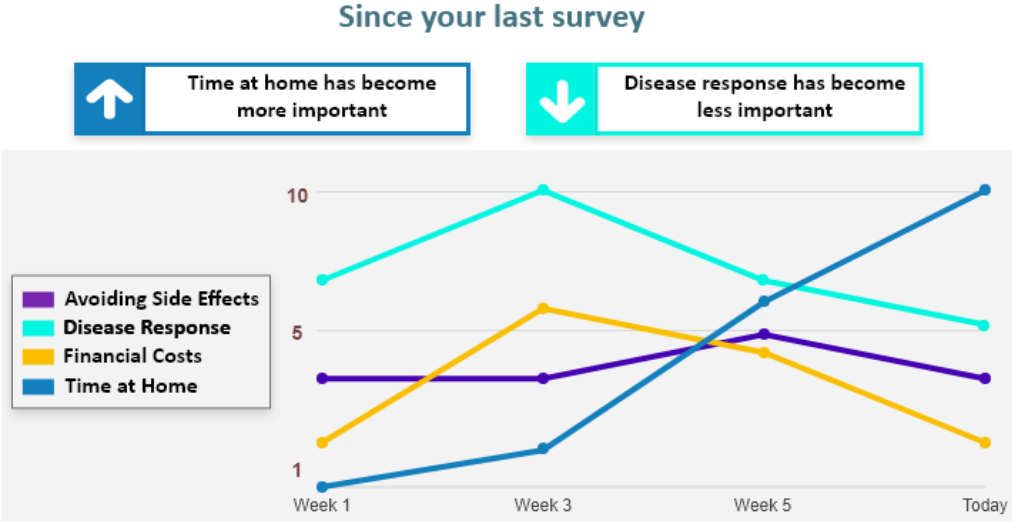

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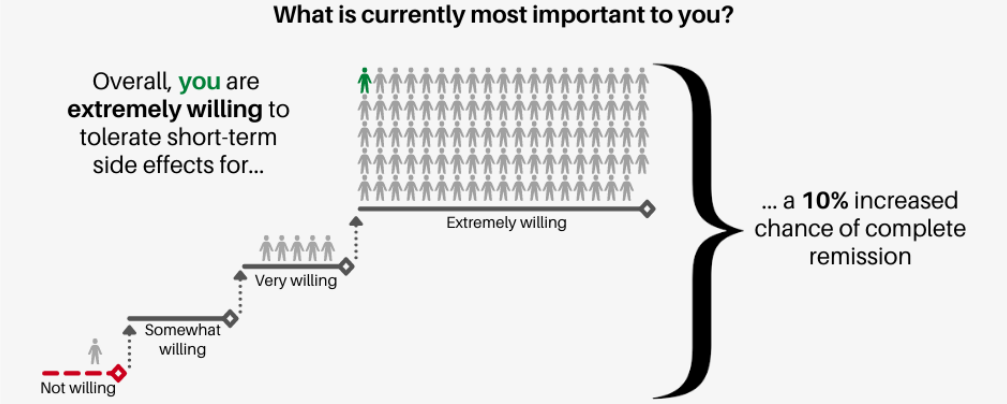
Figure 7. Narrative visualization.



Participants and Setting

This study involves 4 participant types including healthy volunteers, patients, caregivers, and health care workers. Healthy volunteers will be recruited from the general population through the Research for Me at UNC platform and must be 21 years or older [36]. Patients who meet the following criteria will be eligible to participate: (1) have a confirmed diagnosis of a hematologic malignancy including leukemia, lymphoma, or myeloma; (2) be on active chemotherapy (not including maintenance therapy for myeloma); (3) be able to read and understand English; (4) age 60 years or older; and (5) be willing to provide consent. Caregivers must be (1) 21 years and older, and (2) identified as the primary caregiver by the patient. Health care workers must be employed within hematologic malignancies (inpatient or outpatient) units as a nurse, nurse navigator, advanced practitioner, or physician. Administrators that oversee patients with hematologic malignancy and have experience working with patients with AML will also be eligible. Exclusion from the study will occur if participants have dementia, altered mental status, or a psychiatric condition that would prohibit the understanding or rendering of informed consent or participation in the user testing.

We have chosen to include patients, caregivers, and health care workers in the design process to better understand patients' physical characteristics, the mental characteristics of patients and caregivers, the needs and behaviors of all participants, as well as the sociotechnical context in which each participant engages with technology and manages treatment decisions [37]. The purpose of this EHT is to facilitate dialog among patients, caregivers, and health care workers, and therefore it is important to understand the perspective of each stakeholder, and identify related themes and insights that will be used to define the direction of the final prototype [37]. We have chosen to include healthy volunteers to both establish standards for validating our results as well as to identify usability issues before conducting testing with our target population. We intend to engage all stakeholders in the design process by inviting them to participate at levels that will promote empowerment in the shared decision-making process [38].

Participants will be informed through the consent process that they will receive compensation for their participation in the study. Participants will receive a US $25 gift card upon completion of all tasks related to each PRIME prototype.

This study is taking place in the Human Factors Laboratory housed within the Department of Radiation Oncology at the University of North Carolina, Chapel Hill, NC. Eligible health care workers will participate in the study via an online session in Zoom (Zoom Video Communications, Inc.).

Usability Testing and Data Collection

Phases and Measures

While some evaluation measures are conducted in all phases, as noted in Table 1, within each phase our study team will focus on a specific aspect of the prototype and data collection measure as described below.

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Table 1. Usability testing objectives and measures.

Phase	Participants	Objective	Evaluation measures
Phase 1: Planning (heuristic evaluation)	Study team	To evaluate the general usability issues of each prototype	• Heuristic evaluation

Phase 2: Evaluation with healthy volunteers	Healthy volunteers	• To evaluate the usability and CWL[a] of the DCE[b] and BWS[c] within the prototypes
		• To evaluate the usability of the Personalized Treatment Preferences Dashboard
			Usability
			• Quantitative assessment:
			  • PSSUQ[d]
			• Qualitative assessments:
			  • Think-aloud sessions
			  • Semistructured interviews
			Cognitive workload
			• Quantitative assessments:
			  • NASA-TLX[e]

Phase 3: Evaluation with patients, caregivers, and health care workers	• Patients
	• Caregivers
		To evaluate the usability and CWL of the DCE and BWS within the prototypes	**Usability**
			• Quantitative assessment:
			  • PSSUQ
			• Qualitative assessments:
			  • Think-aloud sessions
			  • Semistructured interviews
			Cognitive workload
			• Quantitative assessments:
			  • NASA-TLX
			• Qualitative assessment:
			  • Cognitive task analysis

	Health care workers	To evaluate the usability of the DCE and BWS within the prototypes	**Usability**
			• Qualitative assessments:
			  • Think-aloud sessions
			  • Semistructured interviews

Phase 4: Final evaluation of usability, CWL, and performance	• Patients
	• Caregivers
		To evaluate the usability, CWL, and performance of the DCE and BWS within the prototypes	**Usability**
			• Quantitative assessments:
			  • SEQ[f]
			  • PSSUQ
			• Qualitative assessments:
			• Semistructured interviews
			Cognitive workload
			• Quantitative assessments:
			  • NASA-TLX
			• Qualitative assessment
			  • Cognitive task analysis
			Performance
			• Quantitative assessments:
			  • Time to complete
			  • Number of errors
			  • Eye-tracking

	Health care workers	To evaluate the usability of the DCE and BWS within the prototypes	**Usability**
			• Qualitative assessments:
			  • Think-aloud sessions
			  • Semistructured interviews

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[a]CWL: cognitive workload.

[b]DCE: discrete choice experiment.

[c]BWS: best-worst scaling.

[d]PSSUQ: Post-Study System Usability Questionnaire.

[e]NASA-TLX: National Aeronautical and Space Administration's Task Load Index.

[f]SEQ: Single Easy Questionnaire.

Phase 1: Planning (Heuristic Evaluation)

A group of 3-5 experts will conduct a heuristic evaluation of each prototype and provide feedback based on Dowding's Usability Principles [39]. These principles incorporate Nielsen's rating system [39,40] from "1=cosmetic problem only" to "4=usability catastrophe," and consist of 7 general principles and 3 principles specific to information visualization. This process will ensure general usability issues are addressed. We anticipate that aggregating the results of our experts will help us to discover approximately 50%-75% of usability issues through this process, based on Nielson and Landauer's model [41,42] for predicting usability problems. Dowding's checklist of usability heuristics is an appropriate tool, as it provides guidance for evaluating both EHTs and data visualizations.

Phase 2: Evaluation With Healthy Volunteers

Overview

Healthy volunteers will be asked to complete a baseline questionnaire online via REDCap before the user testing session. Healthy volunteers will complete a short demographic questionnaire and will be asked to report on their race, ethnicity, education, household income, employment, and technology comfort level.

During the user testing session, healthy volunteers will be asked to compare and evaluate both the DCE and BWS prototypes as well as the visualizations within the Personalized Treatment Preferences Dashboard. Participants within this phase will be divided into 3 groups, each consisting of 5 users. Based on Nielson's [43] user testing recommendations, user groups of 5 should be sufficient to resolve approximately 75% of usability issues.

Data gathered will be used to make iterative improvements to each prototype and then presented to subsequent groups for further evaluation.

Healthy volunteers will provide subjective and objective feedback about each prototype utilizing the following assessment methods.

Quantitative Assessments: Usability

Participants will evaluate the usability of each prototype by completing questions related to perceived usability in the Post-Study System Usability Questionnaire (PSSUQ). The PSSUQ is one of the most widely used poststudy standardized questionnaires, consisting of 16 questions divided into 3 subconstructs: system usefulness, information quality, and interface quality [44]. Based on 21 studies and 210 participants, the benchmark scores derived from Sauro and Lewis [45] provide the following means to interpret PSSUQ scores: overall (2.82), system quality (2.80), information quality (3.02), and interface quality (2.49). Better performance and satisfaction are reflected in a lower PSSUQ score [45]. The PSSUQ was chosen as it is a relatively quick assessment that can quantify the overall perceived usability of each prototype.

Quantitative Assessments: Cognitive Workload

The impact of each prototype on CWL will be quantified subjectively using the National Aeronautical and Space Administration's Task Load Index (NASA-TLX) questionnaire. The NASA-TLX is widely considered to be a valid and reliable subjective measure of mental workload and is used across many disciplines [46-48]. The NASA-TLX measures 6 dimensions of CWL: mental, physical, and temporal demands, frustration, effort, and performance, with scores of 55 or more associated with reduced performance in numerous settings, including oncology [49]. NASA-TLX is considered to be the most commonly used subjective measure of CWL in health information technology and is a reliable measure of CWL in older adults [50]. As the NASA-TLX is easy to administer and has a low responder burden, this assessment was chosen as the appropriate measure to quantify the subjective CWL of users performing tasks within each prototype.

Qualitative Assessments: Usability

Participants will perform think-aloud sessions throughout the user testing to share how each prototype has been able to capture their preferences for treatment outcomes or whether the display of preferences is useful. We will engage participants as co-designers, soliciting feedback on the available functions in the current prototypes and encouraging them to make suggested improvements to the design of the EHT as well as the visualization depicting user preferences. Information obtained during user testing will be aggregated per group and used for iterative improvements to the prototype. Each group will evaluate prototypes that have been revised based on stakeholder feedback from the previous groups.

Qualitative Assessments: Semistructured Interviews

Semistructured interviews will be conducted to elicit feedback from participants on whether they understood various aspects of the tool, including but not limited to (1) definitions of the attributes, (2) ability to distinguish between the levels of attributes as presented, (3) which choice task series (BWS or DCE) was preferrable, and (4) whether they feel patients and family caregivers would utilize this tool. Data will be collected through the recording of interviews.

Participant Characteristics: Additional Validated Measures

Additional validated assessment measures will be included in the study to assess whether various attributes are correlated with treatment decisions (Multimedia Appendix 2). Participants will be assessed on memory skills, as well as on their electronic health literacy skills.

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Participant Characteristics: Memory Skills

Participants will be asked to repeat a series of numbers during both the forward and backward assessments of the Digit Span test, a subset of the Wechsler Intelligence Scale, which when used separately, are considered validated measures of working memory [51,52]. Participants will be assessed on their ability to repeat strings of numbers, increasing in length by 1, until an error occurs on the reiteration of the string, or they reach a string length equal to 9. Participants will run through all forward strings before moving to the digit span backward test, in which they will be asked to repeat strings of numbers in reverse order. While the digit span test can be conducted by a verbal facilitator using only pencil and paper, we have chosen to use the computerized version, as there are benefits to the accessibility of both participants with hearing abilities and participants with hearing impairment, and elimination of verbal discrepancies (ie, rate or clarity of speech) that may exist among facilitators [53]. The computerized version of the digit span test is an appropriate measure to assess the working memory of users performing tasks on each prototype.

Participant Characteristics: Health Literacy

The eHealth Literacy Scale (eHEALS) and the eHealth Literacy Scale for Carers (eHEALS-Carer) are validated measures to assess the skills in acquiring health information through the use of technology, for oneself or the care of others, respectively [54]. The eHEALS assessment was developed to measure 6 skills: traditional literacy, health literacy, information literacy, scientific literacy, media literacy, and computer literacy [55]. The eHEALS model was further adapted to validate these same literacies among primary caregivers [56]. Each assessment consists of 8 questions, each measured on a 5-point Likert scale, ranging from “strongly agree” to “strongly disagree.” A score upon completion can range from 8 to 40, with higher scores representing higher eHealth literacy [57]. The eHEALS and eHEALS-Carer assessments are appropriate measures to evaluate the health literacy of users performing tasks on each prototype and will allow us to determine whether variability exists between participant types.

All in-person assessments and subjective measures have been converted to electronic surveys, and the data collected will be entered directly into REDCap. Paper assessments will be made available for participants who prefer this method, in which case all responses will then be manually transferred from the paper assessment to REDCap by a member of the study team.

Phase 3: Evaluation With Patients, Caregivers, and Health Care Workers

Overview

Participants will be asked to complete a baseline questionnaire online via REDCap before the user testing session. Questions related to the following domains will be asked of patients: race, ethnicity, education, household income, marital status, living situation, employment, technology comfort level, and insurance. Questions related to the following domains will be asked of caregivers: race, ethnicity, education, household income, marital status, living situation, employment, technology comfort level, insurance, length of time as a caregiver, and relationship to the patient. Health care workers will complete a short demographic questionnaire related to their role, their time in this role, and their exposure to patients with AML.

Further, patients will be asked to self-report on 2 of the 3 Simplified Geriatric Assessment (sGA) measures, which include the activities of daily living and the instrumental activities of daily living (Multimedia Appendix 2). The sGA tool was selected for reliability, brevity, and prognostic value in classifying the fitness level of older adults. Study coordinators will work with physicians to help participants complete the Cumulative Illness Rating Scale-Geriatric (CIRS-G), an assessment of comorbidity for enrolled patients [58]. Results from the activities of daily living, instrumental activities of daily living, CIRS-G, along with patient’s ages, will be calculated and used to classify patients as either fit, unfit, or frail [59].

If participants are unable to complete the self-reported preassessments online, they will be administered by study personnel either in person or over the phone.

Patient-caregiver pairs will be divided into 2 groups, each consisting of 10 patients and 10 caregivers. Patients and caregivers will be asked to participate in think-aloud sessions and semistructured interviews providing evidence on the usability of both the DCE and BWS within the prototypes, whether they understood various aspects of the tool, and whether they feel patients and family caregivers would utilize this tool. In addition to the assessments listed below, patients and caregivers will be involved in the same quantitative and qualitative assessments described in phase 2.

Health care workers will be divided into 2 groups, each consisting of up to 5 users. Health care workers will participate in qualitative assessments as described in phase 2 to assess the general usability of both the DCE and BWS within the prototypes and whether they would find this tool beneficial and would recommend its use for patients and caregivers.

Following recommendations from Francis et al [60], we have established sampling sizes within each group (up to 20 patient-caregiver pairs and 5 health care workers), a stopping criterion (set at 3 interviews), and the number of additional interviews we will conduct, to demonstrate that all themes have been introduced.

Qualitative Assessments: Cognitive Workload

Cognitive task analysis will be performed to gain insight into the thought processes and mental strategies of patients as they work through each prototype [61]. After completion of the task, a member of the study team will ask the participant to walk them through their process for selecting each treatment preference. Data will be collected through the recording of interviews.

Participant Characteristics

Patients and caregivers will complete the additional assessments (memory skills and health literacy) as described in phase 2. Patients will also take an additional assessment of cognition levels, as described below.

The Blessed Orientation Memory Concentration (BOMC) assessment is a validated measure of cognitive function. This

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assessment will be conducted through verbal facilitation by a study team member, in which patients will be asked to repeat and recall information, replicating their memory and concentration skills [62]. The final score is based on a weighted calculation and assesses the likelihood of cognitive disability, with a higher score representative of a clinically meaningful cognitive impairment [63]. The BOMC assessment tool is an appropriate measure to evaluate the memory and concentration of users performing tasks in each prototype.

Phase 4: Final Evaluation of Usability, CWL, and Performance

Overview

Patients, caregivers, and health care workers will complete the preassessments as described in phase 3. Patients and caregivers will continue to participate in quantitative and qualitative assessments as described in phase 3, excluding the think-aloud sessions. In phase 4, patients and caregivers will also be asked to participate in task analysis and performance assessments of the DCE and BWS within the prototypes, including the evaluation of tasks using the Single Easy Questionnaire (SEQ), tracking time to complete, and the number of errors.

Health care workers will continue to participate as described in phase 3.

Quantitative Assessments: Usability

The DCE and BWS choice tasks within each prototype will be treated as a task. During phase 3, participants will evaluate the usability of the prototypes by completing the SEQ after each task within each prototype. The SEQ is an experimentally validated tool and demonstrated as reliable, valid, and sensitive [64]. The SEQ is based on a 7-point scale, assessing how difficult users found a task, with average scores reported to be between 5.3 and 5.6 [64]. This posttask questionnaire will allow us to compare parts of the interface or workflows that are perceived as most problematic. As participants will be completing a series of assessments, we have chosen the SEQ as it is minimally disruptive, and helps understand participants' attitudes toward the interface without subsequent tasks interfering with the user's memory of the task just completed [47].

Quantitative Assessments: Performance

Participants will perform simulated tasks within the prototype and their responses will be recorded via the screen capture video software included in iPad OS14. As patients and caregivers in phase 4 perform tasks, they will be observed by 2 human factors experts and screen capture (touchscreen strokes, eye movement, and pupillary dilation into the captured video for analysis of pupillary response) will be performed. Their performance will be recorded as the time to complete each prototype, as well as the number of errors encountered.

Participant Characteristics

Patients and caregivers will complete the additional assessments as described in phase 3.

Data Analysis

Statistical Testing

The study is primarily descriptive, as we aim to capture the usability, CWL, and performance of participants using EHTs that include the DCE and BWS instruments.

Within-subjects testing will be conducted to compare preferences regarding the presentation of information, usability, CWL, and performance of the DCE and BWS within the prototypes. The order of presentation will be randomized for each participant to account for the effect of order and to ensure that information is not transferred across prototypes [65].

Quantitative

The paired *t* test will be utilized to evaluate the statistical significance of the PSSUQ, SEQ, NASA-TLX, and performance (time taken for task completion and the number of errors committed) of participants using both the DCE and BWS within the prototypes for each group in all relevant phases. Analysis of variance tests will be utilized to evaluate whether statistical differences in the DCE and BWS occur across groups for these same measures. We will consider *P* values of less than .05 to have statistical significance, and 95% CIs will be used to establish differences between the DCE and BWS both within and across groups.

We aim to use the data from preassessments (demographics, geriatric assessment), in-person assessments (cognition, memory, and health literacy), digit span, and health records to determine predictor variables with patient treatment preferences, and to determine whether health literacy variance exists between patients and caregivers. Analysis of preassessments will include basic statistics (eg, mean, SD, and range).

All analysis will be performed in SAS JMP Pro (SAS Institute) for summarizing and grouping study results both between and across groups. We will work with an experienced statistician to ensure that we utilize appropriate methods and theories for data analysis.

Qualitative

Qualitative data obtained through think-aloud sessions, interviews, and cognitive task analysis will be analyzed for each group and coded using thematic analysis [66,67]. Analysis of qualitative responses will include creating contingency tables and converting data into charts and graphs for identifying patterns and gaps. One-way contingency tables will be used to evaluate whether participants (1) found the prototypes challenging to complete, (2) understood the definitions of the attributes, (3) could distinguish between the attribute levels, (4) preferred either the DCE or BWS, and (5) felt patients or family caregivers would use this tool.

Ethics Approval

This study, reference ID number 321807, received institutional review board (IRB) approval from the University of North Carolina Office of Research Information Systems in June 2021. It has been determined that the risk involved in this research is no more than minimal. This research requires annual UNC administrative review. Under the revised "Common Rule" of

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2018, this study does not require continuing review and IRB approval will not expire. This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA [Health Insurance Portability and Accountability Act]), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

Privacy and Security

We will do a chart review on patient electronic medical records, including age, race, treatment, and diagnosis. A message will be sent to the treating physician (oncologist) or principal investigator (DRR) to inquire as to whether the patient would be appropriate for the study.

The interview and usability testing will be conducted in the human factors laboratory that can be accessed only by the study team. In the laboratory, participants and researchers can work from their respective workstations, which are separated by glass and can communicate effectively using the devices available in the laboratory.

Health care workers will complete user testing via Zoom, which is HIPAA enabled through the UNC School of Medicine. The other questionnaires (eg, geriatric assessments) will be sent to the participants using REDCap, a secure web application. During the data collection in the laboratory, we will ensure that those not connected with this study are unable to see participants or hear the information that is shared. When reporting the research findings, data will be presented in a way that prevents individual participants from being identified.

This trial will be audited by the Lineberger Comprehensive Cancer Center data safety and monitoring committee every 6 or 12 months.

Results

This study received approval from the Lineberger Comprehensive Cancer Center Oncology Protocol Review Committee in March 2021 and IRB approval from the University of North Carolina Office of Research Information Systems in June 2021. We began recruitment of healthy volunteers in August 2021. This study is expected to conclude in February 2023.

Discussion

Principal Findings

To the best of our knowledge, this study is the first to conduct comparative assessments of the usability, CWL, and performance between DCEs and BWS instruments when developed as an EHT. We designed this as a mixed methods study using an iterative co-design approach that includes healthy volunteers, patients, caregivers, and health care workers. One limitation of this methodology is that participants in phase 2 of this study are all healthy volunteers and likely have different life experience to our target population of older adults with hematologic malignancies. While our target population will likely experience the EHT differently than these volunteers, our study team anticipated that the findings from both qualitative and quantitative assessments would lead to usability improvements for phase 3 participants, which include patients and caregivers. This is consistent with previous studies that have first recruited healthy volunteers to effectively resolve usability problems prior to the definitive work with the target population [68,69].

Dissemination

In December 2021, our findings from phase 2 were accepted for a publication in the conference proceedings in Springer Nature and for presentation at the virtual Human-Computer Interaction 2022 Conference [70]. Our study team is highly interdisciplinary; therefore, we aim to disseminate our findings across a more diverse audience within both medicine and health care engineering conferences and journals.

Conclusion

Our findings will help differentiate the usability, CWL, performance, and alignment of patient preferences for both the DCE and BWS within the prototypes. This study has the potential for optimizing the collaboration and empowerment of older adults in the development of an EHT, improving elicitation of treatment preferences, and improving communication between patients and health care workers. Future research should continue to evaluate the levels at which older adults participate in the full development process, and how this can either limit or encourage their collaboration and empowerment.

Acknowledgments

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Data Availability

The data sets generated during or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

DRR conceived the study topic. The study design was a collaboration between all authors. The protocol was written by AC, with input from DRR, KA, AK and LM. DRR, NC, and JFPB designed and revised the best-worst scaling and discrete choice experiment instruments. All authors approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed involvement processes based on Leinonen's framework.
[PDF File (Adobe PDF File), 118 KB - resprot_v11i6e39586_app1.pdf]

Multimedia Appendix 2
Proposed validated assessments.
[PDF File (Adobe PDF File), 125 KB - resprot_v11i6e39586_app2.pdf]

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Abbreviations

AML: acute myeloid leukemia
BOMC: Blessed Orientation Memory Concentration
BWS: best-worst scaling
CIRS-G: Cumulative Illness Rating Scale-Geriatric
CWL: cognitive workload
DCE: discrete choice experiment
eHEALS: eHealth Literacy Scale
eHEALS-Carer: eHealth Literacy Scale for Carers
EHT: electronic health care tool
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
NASA-TLX: National Aeronautical and Space Administration's Task Load Index
PRIME: *P*reference *R*eporting to *I*mprove *M*anagement and *E*xperience
PSSUQ: Post-Study System Usability Questionnaire
SEQ: Single Easy Questionnaire
sGA: Simplified Geriatric Assessment
UNC: University of North Carolina

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Protocol

Investigating the Efficacy of an 18-Week Postpartum Rehabilitation and Physical Development Intervention on Occupational Physical Performance and Musculoskeletal Health in UK Servicewomen: Protocol for an Independent Group Study Design

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Abstract

Background: Postpartum women are at an increased risk of pelvic floor dysfunction, musculoskeletal injury, and poor psychological health and have reduced physical fitness compared to before pregnancy. There is no formal, evidence-based rehabilitation and physical development program for returning UK servicewomen to work following childbirth.

Objective: This study aims to examine the efficacy of a rehabilitation and physical development intervention for returning postpartum UK servicewomen to occupational fitness.

Methods: Eligible servicewomen will be assigned to a training or control group in a nonrandomized controlled trial 6 weeks after childbirth. Group allocation will be based on the location of standard pregnancy and postpartum care. The control group will receive standard care, with no prescribed intervention. The training group will start an 18-week core and pelvic health rehabilitation program 6 weeks post partum and a 12-week resistance and high-intensity interval training program 12 weeks post partum. All participants will attend 4 testing sessions at 6, 12, 18, and 24 weeks post partum for the assessment of occupational physical performance, pelvic health, psychological well-being, quality of life, and musculoskeletal health outcomes. Occupational physical performance tests will include vertical jump, mid-thigh pull, seated medicine ball throw, and a timed 2-km run. Pelvic health tests will include the Pelvic Organ Prolapse Quantification system, the PERFECT (power, endurance, repetitions, fast, every contraction timed) scheme for pelvic floor strength, musculoskeletal physiotherapy assessment, the Pelvic Floor Distress Inventory–20 questionnaire, and the International Consultation on Incontinence Questionnaire–Vaginal Symptoms. Psychological well-being and quality of life tests will include the World Health Organization Quality of Life questionnaire and the Edinburgh Postnatal Depression Scale. Musculoskeletal health outcomes will include body composition; whole-body areal bone mineral density; tibial volumetric bone mineral density, geometry, and microarchitecture; patella tendon properties; muscle architecture; muscle protein and collagen turnover; and muscle mass and muscle breakdown. Data will be analyzed using linear mixed-effects models, with participants included as random effects, and group and time as fixed effects to assess within- and between-group differences over time.

Results: This study received ethical approval in April 2019 and recruitment started in July 2019. The study was paused in March 2020 owing to the COVID-19 pandemic. Recruitment restarted in May 2021. The results are expected in September 2022.

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Conclusions: This study will inform the best practice for the safe and optimal return of postpartum servicewomen to physically and mentally demanding jobs.

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International Registered Report Identifier (IRRID): DERR1-10.2196/32315

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KEYWORDS

performance; servicewomen; postnatal; pelvic health; exercise; intervention; musculoskeletal; well-being

Introduction

Background

Women experience physiological changes during pregnancy and following childbirth, which can lead to pelvic health dysfunction [1-10], musculoskeletal injury [11], increased ligament laxity [12,13], and decreased bone mineral content [14-18]. After childbirth, the pelvic floor can be weakened and sometimes injured, with symptoms of urinary incontinence [1,2,4,7,9], fecal incontinence [1,3,6], and pelvic organ prolapse [1,2,7] commonly reported. Postpartum health problems may negatively influence quality of life and emotional well-being [19]. Postpartum depression is common in the months after childbirth [20-22]; a *m*-analysis of 58 studies reported a prevalence of 17% in mothers [20].

Evidence suggests that exercise is an important consideration for improving maternal health after childbirth [23]; however, few studies exist whereby training interventions seek to address musculoskeletal, physiological, and psychological implications of pregnancy. Previous training interventions in women without pregnancy- or childbirth-related medical pathologies have included home-based pelvic floor exercise programs [24-27], resistance training programs [28], or combined aerobic and resistance training programs [29,30]. Pelvic floor muscle exercise interventions have been predominantly home-based pelvic floor exercises, with limited supervision and consideration of functional rehabilitation of the pelvic floor muscles, which may account for the variability in the success of improving outcomes, including pelvic organ prolapse [24], urinary incontinence [25], vaginal symptoms [24,26], sexual function [26], and diastasis rectus abdominis [27]. Resistance training interventions have resulted in improved muscle strength in postpartum women [28], although a combined intervention of supervised resistance and aerobic training [29,30] may have superior health benefits. No studies have used a combined training intervention including pelvic floor rehabilitation, resistance training, and high-intensity interval training (HIIT) for postpartum women.

Physically arduous occupations often require women to complete physical activities, such as load carriage and heavy lifting. UK servicewomen can return to physically and psychologically demanding roles after 2 weeks of compulsory maternity leave. Previous data show that British Army servicewomen return to work within the first year after childbirth and are at greater risk of illness and injury during this time than before pregnancy [31]. US military servicewomen do not achieve prepregnancy fitness levels at 6 months following childbirth [32-34], and servicewomen commonly experience symptoms of fatigue, depression, and anxiety upon returning to work [33,35].

In the UK Armed Forces, there are differences among services in the approach to returning women to physical training following childbirth. Army servicewomen are provided with a 6-to 12-week return to fitness program before they are (1) permitted to resume normal military duties and (2) required to undergo annual fitness testing. Royal Air Force and Royal Navy servicewomen do not receive a phased return to physical activity, unless specifically requested; an 18-month opt-out of mandatory fitness testing can be requested following childbirth.

Objectives

The *Interim Report on the Health Risks to Women in Ground Close Combat Roles* calls for strategies to optimize the physical and mental resilience of postpartum servicewomen on return to work to achieve safe and effective integration of women into the military workforce [36]. There is no evidence on how to rehabilitate to full duty following childbirth. This study aims to investigate the efficacy of a postpartum combined rehabilitation (ie, pelvis, hip, and abdominal specific exercises) and physical development (ie, resistance training and HIIT) program on occupational physical performance, musculoskeletal health, pelvic health, psychological well-being, and quality of life. The rehabilitation element of the exercise intervention will target strengthening of the pelvis, hip, and abdominal muscles 6 weeks before commencing the high-intensity aerobic and resistance training.

Methods

Study Design and Setting

This study is known as the PERFORM (Postpartum Exercise and Return to Fitness: Optimize Readiness for Military Mums) study (ClinicalTrials.gov NCT04332757). This study will use an independent group design; participants will join either a control or intervention group based on their location of standard pregnancy/postpartum care. This design was chosen to geographically separate groups and reduce the likelihood of the intervention being shared with control participants, who may change their usual behavior. The intervention sites will be selected based on their proximity to the training facilities. The control group will receive standard postpartum care with no formal intervention, whereas the intervention group will receive standard postpartum care plus an 18-week phased rehabilitation and physical development program between 6 and 24 weeks post partum.

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Participants will attend 4 laboratory-based testing sessions, completed at 6, 12, 18, and 24 weeks post partum (Figure 1). Testing session 1 will be completed as soon as possible after the participants have had their 6-week postpartum general practitioner check. Measurements being completed at each testing session are summarized in Figure 2.

Figure 1. Study schematic.

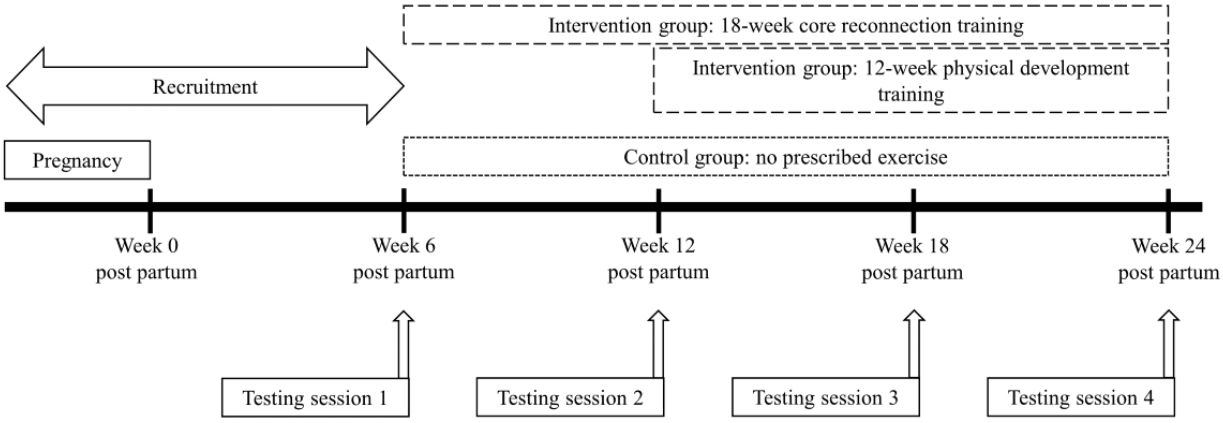
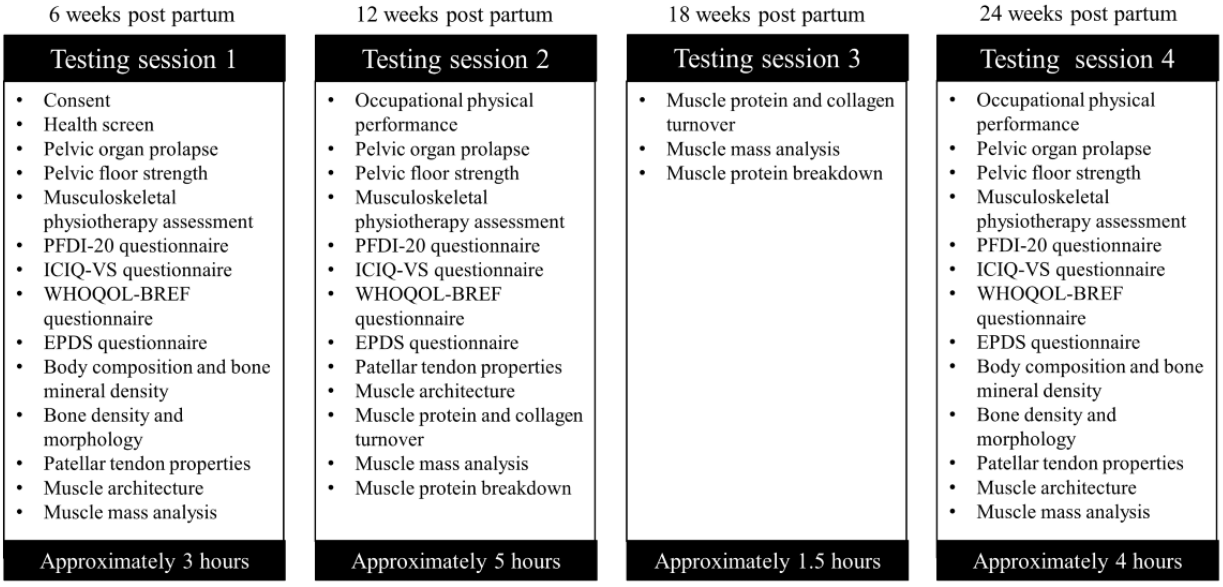


Figure 2. Testing procedures. EPDS: Edinburgh Postnatal Depression Scale; ICIQ-VS: International Consultation on Incontinence Questionnaire–Vaginal Symptoms; PFDI-20: Pelvic Floor Distress Inventory–20; WHOQOL-BREF: World Health Organization Quality of Life.



Recruitment Strategies

Participants will be recruited through leaflets provided by their midwife or through posters and leaflets displayed around the targeted garrisons. Recruitment information will be included in routine information downloads to staff at chosen units, and the study will be promoted through internal social media channels. Recruitment will be performed on an opt-in basis, wherein the participants contact the research team.

Participants and Eligibility Criteria

Participants will be healthy servicewomen aged ≥18 years, recruited in the antenatal and postpartum periods, before 6 weeks post partum. Participants will have completed their 6-week postpartum checkup with their general practitioner and will have been cleared to exercise. Participants will be excluded if they have been diagnosed with postnatal depression or other mental health conditions that require specialist psychiatric secondary care. Participants will complete a health screening questionnaire when attending their first testing session to confirm the absence of any condition or injury that may affect their ability to exercise. On their first testing session, participants must be free from gynecological-based contraindications to exercise, as assessed by the study's specialist pelvic health physiotherapist. During each testing session, participants will be asked to declare their menstrual, contraceptive, and breastfeeding status. Participants must consent to a pregnancy test before scans at 6 and 24 weeks post partum.

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Intervention

Overview

The control group will receive standard postpartum care only, which consists of a 6-week postpartum check at a civilian general practice or a Defence primary health care facility and referral to (1) secondary care pelvic health physiotherapy if women present with symptoms of urinary incontinence and (2) musculoskeletal physiotherapy if they present with *rectus diastasis* or a musculoskeletal injury. Control participants will not be prescribed exercises but will not be prevented from choosing to exercise during the study period. A log of all exercise activities will be collected from control participants. The intervention group will receive standard postpartum care and complete a phased 18-week combined rehabilitation and physical development program. The rehabilitation element of the program was designed for this study by specialist pelvic health physiotherapists. The program, known collectively as *core reconnection training*, targets pelvic floor function and pelvic, hip, and abdominal strength. The *physical development training* is an adapted version of the SPARTA (Soldier Performance and Readiness as Tactical Athletes) training program [37] and consists of resistance training and HIIT.

Core Reconnection Training

Following testing session 1, participants in the intervention group will commence 18 weeks of home-based core reconnection training from weeks 6 to 24 post partum (Table 1). Participants will complete 3 core reconnection training sessions per week, each lasting approximately 30 minutes. Each session will include 6 exercises progressing in difficulty throughout the intervention. Participants will complete 3 to 4 sets of 8 to 12 repetitions of each exercise. Participants will be advised to reduce the number of repetitions of more challenging exercises (eg, press-ups) to 3 to 4 sets of 5 repetitions. Exercises will be modifiable depending on individual ability and symptoms. Participants will be advised to be aware of symptoms of incontinence, a heaviness or dragging sensation in the pelvic area (ie, indicator of prolapse), a pendular abdomen or noticeable gap in the midline of the abdominal wall (ie, indicator of *rectus diastasis*), and pelvic or lower back pain. If any of these symptoms are experienced, participants will be asked to contact the study's pelvic health physiotherapist before continuing with training. Participants will be given written instructions with images of each exercise and will be provided with access to all exercises in video form with verbal instructions. Core reconnection training sessions will not be routinely supervised.

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Table 1. Core reconnection training.

	Exercise 1	Exercise 2	Exercise 3	Exercise 4	Exercise 5	Exercise 6
Week 1	Arm circles + heel slide	Glute bridge + squeeze	Side kick	Bent knee fall out	Toe slide all fours	Tempo squat to chair
Week 2	Toe taps + arms	Glute bridge + band pull	Side kick straight leg	Eccentric curl down	Toe slide + arm slide	Tempo squat to chair
Week 3	Arm circles + heel slide in tabletop	Single-leg glute bridge	Sidestep + band	Abdominal prep	Superman	Squat to tip toes
Week 4	Running man	Monster walk + band	Mountain climber	Eccentric curl down + rotation	Superman knee to elbow	Static lunge + arms overhead
Week 5	Knee pull	Banded deadlift	Mountain climber knee to elbow	Oblique prep	All four hover	Lunge + rotation band pull
Week 6	Single-leg squat + rotation	Banded deadlift	Mountain climber (increased pace)	Russian twist	Bear crawl	Lunge + rotation band pull
Week 7	Opposite knee to elbow in standing	Single-leg deadlift	Press-up to chair	Side-lying double-leg lifts	Plank to pike	Lateral lunge
Week 8	Dead bug	Single-leg deadlift	Press-up to chair	Side-lying lift legs + hip abduction	Plank to pike + opposite toe touch	Lateral lunge + weight
Week 9	Dead bug	Single-leg deadlift + weight	Walkout to plank wide stance	Side plank bent knees (on elbow)	Plank from knees	Lateral lunge + weight
Week 10	Dead bug + curl up	Single-leg deadlift + weight	Walkout narrow stance	Side plank bent knee + rotation	Prone pull with hip extension	Hip thrust on sofa
Week 11	Dead bug + curl up	Running man	Walkout chest to floor	Side plank straight leg + rotation	Plank holds on chair	Hip thrust
Week 12	Dead bug + hand weights	Running man	Walkout chest to floor	Side plank knee to elbow	Plank holds on chair	Hip thrust + weight
Week 13	Opposite knee to elbow supine	Single-leg deadlift + weight	Press-up	Side plank knee to elbow	Plank + shoulder taps	Crab raises
Week 14	Bicycle crunch + knee extension	Single-leg deadlift + weight	Press-up	Side plank + clam	Plank with hip abduction	Crab raises
Week 15	Russian twist legs raised	Hydrant	Press-up + single-arm row	Side plank + clam + sofa or step	Plank to half inch worm	Bridge on sofa or step
Week 16	Russian twist legs raised	Hydrant + hip extension	Press-up + single-arm row	30-second side plank	30-second plank hold	Bridge on sofa or step
Week 17	Bicycle crunch + knee extension	Hydrant + hip extension	Press-up	30-second side plank	Plank to half inchworm	Crab raises
Week 18	Bicycle crunch + knee extension	Hydrant	Press-up	Side plank pulses	30-second plank hold	Crab raises

Physical Development Training

Overview

Following testing session 2, the intervention group will undergo a supervised 12-week combined resistance and HIIT program (collectively known as physical development training) from 12 to 24 weeks post partum. Participants will attend 3 supervised sessions per week in a designated gym space. Resistance training and HIIT sections of the program will consist of three 4-week training blocks, with the first 3 weeks of each block for training and the final week of each block for *deload* and assessing 1 repetition maximum (RM; Figure 3). The program incorporates training periods (known as mesocycles), with specific training adaptations at the focus of each mesocycle. The physical development training aims to improve athletic and task-specific capabilities while minimizing the risk of injury. The program is designed to induce physiological adaptation and promote recovery to enhance performance while avoiding overtraining. A warm-up will be completed before each training session, including 12 of the exercises listed in Table 2.

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Figure 3. Physical development training mesocycles and training blocks. RM: repetition maximum.

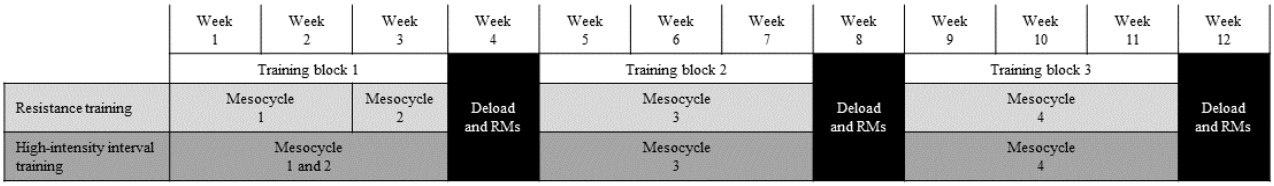

Table 2. Physical development training warm-up exercises.

Exercise	Repetitions	Sets, n
On hands and knees or supine		
Fire hydrants	10 each side	1
Thread the needle	10 each side	1
Lumbar rotations (knee rolls)	10 each side	1
T-spine mobility rotations	10 each side	1
Standing		
Single-leg banded sprinter kickback	10 each side	1
Single-leg lateral band quarter squat	10 each side	1
Bent over Ys, Ts, and Ws	10 each side	1
External shoulder rotations (banded)	10	1
Running man	10 each side	1
Air squat	10	1
Single-leg banded adductor squeeze	10 each side	1
Walking		
Quad stretch and reach	9 m	1
Step and scoop	9 m	1
Leg cradle to lateral lunge	9 m	1
Toy soldiers	9 m	1
Grapevines	9 m	1
Bounds (single leg)	9 m	1
Bum kicks	9 m	1
High knees (walk or run)	9 m	1

Resistance Training Program

Every resistance training session will include five exercises: an upper-body pull, an upper-body push, a lower-body pull, a lower-body push, and a core-focused exercise (Table 3). Only mesocycle 1, day 2, will have 4 exercises, and mesocycle 4, day 3, will have 6 exercises in total. Each of the 3 training days across all mesocycles will have a different focus: day 1 will focus on power, day 2 on strength, and day 3 on stability. Table 4 summarizes the goals of the resistance training blocks. The first mesocycle is designed to prepare the individual with emphasis on form and volume. Mesocycle 2 will include the same movements but under a greater load. Mesocycle 3 will aim to develop greater force production. Mesocycle 4 will serve as the peaking phase for the end points of this study, and the exercises used will be task-specific for active duty.

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Table 3. Physical development training: resistance training.

Exercise	Sets, n	Repetitions	Rest (minutes)
Mesocycle 1, day 1			
Step up on to box	10	3	0.5
Mid-thigh clean pull	10	3	0.5
Medicine ball throw	10	3	0.5
Lawnmower row	10	3	0.5
All four hovers	3	30 seconds	1
Mesocycle 1, day 2			
Box squat (below parallel)	10	3	1
Incline chest press	10	3	1
Deadlift	10	3	1
Modified pull-ups	10	3	1
Mesocycle 1, day 3			
Single KB[a] front squat	3	12	1
SA[b] KB neutral press	3	12	1
SL[c] deadlift	3	12	1
All fours SA row	3	12	1
SA farmer's walk	3	30 meters	1
Mesocycle 2, day 1			
Step up on to box	4	5	1
Mid-thigh clean pull	4	5	1
Medicine ball throw	4	5	1
Lawnmower row	4	5	1
All four hovers	3	30 seconds	1
Mesocycle 2, day 2			
Box squat (below parallel)	4	5	1
Incline chest press	4	5	1
Deadlift	4	5	1
Modified pull-ups	4	5	1
Pallof press	3	10	1
Mesocycle 2, day 3			
Single KB front squat	3	12	1
SA KB neutral press	3	12	1
SL deadlift	3	12	1
All fours SA row	3	12	1
SA farmer's walk	4	30 meters	1
Mesocycle 3, day 1			
Depth drop jump	3	3	2
Power shrug (from floor)	3	3	2
Chest press on bench	3	5	2
Bent over row	3	5	2
Mountain climbers	4	10 seconds	2

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Exercise	Sets, n	Repetitions	Rest (minutes)
Mesocycle 3, day 2			
Back squat	3	3	2
Close grip chest press	3	3	2
Deadlift	3	3	2
Barbell bicep curl	3	3	2
Bear crawls (forward and back)	3	30 seconds	2
Mesocycle 3, day 3			
Front squat	10	3	1
Standing military press	10	3	1
Bent over row	10	4	1
Bent over lateral raise	3	10	1
KB swings	3	10	1
Mesocycle 4, day 1			
Depth jump to broad jump	3	3	2
Modified pull-ups	3	3	2
Mid-thigh high pull	3	5	2
SA KB press	3	5	2
Plate push	4	20 seconds	2
Mesocycle 4, day 2			
Zercher squat	3	2	2
Incline chest press	3	2	2
Sumo deadlift	3	2	2
Inverse row (wide grip)	3	4	2
Woodchopper circuit	3	5	2
Mesocycle 4, day 3			
Lift and carry task	3	10	1
Burpee with DB[d] press	3	8	1
Sandbag lunge	3	20	1
Bent over alternate row	3	20	1
Turkish get-up (first phase)	3	10	1
Zercher farmer's walk	3	18 m	1

[a]KB: kettlebell.
[b]SA: single arm.
[c]SL: single leg.
[d]DB: dumbbell.

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Table 4. Summary of resistance training blocks.

Training block	Mesocycle	Weeks	Mesocycle goal	Example sets and repetitions
Training block 1	1	1-2	General physical preparedness	High number of sets and low number of repetitions (eg, 10 sets of 3 repetitions)
Training block 1	2	3	Preparation for peak force	Lower number of sets and more repetitions (eg, 4 sets of 5 repetitions)
Training block 2	3	5-7	Peak force development	Low number of sets and repetitions (eg, 3 sets of 3 repetitions)
Training block 3	4	9-11	Developing anaerobic power capacity	Low number of sets and repetitions (eg, 3 sets of 3 repetitions); more complex and task-specific exercises for active duty

RM lifts will be completed for the squat, bench press, deadlift, and military press in week 1 of the resistance training program. The deload and RM testing weeks (Figure 3) will be used to reassess RM lifts and ensure recovery between mesocycles and the final testing session. Participants will complete a 1, 2, 3, 4, or 5 RM to avoid overlifting and injury. If a participant completes a 2, 3, 4, or 5 RM, the third column of Table 5 will be used to approximate 1 RM. The 1-RM value will be used to prescribe the training loads for weeks 1, 2, and 3 of each mesocycle. For mesocycle 1, the following steps will be performed:

1. The 1-RM value will be used to calculate an *adjusted RM* at 75% of the 1-RM value.
2. The proportion will be either 85%, 90%, or 95% of the *adjusted RM* and will be used to calculate the training loads for weeks 1, 2, and 3 of the mesocycle.

For mesocycles 2, 3, and 4, the following steps will be performed:

1. The 1-RM value will be used to calculate an *adjusted RM*. This will be based on the number of repetitions they are expected to lift. For example, if they are expected to perform five repetitions, the 5-RM equivalent is calculated using Table 5 and is used as the *adjusted RM*.
2. The proportion will be either 85%, 90%, or 95% of the *adjusted RM* and will be used to calculate the training loads for weeks 1, 2, and 3 of the mesocycle.

For all other weight-related exercises (ie, not squat, bench press, deadlift, and military press), researchers will make a judgment call for the starting weights and will aim to progress the weight lifted across each mesocycle. If participants reach maximum effort during the mesocycle, the weight will be lowered. To monitor the effort during training, a 1 to 10 rating of perceived exertion (RPE) scale will be used. Participants will aim to achieve a score of 6 to 7, 7 to 8, and 9 during weeks 1, 2, and 3 of the mesocycle, respectively. Priority will be given to the correct volume of training, rather than to the correct effort during training, to reduce the risk of injury associated with repetitive maximum efforts. Although the weights to be lifted will be predetermined, there will still be an element of coaching and modification.

Table 5. Conversion table for repetition maximum values.[a]

Number of repetitions performed	Percentage of 1 repetition maximum	Multiply weight lifted by:
1	100	1.00
2	95	1.05
3	93	1.08
4	90	1.11
5	87	1.15
6	85	1.18
7	83	1.20
8	80	1.25
9	77	1.30
10	75	1.33
11	70	1.43
12	67	1.49
15	65	1.54

[a]Adapted from the study by Haff and Triplett [38].

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HIIT Program

HIIT exercises (Table 6) will be completed in the same session as the resistance training program. Exercises on each day of the HIIT program will target a different outcome (Table 7). A polar heart rate (HR) monitor will be worn during sessions to monitor the HR and ensure that the participants are exercising at the prescribed intensity (Polar H7 Bluetooth 4.0 and Polar Beat app, version 3.4.4). The target HR will be calculated as a percentage of the maximum HR based on the following equation: 220 − age. The average HR and peak HR will be recorded after each HIIT session. A 1 to 10 RPE scale will be used to monitor perceived exertion during the HIIT exercises. The HR will be monitored throughout the HIIT exercises and will be used alongside RPE to achieve the target HR as closely as possible throughout the sessions.

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Table 6. Physical development training: high-intensity interval training.

Mesocycle, day, and exercise	Sets, n	Work, seconds	Rest, seconds
Mesocycle 1 and 2			
Day 1			
Bike	4	120	30
Sandbag lift and carry	2	240	60
Reverse lunges alternate legs	7	20	30
Day 2			
Rope slams (slow cadence)	10	30	30
Farmer's walk (speed walk)	2	240	60
Kettlebell high pulls	7	20	30
Day 3			
Bike	3	180	60
Side to side step ups to box	10	30	30
Triceps dips	7	20	30
Mesocycle 3			
Day 1			
Bike with resistance	5	90	30
Sandbag shoulder to shoulder	10	30	20
Ladders forward and backward	5	20	60
Day 2			
Rope slams	5	20	50
Sandbag carry walk	3	150	60
Suspension trainer rows	10	30	30
Day 3			
Run	2	240	120
Push-ups (Suspension trainer)	10	30	30
Side-to-side jumps	5	20	60
Mesocycle 4			
Day 1			
Sprint (20 m)	10	N/A[a]	30
Farmer's carries	15	5	30
Skater jumps	10	30	30
Day 2			
Weighted vest jog	3	60	120
Ropes (drumming)	9	20	45
Suspension trainer rows (overhand grip)	10	30	30
Day 3			
Jog	1	480	120
Push ups	10	30	30
Scissor jumps	10	10	45

[a]N/A: not applicable.

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Table 7. Summary of high-intensity interval training blocks.

Mesocycle, day, and goal for the session	Target HR[a] (% maximum HR)
Mesocycle 1 and 2	
Day 1: aerobic power	
Week 1	75
Week 2	80
Week 3	85
Day 2: upper-body localized anaerobic power	
Week 1	75
Week 2	80
Week 3	85
Day 3: cardiac output	
Week 1	65
Week 2	70
Week 3	75
Mesocycle 3	
Day 1: lower-body anaerobic power	
Week 1	80
Week 2	85
Week 3	90
Day 2: upper-body localized anaerobic power	
Week 1	80
Week 2	85
Week 3	90
Day 3: aerobic maintenance	
Week 1	65
Week 2	70
Week 3	75
Mesocycle 4	
Day 1: lower-body anaerobic power	
Week 1	85
Week 2	90
Week 3	95
Day 2: upper-body localized anaerobic power	
Week 1	80
Week 2	85
Week 3	90
Day 3: aerobic maintenance	
Week 1	65
Week 2	70
Week 3	75

[a]HR: heart rate.

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Exercise Logs

Participants in both groups will be provided with a log to record the exercises performed outside of the supervised study training. Participants will record RPE, exercise type, duration, setting (eg, home or gym), date, and how the session felt. Exercise will be described to participants as a specific form of physical activity that is planned and structured and includes intentional movements intended to improve or maintain physical fitness. An RPE scale will be provided, and participants will select a number between 1 and 10 to express their RPE, ranging from very light (1-2) to maximum effort (9-10). The control group will record all the exercises performed during the 18-week study period. The intervention group will record the core reconnection training sessions as a metric of compliance and any other exercise in addition to the physical development training sessions performed during the study period.

Intervention Compliance (Intervention Group Only)

Compliance with weekly core reconnection training will be checked verbally and by using exercise logs. A participant who misses >25% (>3/12) of sessions over 2 consecutive weeks or who fails to achieve at least two of the three supervised physical development training sessions over 2 consecutive weeks, will be approached by one of the research team members to understand the reason for low compliance. These participants will be given an opportunity to increase their participation rate over the following week, if appropriate. Failure to increase participation during this week will result in a participant being considered noncompliant. Before recruitment, participants will be made aware of noncompliance thresholds. Cases of noncompliance will be reported to a trial committee that will attempt to contact the participant before deciding to exclude the individual from further participation in the trial.

Primary Outcome Measures

Occupational Physical Performance Overview

Occupational physical performance will be measured at weeks 12 and 24 using the Role Fitness Test (Entry), which is used by the British Army as a selection standard to confirm the appropriate level of fitness to commence basic training. It involves an isometric mid-thigh pull, seated medicine ball throw, and a timed 2-km run. A vertical jump test will be completed as a military-relevant field-based measure of power. The occupational physical performance tests will be conducted using military equipment and following military procedures (field-expedient measures). As part of military physical performance testing, there is a minimum standard that individuals must achieve, and maximum scores or values are used across these tests. The maximum values will be reported for the occupational physical performance tests in this study.

Occupational Physical Performance Tests

Isometric Mid-Thigh Pull

An isometric mid-thigh pull will be used to measure the lower-body maximal strength. The isometric mid-thigh pull test will be conducted using a military mid-thigh pull rig, and the test will be conducted in line with military procedures. The bar will be fixed at the height of the participants' mid-thigh while in slight knee and ankle flexion. Participants will step onto the force platform with their thighs touching the bar, shoulders back, and chest up and them looking straight ahead. After stepping onto the platform, participants will be required to stand still for 1 to 2 seconds while their body mass is recorded, and the system is zeroed. Participants will then adopt the pull position and remove the slack from the bar. They will be instructed, on a count of 3, to pull as hard and fast as possible for 5 seconds. Participants will be familiarized with the technique and given 2 practice attempts before completing a maximal pull. Each participant will complete 3 maximal pulls against the fixed bar with a maximal effort for 5 seconds, with a 2-minute rest between attempts. After each attempt, the maximum score taken from the mid-thigh pull display screen will be recorded, and the best of the three attempts will be reported.

Seated Medicine Ball Throw

A seated medicine ball throw will be used to assess upper-body power. Participants will sit with their backs pressed against a wall and legs flat to the floor straight out in front of them. The participants will be instructed to push a 4-kg ball from their chest upward and outward at a 45° angle to try and achieve a maximum distance thrown. Participants will be familiarized with the technique and angle of release before testing. The participants will throw the ball once, and the distance achieved will be recorded. All participants will use the same 4-kg ball when performing this test.

2-km Best-Effort Run

A 2-km best-effort run will be used to assess aerobic fitness. Participants will complete 5 laps of a 400-m running track as quickly as they feel comfortable to do so, and the time will be recorded.

Vertical Jump

A vertical jump will be used to assess lower-body power. Participants will complete three maximal vertical jumps using a Takei Vertical Jump Meter (Takei Scientific Instrument Co) to determine jump height and estimate leg power. Participants will be instructed to jump as high as possible while keeping their hands on their hips. There will be a 2-minute rest period between attempts, and the best score of the 3 jumps will be recorded. Participants will be allowed time to familiarize themselves with the procedure before starting the test jumps.

Secondary Outcome Measures

Pelvic Organ Prolapse

Pelvic organ prolapse will be measured by a pelvic health physiotherapist at weeks 6, 12, and 24. Vaginal examination will assess for prolapse using the Pelvic Organ Prolapse Quantification system (POP-Q) [39,40], quantifying pelvic support in stages from 0 to 4, with 0 indicating no prolapse demonstrated and 4 demonstrating full procidentia. A total of 6 defined points (Aa, Ba, C, D, Ap, and Bp) and 3 landmarks (genital hiatus, total vaginal length, and perineal body) will be measured using a *POP-Stix* (POPstix) tool. The hymen will be the fixed point of reference throughout the completion of the POP-Q. Each measurement will be taken in centimeters above

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or proximal to the hymen (positive number), with the plane of the hymen defined as 0 (Table 8) [39]. All measurements, except for total vaginal length, will be performed with maximal Valsalva. The POP-Q staging criteria are listed in Table 9 [39].

Table 8. Description of the 9 measures of the Pelvic Organ Prolapse Quantification system.[a]

Points	Description	Range of values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	−3 to +3 cm
Ba	Most distal position of the remaining upper anterior vaginal wall	−3 cm to +tvl
C	Most distal edge of cervix or vaginal cuff scar	N/A[b]
D	Posterior fornix	N/A
Ap	Posterior vaginal wall 3 cm proximal to the hymen	−3 to +3 cm
Bp	Most distal position of the remaining upper posterior vaginal wall	−3 cm to +tvl
gh[c]	Measured from middle of external urethral meatus to posterior midline hymen	N/A
pb[d]	Measured from posterior margin of gh to middle of anal opening	N/A
tvl[e]	Depth of vagina when point D or C is reduced to normal position	N/A

[a]Adapted from Bump et al [39].
[b]N/A: not applicable.
[c]gh: genital hiatus.
[d]pb: perineal body.
[e]tvl: total vaginal length.

Table 9. Pelvic Organ Prolapse Quantification system staging criteria.[a]

Stage	Description
0	Aa, Ap, Ba, Bp=−3 cm and C or D≤−(tvl[b] − 2) cm
1	Stage 0 criteria not met and leading edge <−1 cm
2	Leading edge≥−1 cm but ≤+1 cm
3	Leading edge>+1 cm but <+(tvl − 2) cm
4	Leading edge≥+(tvl − 2) cm

[a]Adapted from Bump et al [39].
[b]tvl: total vaginal length.

Pelvic Floor Strength

Pelvic floor strength will be measured by a pelvic health physiotherapist at weeks 6, 12, and 24 using the PERFECT (power, endurance, repetitions, fast, every contraction timed) scheme [41]. The participant will perform maximum-effort pelvic floor contraction following instructions and a practice attempt. Power will be recorded on a modified Oxford scale of 0 to 5. Endurance will be assessed by counting the number of seconds until maximum voluntary contraction can no longer be sustained and fatigue is reached. Repetitions of this sustained contraction will be performed with a 4-second rest between each contraction. Fast contractions will be performed by 1-second maximum voluntary pelvic floor contraction and 1-second relaxation until a maximum voluntary contraction can no longer be achieved. Overactivity, coordination, and relaxation of the pelvic floor muscle contraction will also be assessed during the digital vaginal examination.

Musculoskeletal Physiotherapy Assessment

Musculoskeletal physiotherapy assessments will be performed by a pelvic health physiotherapist at weeks 6, 12, and 24. *Rectus diastasis* will be assessed by measuring the distance between the internal borders of the *m. rectus abdominis*; fingers will be placed vertically on the *linea alba* 4 cm above and below the umbilicus and at the umbilicus during a curl-up movement. Scoring is an approximation of the width separation and the tone and tension of the *linea alba* structure. The larger the score (cm), the greater the separation of the *m. rectus abdominis*.

At weeks 6, 12, and 24, the pelvic health physiotherapist will observe all participants' posture, movement patterns, and breathing. If the pelvic health physiotherapist deems participants' movement or breathing patterns to be dysfunctional, exercises included in the core reconnection and physical development training may be modified slightly or additional advice and guidance provided to ensure that the desired outcome of the exercise is achieved.

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Load and impact management tests will be performed during testing session 2, before occupational physical performance tests. These tests will be used to establish the participants' capacity for safe return to running and further participation in the occupational physical fitness tests [42]. Participants will be asked to perform single-leg balance on each leg (10 seconds), 10 single squats on each leg, a jog on the spot for 1 minute, 10 forward bounds, 10 hops in place on each leg, and 10 single-leg running man motions on each leg. After each functional test, participants will be asked to report any symptoms of pain, heaviness or dragging in the vagina, or incontinence.

Pelvic Floor Distress Inventory Questionnaire

The Pelvic Floor Distress Inventory–20 (PFDI-20) [43] will be completed at weeks 6, 12, and 24. The PFDI-20 includes 20 questions and 3 scales. The 3 scales are the Pelvic Organ Prolapse Distress Inventory (6 questions), Colorectal-Anal Distress Inventory (8 questions), and Urinary Distress Inventory (6 questions). Participants will record their answers reflecting on the last 6 weeks and use the scale of 0 to 4 to indicate how bothersome the symptoms are. Each scale is scored from 0 (least distress) to 100 (greatest distress). A scale score will be given according to the mean value of all answered items, with the corresponding scale (possible value 0-4) multiplied by 25 (range 0-100). The sum of the scores from the 3 scales combined, ranging from 0 to 300, provides an overall summary score of the PFDI-20.

International Consultation on Incontinence Questionnaire–Vaginal Symptoms

The International Consultation on Incontinence Questionnaire–Vaginal Symptoms [44] will be completed at weeks 6, 12, and 24 and uses 3 subscales to evaluate vaginal symptoms (0-53), associated sexual matters (0-58) and impact on quality of life (0-10) over the previous 4 weeks. There are 14 questions for which participants will record the severity of each symptom. Each item includes a bother scale, where 0 represents the least bothersome in each subscale. The bother scales are not incorporated in the overall score but indicate the impact of individual symptoms.

World Health Organization Quality of Life Questionnaire

The World Health Organization Quality of Life-BREF questionnaire [45] will be completed at weeks 6, 12, and 24. Participants will respond to the 26 questions reflecting the last 2 weeks. The World Health Organization Quality of Life-BREF questionnaire provides an overall quality of life and well-being score and allows the calculation of four domain scores: physical health, psychological health, social relationships, and environment.

Edinburgh Postnatal Depression Scale

The Edinburgh Postnatal Depression Scale will be completed at weeks 6, 12, and 24. The Edinburgh Postnatal Depression Scale contains 10 questions reflecting the past 7 days [46]. The questionnaire will produce a total score of postnatal depression symptoms (range 0-30) with a score of ≥13, indicating a high likelihood of depressive illness. Participants will be informed that they can omit any questions that they do not wish to answer. However, if >20% of the data are missing for an individual, their data will not be included in the subsequent analysis.

Body Composition and Bone Mineral Density

Body composition (whole-body fat mass and fat-free mass) and whole-body areal bone mineral density will be measured at weeks 6 and 24 using a whole-body dual-energy x-ray absorptiometry scan (Lunar iDXA, GE Healthcare). Participants will be scanned in minimal clothing and instructed to lie as still as possible for the approximately 7-minute scan. Participants will arrive at the laboratory in a rested state, at least 3 hours in the postprandial state, and euhydrated, having consumed 500 mL of water in the 2 hours before scanning [47].

Bone Density and Morphology

A 3D high-resolution peripheral quantitative computed tomography system (XtremeCT II, Scanco Medical AG) will be used to assess volumetric bone mineral density (vBMD), geometry, microarchitecture, and estimated mechanical strength of the nondominant (self-reported) tibia at 6 and 24 weeks post partum. A 3D representation of approximately 10 mm of the tibia in the axial direction, at both the metaphyseal (4% site) and diaphyseal (30% site) tibia, will be obtained from 165 computed tomography slices with an isotropic voxel size of 61 µm. Tibial length will be measured before the first scan, taken as the distance between the medial malleolus and the tibial end plate. The leg of each participant will be fitted into a carbon fiber shell and immobilized within the gantry of the scanner for the duration of the scan. A reference line will be placed at the tibial end plate, with the first computed tomography slice taken at 4% and 30% of the tibial length from the reference line for the metaphyseal and diaphyseal tibia. For follow-up measurements at the 4% site, automatic algorithms will match the volumes of interest to baseline scans, using the cross-sectional area (CSA) within the periosteal boundary, so only the bone volume common to the baseline scans will be assessed [48]. The matching algorithms will be disabled for analysis at the 30% site [49]. Daily quality control scans will be performed using a phantom containing hydroxyapatite (HA) rods. The quality of each high-resolution peripheral quantitative computed tomography scan will be reviewed according to the manufacturer's visual grading system, and poor-quality scans will be excluded. Data processing will be performed as per Boutroy et al [48] and Burghardt et al [50]. The manufacturer's standard evaluation procedure will be used to derive the following outcomes: total vBMD (mg HA·cm^3), trabecular vBMD (mg HA·cm^3), cortical vBMD (mg HA·cm^3), trabecular bone volume fraction (%), trabecular area (mm^2), cortical area (mm^2), cortical thickness (mm), trabecular thickness (mm), trabecular number (mm^{-1}), trabecular separation (mm), cortical porosity (%), and cortical pore diameter (mm). The biomechanical properties under uniaxial compression, specifically stiffness (kN/mm) and failure load (kN), will be determined by micro–finite element analysis [51]. Evaluations will be performed by the same researcher to ensure consistency of periosteal and endosteal contouring. The coefficient of variation at the 4% site is 0.2% for total vBMD, 0.4% for

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trabecular vBMD, 0.9% for cortical vBMD, ≤1.3% for geometry, ≤2.1% for trabecular microarchitecture, 7.8% for cortical porosity, and ≤3.2% for stiffness and failure load [52]. The coefficient of variation at the 30% site is 0.3% for total vBMD, 0.2% for cortical vBMD, ≤0.8% for geometry, 4.9% for cortical porosity, and ≤0.7% for stiffness and failure load [52].

Patellar Tendon Properties

Overview

Measures of patellar tendon biomechanical properties will be obtained in vivo during voluntary isometric ramped contractions [53] at 6, 12, and 24 weeks post partum. All measurements on the dominant limb will be performed by the same researcher.

Tendon Elongation

Patellar tendon elongation will be assessed using real-time B-mode ultrasonography during ramped isometric contractions performed at a 90° knee angle on an isokinetic dynamometer (Biodex Isokinetic Dynamometer, System 4). The participants' dominant leg will be strapped at the ankle to the knee extension and flexion attachment. Straps will be tightly positioned at the shoulder and hip and across the thigh of the leg being measured. Isometric ramped contractions will be performed over 5 seconds. Participants will gradually increase the push against the dynamometer, aiming to reach maximum force within 5 seconds. Each participant will perform 4 preconditioning contractions to ensure reproducibility of the measurements [53] before completing 3 trial attempts. An ecoabsorptive external marker will be fixed to the skin using surgical tape. The ultrasound transducer will be positioned over the patellar tendon and the external marker. Tendon displacement will be measured as the distance between the line cast by the external marker and the patellar apex. Trials will not be analyzed if the line cast by the external marker moves on the ultrasound image. A calibrated goniometer will be attached to the lateral side of the tested knee to prevent an overestimation of tendon elongation due to tibial translation.

Surface Electromyography

Surface electromyography (EMG) will be used to measure muscle activity (DataLOG system, MWX8, Biometrics) from the long head of the *m. biceps femoris*. An EMG sensor (SX230, Biometrics) with 20-mm contact sensor spacing will be applied at a site corresponding to the distal one-third of the length of the muscle [53]. The location of the electrode will be traced onto an acetate sheet to ensure its accurate placement for subsequent tests. The raw EMG signal will be preamplified and filtered using high- and low-pass cutoff filters set at 10 and 500 Hz. The root-mean-square EMG activity of the biceps femoris will be measured during ramped contractions to assess the antagonistic coactivation level of the knee flexors. A maximal knee flexion isometric contraction will be performed to determine biceps femoris maximal activation when acting as an agonist. The maximal activation of the bicep femoris will be measured over a 50-millisecond window at the point of the maximum torque. The antagonistic torque of the knee flexors during a knee extension contraction will be calculated assuming a linear relationship between EMG and the torque [54] to calculate the true knee extensor torque.

Patellar Tendon Length and CSA

Resting patellar tendon length and patellar tendon CSA will be measured using real-time B-mode ultrasonography at a fixed 90° knee angle. The distance between the apex of the patella and the tibial tuberosity, recorded using sagittal ultrasound images, will be taken as resting patellar tendon length. Patellar tendon CSA will be measured using the ultrasound probe placed in the transverse plane, and images will be captured at 25%, 50%, and 75% of tendon length. Images will be analyzed offline using ImageJ (v1.50c; National Institute of Health), 3 images will be averaged at each site, and the mean will be used for calculating tendon stress.

Patellar Tendon Stiffness and Young Modulus

Patellar tendon force will be calculated by dividing the true knee extensor torque by the estimated patellar tendon moment arm [55]. Patellar tendon stress will be calculated by dividing the tendon force by the tendon CSA. Tendon strain will be calculated as the ratio (%) of tendon displacement to the initial resting tendon length. Force-elongation data will be fitted with a second-order polynomial curve, allowing the assessment of patellar tendon stiffness. The Young modulus will be calculated as tendon stiffness multiplied by the ratio of tendon length to tendon CSA.

Muscle Architecture

The muscle architecture of the *m. vastus lateralis* will be assessed at 6, 12, and 24 weeks post partum by the acquisition and analysis of B-mode ultrasonography (MyLab Omega, Esaote) images with a 4- to 15-MHz linear array probe, with the participant lying supine. Images of the dominant leg will be taken at 50% of the length of the and at the midsagittal line of the *m. vastus lateralis*. The scan site will be marked and traced onto acetate with reference points for subsequent tests. The transducer will be aligned to the fascicle plane to allow optimal capture of the fascicles [56]. Muscle thickness, fascicle length, and pennation angle will be assessed using digitizing software (ImageJ v1.50c). Muscle thickness will be measured as the distance between the superficial and deep aponeuroses of the *m. vastus lateralis*. Muscle thickness values will be calculated as the mean of measurements taken at the proximal, central, and distal locations on the captured ultrasound image. The visible portion of the fascicle within the scan window will be measured. The nonvisible portion of the fascicle will be estimated by linear extrapolation of the fascicles and aponeuroses. The linear extrapolation method is a valid technique for measuring vastus lateralis fascicle length [57], and to reduce fascicle extrapolation error (reported as approximately 4% [58]), an average of 3 fascicles across the image will be taken. The pennation angle will be determined as the angle created from the visible insertion of the fascicle into the deep aponeurosis. An average of 3 pennation angles will be taken across the image.

Muscle Protein and Collagen Turnover

Overview

Muscle protein and collagen turnover will be measured between 12 and 18 weeks post partum (Figure 4). Baseline blood and saliva samples will be collected at testing session 2. Participants

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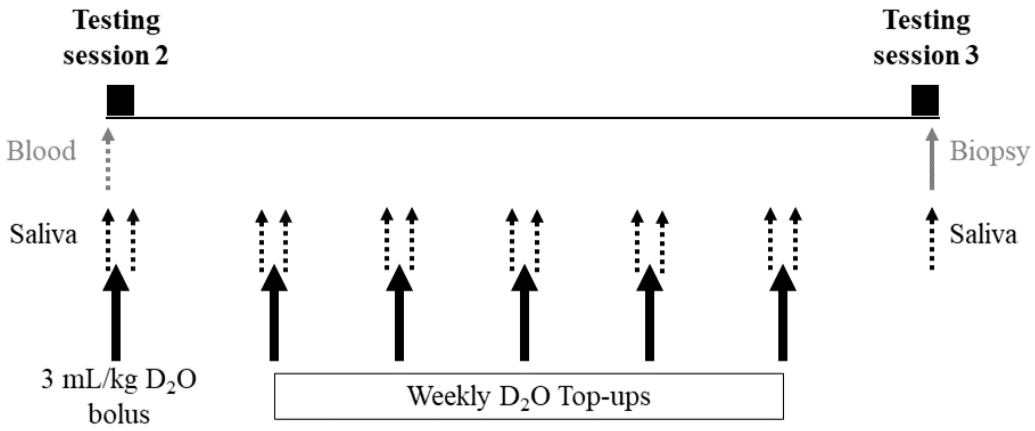
will then be given a labeled stable isotope tracer (deuterium oxide [D_2O]) at a dose of 3 mL/kg body weight, divided into 5 smaller doses, and given over 1 hour immediately after the baseline blood and saliva samples are collected. A saliva sample will also be collected 2 to 3 hours after D_2O ingestion. At testing session 3, a saliva sample and a muscle microbiopsy will be collected.

Figure 4. Procedures for muscle protein and collagen turnover using deuterium oxide (D_2O).



The blood sample and muscle biopsy will be collected 6 weeks apart. During this 6-week period, participants will take a weekly *top-up* of D_2O (approximately one-third of the original bolus) at home and will be asked to provide a saliva sample immediately before and 2 to 3 hours after each dose. Because participants will be D_2O naïve, alanine labeling in plasma proteins reflects the baseline enrichment of body proteins and will be used as a proxy for baseline muscle enrichment. The body water pool will be enriched with D_2O, and the background enrichment measured from saliva will be compared with the enrichment measured in muscle.

Blood Samples

Venous blood will be collected in lithium heparin vacutainers and thereafter centrifuged at 1843 × g and 4 °C for 20 minutes. Plasma will be separated and stored at −80 °C until analysis.

Saliva Samples

Saliva will be centrifuged at 4472 × g at 4 °C for 10 minutes to pellet cell debris. The supernatant will be transferred into a clean vial and capped to be stored at −20 °C until analysis.

Skeletal Muscle Biopsy

A rested muscle microbiopsy will be collected (Biofeather 14G needle with coaxial cannula [Medax]) from the *m. vastus lateralis* under local anesthetic. Muscle tissue will be immediately stored in dry ice and transferred to a −80 °C freezer for storage pending analysis.

Determination of Deuterium Body Water Enrichment

The protocol has been previously described [59,60]; briefly, 100 µL of saliva will be heated in inverted 2-mL vials for 4 hours at 95 °C to purify fractions of body water. The vials will then be cooled on ice and the condensed body water transferred to a clean vial ready for injection on a high-temperature conversion elemental analyzer (Thermo Finnigan, Thermo Scientific) connected to an isotope ratio mass spectrometer (Delta V advantage, Thermo Scientific).

Determination of Protein-Bound Alanine Enrichment

To assess protein-bound alanine muscle fraction enrichment, approximately 30 mg of muscle will be homogenized in ice-cold homogenization buffer to isolate myofibrillar proteins. After 10 minutes of mixing, samples will be centrifuged at 11,000 × g for 15 minutes at 4 °C. The supernatant (sarcoplasmic fraction) will be separated, and the pellet will be resuspended in 500 µL of mitochondrial extraction buffer. The pellet will then be homogenized using a Dounce homogenizer and centrifuged at 1000 × g for 5 minutes at 4 °C. Insoluble collagen will be separated following centrifugation from myofibrillar proteins, which will be solubilized in 750 µL NaOH, precipitated using 1 M perchloric acid, and pelleted by centrifugation.

The plasma will be deproteinized using ice-cold ethanol (100%) and centrifuged at 17,000 × g for 10 minutes. The myofibrillar, collagen, and plasma pellets will be transferred to boiling tubes containing Dowex with 0.1 M HCl and hydrolyzed overnight at 110 °C for 16 to 20 hours. Following overnight hydrolysis, amino acids will be eluted with 2 M NH_4OH and dried.

Dried samples will be resuspended in 60 µL of distilled water, 32 µL of methanol, 10 µL of pyridine, and 8 µL of methyl chloroformate with intermittent vortexing. The *n*-methoxycarbonyl methyl esters of the amino acids will then be extracted after adding 100 µL of chloroform. A molecular sieve will be added to remove water for approximately 20 seconds before being transferred to vials. Incorporation of deuterium into the protein-bound alanine will be determined by gas chromatography–pyrolysis–isotope ratio mass spectrometry (Delta V Advantage, Thermo).

Calculation of Fractional Synthetic Rate

The fractional synthetic rate (FSR) will be calculated using the incorporation of deuterium in alanine in myofibrillar, collagen, and plasma proteins ($APE_{Alanine}$) and deuterium enrichment of body water from saliva, representing the precursor labeling between the blood sample and the muscle biopsy ($APE_{Precursor}$),

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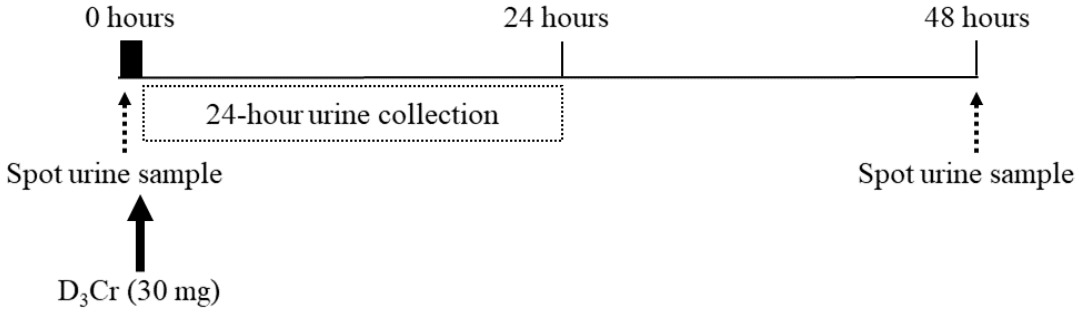
corrected for the mean number of deuterium moieties incorporated per alanine, 3.7, and the dilution from the total number of hydrogens in the derivative (ie, 11). The following calculation (Equation 1) will be used, where *t* represents the time between the baseline blood sample and the muscle biopsy:

Muscle Mass Analyses Using D3-Creatine

Whole-body muscle mass will be estimated using urinary D_3-creatine at weeks 6, 12, 18, and 24 post partum (Figure 5).

Figure 5. Procedures for muscle mass analyses using D_3-creatine (D_3Cr).



A single urine sample will be collected before ingestion of approximately 30 (SD 0.1) mg of D_3-creatine tracer (D_3-creatine, CK Isotopes) dissolved in approximately 50 mL of water. Participants will then collect all urine samples for 24 hours, starting immediately after tracer ingestion. A single urine sample will be collected 48 hours after tracer ingestion. The volume of urine collected over 24 hours will be recorded. Approximately 3 mL of each urine sample will be transferred to Eppendorf tubes and stored at −80 °C for later analysis.

Urine will be thawed at room temperature. A standard curve using ^{12}C- and ^{13}C-creatine will be prepared for the determination of creatine concentration, and a D_3-creatinine enrichment curve of 0% to 0.1% will be prepared. Once thawed, urine will be mixed, and 10 µL of ^{13}C-creatine will be added to 50 µL of urine as an internal standard. A total of 250 µL of ice-cold acetonitrile will be added to samples and standards, vortex mixed, and left to incubate on ice for 30 minutes. Following incubation, samples will be centrifuged at 17,000 × g for 20 minutes. The supernatant will be transferred to vials ready for analysis using high-performance liquid chromatography–mass spectrometry.

From the measurement of urinary D_3-creatinine enrichment it is possible to calculate total creatine pool size and, therefore, total muscle mass (Equation 2) [61], where $MW_{unlabeled}$ and $MW_{labeled}$ represent the molecular weights of both unlabeled and labeled creatine, respectively. The estimated creatine pool size will be divided by 4.3 g/kg, reflecting the concentration of creatine found in whole wet muscle mass.

Muscle Protein Breakdown Analyses Using D3-3-Methyl-Histidine

Muscle protein breakdown will be estimated using D_3-3-methyl-histidine (D_3-3MH) measured in urine at weeks 12 and 18 post partum (Figure 6). A single urine sample will be collected before ingestion of 10 mg of a methyl-D_3-3MH tracer (D_3-3MH, CK Isotopes) dissolved in 50 mL of water. Participants will void urine 18 hours after tracer ingestion before collecting spot samples at 20, 22, 24, and 26 hours after tracer ingestion. Approximately 3 mL of each urine sample will be stored in Eppendorf tubes at −80 °C until analysis.

A 0% to 10% D_3-3MH enrichment curve will be prepared as a serial dilution and run alongside the samples. In total, 100 µL of urine will be aliquoted and deproteinized using 1 mL of MeCN:MeOH (1:1). Samples will be vortex mixed and incubated at −20 °C for 1 hour. Samples will be centrifuged at 17,000 × g for 5 minutes at 4 °C. The supernatant will be dried in the Techne Block at <40 °C using nitrogen gas, resuspended using 100 µL of acetonitrile: doubly deionized H_2O (50:50), and analyzed using high-performance liquid chromatography–mass spectrometry.

The ratio of D_3-3MH to 3-methyl-histidine will be determined, ratios will be corrected relative to the enrichment curve of each batch, and the atom percent excess will be determined. The predose, baseline urine sample will be used to correct for background enrichment and calculation of the atom percent excess. The ratios will be log-transformed and plotted against time to determine the decay rate.

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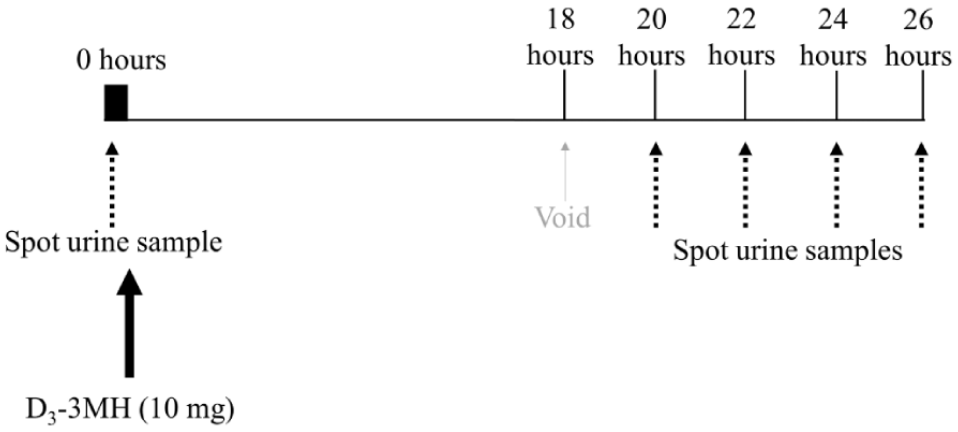
Figure 6. Procedures for muscle protein breakdown using D_3-3-methyl-histidine (D_3-3MH).



Power Calculation

Kraemer et al [62] identified that single-lift strength was 39 (SD 7) kg and 37 (SD 5) kg for women at the end of a 6-month total strength and power and total strength and hypertrophy resistance training protocol, respectively, compared with 32 (SD 4) kg for women undertaking normal field-based military training. Based on the effect sizes between these training and control groups (total strength and power vs control, Cohen *d*=1.23; total strength and hypertrophy vs control, Cohen *d*=1.10), it is anticipated that between 9 and 11 women would be required per group to identify greater posttraining strength in the intervention group than in the control group, with a $1-\beta$ of .80 and α of .05. Hendrickson et al [63] identified that squat and bench press 1 RM were 77 (SD 3) kg and 41 (SD 2) kg, respectively, for women at the end of a 12-week endurance and strength training program, compared with 68 (SD 4) kg and 34 (SD 2) kg for women in the control group, respectively. Based on the effect sizes between the training and control groups (squat, Cohen *d*=2.55; bench press, Cohen *d*=1.62), it is anticipated that between three and six women would be required per group to identify greater posttraining strength in the intervention group than in the control group, with a $1-\beta$ of .80 and α of .05. Hendrickson et al [63], identified that a 3.2-km run time was 18.5 (SD 1.0) minutes for women at the end of a 12-week combined endurance and strength training program, compared with 22.1 (SD 1.2) minutes for women in the control group. Based on the effect sizes between the training and control groups (Cohen *d*=3.26), it is anticipated that 3 women would be required per group to identify greater aerobic fitness in the intervention group than in the control group, with a $1-\beta$ of .80 and α of .05. As such, 11 participants per group would be sufficient to detect improved strength and aerobic fitness in the intervention group compared with the control group. To allow for dropout and noncompliance, we aim to recruit a minimum of 15 participants per group.

Statistical Analysis

To maximize statistical power, outcomes will be analyzed using mixed-effects linear models to leverage the collection of data on more than 2 time points and to facilitate the analysis of unbalanced data based on participant attrition. Participants will be included as random effects, with group and time included as fixed effects, to assess within- and between-group differences over time. Sensitivity analyses will be conducted by including baseline values in models or other data relative to potential confounders to account for nonrandom allocation. Linear models will be structured to assess within- and between-group differences over time (eg, the inclusion of resistance and HIIT exercise), establishing the rate of change of intervention and control and determining whether these rates are distinct. The suitability of the models will be established by assessing model residuals and transformations made if residuals are not normally distributed or homoscedastic. Uncertainty in parameter estimates will be quantified using the Satterthwaite approximation for *df* values or through bootstrapping procedures. To facilitate interpretation of the magnitude of change across different outcomes, analyses will be standardized relative to the baseline SD, thus placing outcomes on a unitless scale. Principal component analysis will be conducted on change scores to investigate the clustering of outcomes relative to the magnitude of change.

Ethical Considerations and Consent

This study received ethical approval from the Ministry of Defence Research Ethics Committee (942/MODREC/18) in April 2019. Participants will be provided with an information sheet at least 24 hours before consenting to participation and given a verbal description of the study. Written informed consent will be obtained at the start of the first testing session. Adverse events and reactions will be reported to the trial committee and considered by a minimum of 3 trial committee members.

Confidentiality and Data Storage

All data will be handled in accordance with the project's data management plan and in compliance with the General Data Protection Regulation. All raw data will be pseudonymized during the trial. Anonymized data will be uploaded to the active research data storage system at Nottingham Trent University for a minimum of ten years following the completion of the study. Data access rights will be provided only to the relevant members of the research team.

Results

This study was funded by the Ministry of Defence in March 2018, awarded by BAE Systems (Operations) Limited, contracted through CORDA business (Award Task 0157

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proposal reference ASC\CMRCL\RFQ\00694). The study received ethical approval from the Ministry of Defence Research Ethics Committee (942/MODREC/18) in April 2019. Data collection initially started in July 2019, and in March 2020, a total of 4 participants (2 intervention and 2 control) had completed all testing sessions. The study was paused in March 2020 because of the COVID-19 pandemic, but recruitment restarted in May 2021. The study is expected to conclude in September 2022 and the results will be made available thereafter.

Discussion

Hypothesis

We hypothesize that occupational physical performance will improve to a greater extent in the training group, who will receive the combined core reconnection and physical development training intervention, than it will in the control group. We also hypothesize that the training group will see greater improvements in all the secondary outcome measures.

Limitations

Nonrandom allocation could influence participant bias, but it was deemed necessary to use the approach of geographical separation of participants to limit the likelihood of the intervention being shared between the training and control groups. It was deemed unethical for the control group to act as a *true control* (ie, to limit control participants' physical activity and exercise patterns and levels), and as such, the participants can complete whatever exercise they choose during the study period. Exercise logs will be used to monitor the exercise conducted by the control group, allowing the comparison of any exercise completed between both groups. In addition, it will not be possible for the research team to be blinded to participant group allocation, as the research associates will be involved in both the testing and training of all study participants.

Dissemination Policy

The trial results will be reported to the Ministry of Defence upon completion of all data collection and analysis. The intent of the Ministry of Defence is to make these core reconnection and physical development training programs available to servicewomen following childbirth under the guidance of their physical training instructors. The evidence provided by this study will inform the management of pregnant and postpartum individuals, building on current Ministry of Defence initiatives such as the provision of female health physiotherapy and bespoke training in pregnancy and postpartum care for physical training instructors. With the approval of the Ministry of Defence, the results will be published in several formats including, but not limited to, peer-reviewed journals, press releases, and conferences.

Conclusions

Women are now fully integrated throughout the UK Armed Forces, including employment in ground close combat roles. Therefore, high-quality evidence supporting the safe return of women to high levels of occupational fitness following childbirth is required. This study will provide (1) data on the efficacy of a postpartum rehabilitation and physical development program in servicewomen and (2) recommendations for return to occupational fitness following childbirth. In addition, the findings from this study can be used to (1) re-evaluate the current Ministry of Defence postpartum policies and (2) provide education on postpartum requirements, with a view to facilitating the safe and optimal return of postpartum servicewomen to military employment.

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Authors' Contributions

CS, KJES, JPG, SLW, and TJOL contributed to the conception and design of the trial. CS and KJES are the joint principal investigators on the trial and substantively revised the manuscript. ELB and TJ are the researchers on the trial who added to the design of the exercise intervention, are responsible for the ongoing acquisition of data, and significantly contributed to the drafting of the manuscript. All authors read and approved the final manuscript.

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Krajewski and the SPARTA research team, University of Pittsburgh, Physical Development Training Program design; and Jane Bonnell, Nottingham Trent University, research data management officer.

Conflicts of Interest

SLW is employed by the UK Ministry of Defence as a defence scientist and is a project officer on this trial. TJOL is employed by the UK Ministry of Defence as a defence scientist. KJES and CS are co-grant holders and co-principal investigators in this trial. JPG is employed by the UK Ministry of Defence as a principal scientist and defence principal investigator on this trial.

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Abbreviations

CSA: cross-sectional area
D_2O: deuterium oxide
D_3-3MH: D3-3-methylhistidine
EMG: electromyography
HA: hydroxyapatite
HIIT: high-intensity interval training
HR: heart rate
PFDI-20: Pelvic Floor Distress Inventory–20
POP-Q: Pelvic Organ Prolapse Quantification system
RM: repetition maximum
RPE: rating of perceived exertion
vBMD: volumetric bone mineral density

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Protocol

Women Physicians in Transition Learning to Navigate the Pipeline from Early to Mid-Career: Protocol for a Qualitative Study

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Abstract

Background: Women physicians face unique obstacles while progressing through their careers, navigating career advancement and seeking balance between professional and personal responsibilities. Systemic changes, along with individual and institutional changes, are needed to overcome obstacles perpetuating physician gender inequities. Developing a deeper understanding of women physicians' experiences during important transition points could reveal both barriers and opportunities for recruitment, retention, and promotion, and inform best practices developed based on these experiences.

Objective: The aim is to learn from the experiences and perspectives of women physicians as they transition from early to mid-career, then develop best practices that can serve to support women physicians as they advance through their careers.

Methods: Semistructured interviews were conducted with women physicians in the United States in 2020 and 2021. Eligibility criteria included self-identification as a woman who is in the process of transitioning or who recently transitioned from early to mid-career stage. Purposeful sampling facilitated identification of participants who represented diversity in career pathway, practice setting, specialty, and race/ethnicity. Each participant was offered compensation for their participation. Interviews were audio-recorded and professionally transcribed. Interview questions were open-ended, exploring participants' perceptions of this transition. Qualitative thematic analysis will be performed. We will use an open coding and grounded theory approach on interview transcripts.

Results: The Ethics Review Committee of the Faculty of Health, Medicine, and Life Sciences at Maastricht University approved the study; Stanford University expedited review approved the study; and the University of California, San Diego certified the study as exempt from review. Twelve in-depth interviews of 50-100 minutes in duration were completed. Preliminary analyses indicate one key theme is a tension resulting from finite time divided between demands from a physician career and demands from family needs. In turn, this results in constant boundary control between these life domains that are inextricable and seemingly competing against each other within a finite space; family needs impinge on planned career goals, if the boundary between them is not carefully managed. To remedy this, women sought resources to help them redistribute home responsibilities, freeing themselves to have more time, especially for children. Women similarly sought resources to help with career advancement, although not with regard to time directly, but to first address foundational knowledge gaps about career milestones and how to achieve them.

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Conclusions: Preliminary results provide initial insights about how women identify or activate a career shift and how they marshaled resources and support to navigate barriers they faced. Further analyses are continuing as of March 2022 and are expected to be completed by June 2022. The dissemination plan includes peer-reviewed open-access journal publication of the results and presentation at the annual meeting of the American Medical Association's Women Physicians Section.

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KEYWORDS

gender equity; women physician; female physicians; career development; professional development; career pipeline; leaky pipeline; mid-career physicians; early-career physicians; physician; healthcare profession; peer support; physician perspective; physician experience; professional learning; healthcare; health care; healthcare education; career support; gender equality; gender bias; healthcare learning

Introduction

Career Advancement Disparities

As women physicians transition through different stages of their careers, their professional skills and personal or family obligations may be evolving in parallel. For example, physicians can transition from early to mid-career as a leader, executive, educator, researcher, advocate, entrepreneur, or a combination thereof. These women, often in their 30s and 40s, are therefore experiencing peak potential for the need to make choices between their professional and personal worlds. The leaky pipeline of women physicians advancing through their careers remains problematic, and focused investigation of important inflection points, such as the transition from early to mid-career, could contribute important insights to our understanding of how to achieve gender equity in medical careers.

The medical profession has achieved significant progress in understanding gender inequity and its consequences [1,2], yet actualized gender equity has not yet been reached in any career pathway for women physicians. Women make up nearly half of US medical school applicants [3,4], and more than half of the physician workforce in certain specialties. In US academia, women make up only 38% of faculty, 21% of full professors, and 16% of deans [3]. Lack of gender equity is also a concern in international academic medical settings, where women clinician educators are less likely to hold academic appointments, and are more likely to be younger, single, and childless [5,6]. Although the number of women at all levels of academic medicine has increased [7], balancing an academic career with raising a family is hard work for women physicians [8]. Women faculty tend to leave an institution because of a lack of professional advancement, low salary, or departmental leadership issues [9].

Women are affected in all other career pathways, in addition to the academic pipeline. Far fewer women in general, including women physicians, hold chief executive positions compared to male physicians and men in general [5,10], and women executives of hospitals are often paid less [11,12]. This may, in part, be related to the higher likelihood for women physicians to experience nonlinear career paths and they often have less access to mentors, sponsors, and leadership positions in general [13,14]. Career satisfaction for women physicians is also more likely to be influenced by work-life balance, mentorship opportunities, supportive leadership, conductive culture, and equal access [5,6,15]. Women and women physicians are also significantly underrepresented among health care startups in the male-dominated industry of health care technology [10].

Compensation Disparities

Other barriers that women physicians face relate to gender equity in compensation [1]; advancing toward leadership in academic medicine [3,4,16], including executive positions [17]; receiving acknowledgement via medical society recognition and awards [18], and maintaining a sustainable level of engagement and fulfillment between professional life and motherhood [8] or even singlehood. Financial implications are significant for women physicians through the course of their careers [19]. Women physicians may negotiate less aggressively and with less confidence than men, or not negotiate at all, and appear to be more likely than men to take on both internal and external service [20] or volunteer for "invisible work" that is less likely to lead to promotions [21,22]. This can have financial and other significant consequences for the woman and her dependents. Among US physicians, men are paid more than women in all specialties at every academic rank; in general, this trend persists even after accounting for specialty, geography, time in practice, and average hours worked per week [23].

Some studies showed marked differences in the compensation of female physicians, which may impact their ability to support a family while pursuing a career [1]. In other cases, some female physicians are the primary breadwinners of their families and may face additional pressures or stressors associated with such a role, especially when also carrying a large share of child and family care responsibilities. Despite evidence of delivering more preventive care and better outcomes [24,25], spending more time with patients and on electronic health record tasks, and generating equal revenue after adjustments for physician, patient, and visit characteristics, women physicians are still at high risk of being undervalued in the current payment system [26].

Work-Life Integration Disparities

Women physicians may experience an increasing need for further developing personal skills in integrating professional and family obligations (including care of young children or aging parents) [17,27-30]; skills as a mentor and sponsor of younger physicians and physician peers, or finding mentors, sponsors, and coaches to help their career advancement [13,14]; skills in negotiation and advocacy as a leader locally or on a broader scale [30]; and/or learning to better recognize their own self-care needs when facing burnout or other mental or physical health issues [31].

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One study sampled male and female residents and faculty to describe physicians' experience of work, work-family factors, and other perspectives that may influence career decision-making; emerging themes identified family obligations as being in balance or not, with motivating factors for being a physician, across a fulcrum of pursuing a career in academic internal medicine [32]. Women faculty physicians were more likely to express experiences of imbalance between their role as a practitioner and nonwork roles, compared to their counterparts who were men. Women physician practitioners also had the fewest strategies for multiple role planning compared to women researchers and educators [32]. Women physicians in transition may also face family planning challenges and infertility, in addition to these other factors [33].

Attrition during residency, for example in general surgery, has been shown to be variably influenced by female gender/sex [34-36]. In a qualitative study, female and male residents who left their general surgery training expressed an absence of a safe space for sharing program-related and personal concerns, as well as a scarcity of role models who worked in surgical careers with work-life balance that was better than the work hours of residency [34]. In addition, women resident physicians commonly strategized their second shift roles (specifically, their role as a parent), whereas men resident physicians strategized protection of personal time [32].

In addition, well-being for women physicians may have unique contributing factors [2,31], for example, women physicians experience high rates of sexism and sexual harassment [37-40], but they also face less explicit biases, such as gendered expectations of how they provided patient care [41] and implicit bias [1,31]. If experiencing burnout, women physicians experience emotional exhaustion first, which differs from male physicians [42]; women physicians are more frequently diagnosed with depression compared to male physicians [43], and they may have higher rates of suicide than male physicians when compared to their gender-matched general population [44].

Study Aims

There is a growing need for best practices at individual, institutional, and systemic levels for overcoming physician gender inequity. We explore the experiences of women physicians who self-identify as being in the process of transitioning or who recently transitioned from early to mid-career to generate ideas that can inform detailed best practices for overcoming gender inequity during this time of career advancement. In this study, the aims are (1) to learn from the experiences and perspectives of women physicians as they transition from early to mid-career and (2) to develop best practices that can inform institutions and organizations in which women physicians work, to better support their advancement through an important transition from the early to mid-career phase.

Methods

Recruitment

We used qualitative methods using one-on-one semistructured interviews with women physicians. Participants will be identified through social media posts with invitations (eg, Facebook groups for Women Physician Entrepreneurs, Women Physician Leaders, etc) and through professional networks, listservs, or discussion forums to which team members belong. Eligibility criteria included self-identification as a woman who is in the process of transitioning or who has recently transitioned from early to mid-career. Purposeful sampling facilitated identification of information-rich cases, with attention to diversity in career pathway (eg, clinical, research, education, executive leadership, entrepreneurship, advocacy), specialty, and race and ethnicity [45]. To facilitate the recruitment process, women physicians could read a brief study description, including ethics review board approval, and voluntarily provide responses to a few initial screening questions (Textbox 1).

Snowball sampling was also intended to identify additional interview participants to enrich the sampled population if needed. Each participant will receive a US $100 Amazon gift card for their participation. We aimed to recruit approximately 20 women physicians for initial interviews. We anticipated the interviews to be approximately 1 hour in length.

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Textbox 1. Initial screening questions and response options.

1. In which US state or territory do you practice? (Response options were classified into 1 of 8 United States Bureau of Economic Analysis regions as part of the participant deidentification process)

2. What is your specialty? Check all that apply.

- Emergency Medicine
- Family Medicine
- General Surgery
- Internal Medicine
- Pediatrics
- Psychiatry
- Obstetrics/Gynecology
- Surgical subspecialties
- Other (please specify)

3. How do you describe your work environment(s)? Check all that apply.

- Academia
- Government or military
- Industry
- Private practice (eg, self-employed individually or in a group)

4. With which statement do you identify? Select one.

- I am in the process of transitioning from early to mid-career.
- I just completed my transition from early to mid-career.
- I'm not sure

Study Procedures

An interview guide was developed by the investigators, who have diverse experiences in academic medicine (TIL, KHW, TLL, GTG, SSP, CYAC), health care administration (SSP), organized medicine (TIL, TLL, CYAC), private practice (TLL), and research (TIL, KHW, GTG, CYAC), including qualitative methods (KHW) (Multimedia Appendix 1). Qualitative interviews were performed via Skype or other acceptable web conferencing software by at least one investigator and recorded for transcription and analysis. Using an open coding approach, we analyzed transcripts using the constant comparative method, developed a code structure in stages in accordance with the grounded theory approach, and developed concepts through memoing [46-48]. Interviews continued until thematic saturation was reached. We plan to conduct participant verification with our original study participants.

Ethics Approval

Study approval was received from the Ethics Review Committee of the Faculty of Health, Medicine, and Life Sciences (FHML-REC) at Maastricht University (FHML-REC/2019/056). Expedited review and approval was received from Stanford University (eProtocol #53654). The study was certified as exempt from review by the University of California, San Diego (Project #200463XX). Ethics approval was not sought from affiliate institutions for two authors (SSP, KHW) as neither author would interact with study participants and therefore would not interact with deidentified data at any time during the study. The study was randomly selected by the FHML-REC at Maastricht University for a research quality audit in October 2020, which was completed to the satisfaction of the Deputy Chair/Research Quality Officer of the FHML-REC.

Participants were informed about the study (the aim, method, data management, and the participants' rights). Specifically, it was noted that some participants may experience psychological distress when remembering and recalling past experiences during one-on-one interviews, especially those that may involve particularly difficult or stressful emotions or memories. However, this was anticipated to be temporary and no harms are anticipated in association with participation in this study. Furthermore, participation was completely voluntary, and participants may withdraw from the study at any time. The researchers ensured that the consent was voluntary. Prior to interviews, the informed consent letter (Multimedia Appendix 2) and information sheet (Multimedia Appendix 3) were reviewed with participants.

Data Management Plan

For participants who gave written informed consent prior to the interviews and therefore provided their name on the informed consent form, pseudonyms or pseudoinformation were used in the transcriptions to refer to the participants; it was not to be reported which names belonged to each transcript.

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Only the primary research team members have access to the data. We established a monthly team meeting schedule to allow for discussion of concerns within the team. Data were anonymized by the primary investigator (TIL) throughout internal and external documents during analysis to remove identifiable personal and institutional information. For example, individual and institutional names, locations, and similar information were replaced with pseudoinformation (eg, an individual name would be substituted with XXX; the name of an academic institution would be replaced with "a large academic medical center").

Data collected during the study are handled confidentially according to the European General Data Protection Regulation (GDPR). All the data are stored according to the rules of data management of Maastricht University (UM) [49]. We used the UM data archiving facilities and procedures to store our data. The data will be retained for 10 years, in accordance with the UM Data Management Code of Conduct. A data transfer and use agreement for anonymized data was established between Maastricht University and Stanford University to be in compliance with data management requirements of Stanford University as an affiliate institution of one of the authors (CYAC).

Results

Twelve in-depth interviews of 50-100 minutes in duration per interview were completed and transcribed. Analysis of the data is expected to be completed by June 2022. Participant demographics of women physicians interviewed are supplied in Table 1.

In preliminary analyses, one key emerging theme is a tension resulting from finite time divided between demands from a physician career and demands from family needs. In turn, this results in constant boundary control between these life domains that are inextricable and seemingly competing against each other within a finite space; family needs impinge on planned career goals, if the boundary between them is not carefully managed. To remedy this, women sought resources to help them redistribute home responsibilities, freeing themselves to have more time, especially for children.

Table 1. Participant demographic characteristics.

Participant	With which statement do you identify?	How do you describe your work environment(s)?	Clinical specialty	US region[a]
1	I am in the process of transitioning from early to mid-career.	Academia	Anesthesiology	Far West[b]
2	I am in the process of transitioning from early to mid-career.	Academia; government/military	Internal Medicine	Far West[b]
3	I am in the process of transitioning from early to mid-career.	Government/military	Pediatrics	Far West[b]
4	I am in the process of transitioning from early to mid-career.	Private practice	Surgical subspecialty	Great Lakes[c]
5	I am in the process of transitioning from early to mid-career.	Private practice	Surgical subspecialty	Southwest[d]
6	I am in the process of transitioning from early to mid-career.	Academia	Emergency Medicine	Mideast[e]
7	I just completed my transition from early to mid-career.	Academia	General Surgery/Surgical Oncology	Plains[f]
8	I just completed my transition from early to mid-career.	Academia; government/military	Internal Medicine	Far West[b]
9	I just completed my transition from early to mid-career.	Private practice	Endocrinology	Southeast[g]
10	I'm not sure	Academia	Family Medicine	Far West[b]
11	I'm not sure	Academia	Internal Medicine	Far West[b]
12	I'm not sure	Private practice	Hospice and Palliative Care	Mideast[e]

[a]United States Bureau of Economic Analysis classifications of 8 US regions.

[b]Far West region includes Alaska, California, Hawaii, Nevada, Oregon, and Washington.

[c]Great Lakes region includes Illinois, Indiana, Ohio, Michigan, and Wisconsin.

[d]Southwest region includes Arizona, New Mexico, Oklahoma, and Texas.

[e]Mideast region includes Delaware, Maryland, Pennsylvania, New Jersey, and New York.

[f]Plains region includes Iowa, Kansas, Minnesota, Montana, Nebraska, North Dakota, and South Dakota.

[g]Southeast region includes Alabama, Arkansas, Florida, Kentucky, Louisiana, Georgia, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia.

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Women similarly sought resources to help with career advancement, although not with regard to time directly, but to first address foundational knowledge gaps about career milestones and how to achieve them. Such resources could be institutional professional development programs and/or relationship-based resources like having knowledgeable mentors. Effective mentorship was especially vital, mediating the translation of knowledge into prioritizing professional activities toward a previously unknown time horizon.

Discussion

Principal Results

Best practices for supporting the early to mid-career transition for women physicians are needed to overcome physician gender inequity. However, women physicians express uncertainty even in self-identifying as going through or completing this transition. The absence of clear signposts of career advancement, combined with variable levels of professional support, and tension generated at the boundary of professional and family life domains, leads to persistent challenges for and limited opportunities to support women physicians while they are navigating this career transition.

Upon completion of data analyses, we anticipate that the development of a set of best practices or at least guiding principles can be derived from the detailed, systematic collection of women physicians' experiences. This may offer an impactful contribution to support women physicians as they advance through their career paths and address issues that arise in the leaky career pipeline. Due to the diverse and multifactorial contexts that women physicians may encounter both at work and at home, learning from the narratives of women physicians would be constructive toward the end goal of addressing such barriers for women.

A strength of this study is that it sought to include not only women physicians in academic medicine or in a single specialty but also to include women physicians in private practice in multiple US geographic locations and in different specialties. Despite this purposeful heterogeneity of the research participants, common themes appear to be emerging from the data, which will be analyzed and published in a future manuscript.

Limitations

First, the recruitment for this study was limited due to difficulties that arose during the COVID-19 pandemic. Initial recruitment for interviews could only begin after multiple institutional review board approvals and data agreements could be obtained given the international collaboration of the coauthorship. By the time these approvals were obtained, the recruitment period coincided with the onset of the first global surges of the COVID-19 pandemic. The target population for recruitment included US women physicians, many who provided either frontline clinical care for patients during the first and subsequent surges of the COVID-19 pandemic or were otherwise engaged in pandemic responses.

Second, the parallel recruitment and interviews that occurred alongside pandemic responses in 2020 and 2021 may have affected the content and responses of participants recruited. Furthermore, this affected the content of the semistructured interviews, and may limit the generalizability of the results outside of the setting of the pandemic. Finally, recruitment was limited to US women physicians, which may limit the generalizability of results and best practice recommendations generated. Although the recruitment procedures were designed to permit inclusion of a diversity of women physicians by work environment, specialty, and geography, those women physicians who responded to the initial screening questions did not include any women physicians who work in industry or who are located in two US regions. The two regions not represented were New England region (Connecticut, Maine, New Hampshire, Rhode Island, and Vermont) and Rocky Mountain region (Colorado, Idaho, Montana, Utah, and Wyoming). Although the sample for this study is limited to the United States, women physicians globally experience gender inequity in career advancement and attrition from the practicing and academic physician workforce [4,5,50]. Future investigation could involve a broader diversity of women physician participants globally to examine additional influences on the early to mid-career transition, such as health care or academic systems and sociocultural considerations and the intersectional experiences of these physicians. Additionally, investigation of within-gender or between-gender differences, for example, by interviewing physicians who are men in the early to mid-career transition period, could offer additional insights about this career transition. There is also increasing acknowledgment that, upon transitioning into mid-career, systemic inequities lead to an "invisibility" of these women physicians as they seek continued career advancement [51]. Further work to mitigate these effects is also needed.

Comparison With Prior Work

The preliminary results of this study are consistent with previous work in this area that examine issues of work-family conflict for women professionals. Work-family tension is encountered when demands from one domain are incompatible with the demands of another domain [52]. Although this study focused on women physicians only, the findings appear consistent with previous work that found that women professionals fit a Family profile compared to men who more commonly fit a Work profile [53]. A Family profile involves high importance given to family, including parental and spousal roles, whereas a Work profile involves high importance given to the work role. In another study, women and men who are junior faculty in an academic medical center were similar in their levels of career interest and career identification [54]. Although this study did not quantitatively assess women physicians' career interest or work commitment, participants expressed an essential need to resolve work-family conflicts by finding personal and professional solutions to manage the boundary between each domain or set of roles.

Although this study was not originally designed to investigate the effects of the COVID-19 pandemic on women physicians and their career advancement, the effects of this major global event cannot be ignored. Several studies during the pandemic have sought to quantify the negative impacts of the pandemic on women physicians, especially those in academia including those in scientific research. For example, women as first authors

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on peer-reviewed publications decreased by 14% from 2019 (the year immediately prior to the onset of the pandemic) to 2020 (the first year of the pandemic) [55]. Additionally, concerns regarding women physicians taking on a disproportionately higher burden of family or caregiving responsibilities during the pandemic may influence their career transitions and advancement [56,57]. Preliminary findings of this study appear to be consistent with these observations, although this study may not have explicitly addressed these topics. Such topics also may have been less relevant for women physicians interviewed who were not in academia. Health care organizations, including academic medical centers, may be able to role model organizational professionalism and ethics, engage in benchmarking and reporting of gender equity data, and engage in meaningful interorganizational partnerships toward dismantling barriers to systematic gender inequities among physicians [58].

Dissemination Plan

Findings will be summarized and described in detail in a manuscript and presented at national and international conferences as available. Findings will be submitted for publication to a peer-reviewed, open-access medical journal, due to the topic's general relevance for women physicians, physician well-being, and health care organizations. Speaking engagements are expected, such as at an annual meeting for the American Medical Association's Women Physicians Section (see Acknowledgments) and other professional societies or venues [59].

Conclusions

Preliminary results provide initial insights about how women identified or activated a career shift and how they marshaled resources and support to navigate barriers they faced. However, further collaborative research and programs are needed to satisfactorily develop and implement best practices to support women physicians' advancement through an important transition from their early to mid-career.

Acknowledgments

TIL, CYAC, TLL, SSP, and KHW conceived the study design and developed study materials. TIL, CYAC, TLL, and GTG collected the data. TIL, CYAC, TLL, GTG, and KHW conducted initial data analyses. TIL wrote the original draft of the manuscript. All authors reviewed, edited, and approved the final manuscript. The primary investigator (TIL) is grateful to Prof dr Frits van Merode for critical discussions about this topic and administrative guidance after the project received grant funding. Funding was provided by the American Medical Association's Joan F. Giambalvo Fund for the Advancement of Women. The funding organization had no involvement in review or approval of the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 10 KB - resprot_v11i6e38126_app1.docx]

Multimedia Appendix 2
Informed consent letter for research participants.
[DOCX File , 173 KB - resprot_v11i6e38126_app2.docx]

Multimedia Appendix 3
Information sheet for research participants.
[DOCX File , 167 KB - resprot_v11i6e38126_app3.docx]

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Abbreviations

FHML-REC: Ethics Review Committee of the Faculty of Health, Medicine, and Life Sciences
GDPR: General Data Protection Regulation
UM: Maastricht University (Universiteit Maastricht)

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Protocol

A Novel, Combined Student and Preceptor Professional Development Session for Optimizing Feedback: Protocol for a Multimethod, Multisite, and Multiyear Intervention

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Abstract

Background: Providing feedback to medical learners is a critical educational activity. Despite the recognition of its importance, most research has focused on training preceptors to give feedback, which neglects the role of learners in receiving feedback. Delivering a combined professional development session for both preceptors and students may facilitate more effective feedback communication and improve both the quality and quantity of feedback.

Objective: The objective of our research project is to examine the impact of a relational feedback intervention on both preceptors and students during a longitudinal integrated clerkship.

Methods: Students and preceptors will attend a 2.5-hour combined professional development session, wherein they will be provided with educational tools for giving and receiving feedback within a coaching relationship and practice feedback giving and receiving skills together. Before the combined professional development session, students will be asked to participate in a 1-hour preparation session that will provide an orientation on their role in receiving feedback and their participation in the combined professional development session. Students and preceptors will be asked to complete a precombined professional development session survey and an immediate postcombined professional development session survey. Preceptors will be asked to complete a follow-up assessment survey, and students will be asked to participate in a follow-up, student-only focus group. Anonymized clinical faculty teaching evaluations and longitudinal integrated clerkship program evaluations will also be used to assess the impact of the intervention.

Results: As of March 1, 2022, a total of 66 preceptors and 29 students have completed the baseline and follow-up measures. Data collection is expected to conclude in December 2023.

Conclusions: Our study is designed to contribute to the literature on the feedback process between preceptors and students within a clinical setting. Including both the preceptors and the students in the same session will improve on the work that has already been conducted in this area, as the students and preceptors can further develop their relationships and coconstruct feedback conversations. We will use social learning theory to interpret the results of our study, which will help us explain the results and potentially make the work generalizable to other fields.

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KEYWORDS

feedback; professional development; undergraduate; medical education; intervention; preceptors; students; medical students; longitudinal integrated clerkship

Introduction

Background

Key components for the training of physicians are precepting and providing supervision within clinical settings. Clerkships are full learning immersion experiences wherein, under the supervision of a preceptor, students have an opportunity to learn by performing different tasks, ranging from taking patient histories to collaborating on diagnosis and treatment while assisting with the provision of patient care [1]. Clerkships are a highly impactful educational experience that can vary greatly among communities, hospitals, rotations, and preceptors. Research has suggested that the quality of a preceptor and their relationship with a student in a clerkship can significantly impact the overall placement and learning experience [2]. One critical component of the student-preceptor relationship is the quality of the feedback that a preceptor provides to a learner. In fact, it has been suggested that feedback is the foundation of effective clinical teaching, and providing feedback has been identified as a key physician competency (scholar role) within the CanMEDS framework [3,4].

Feedback occurs when a learner is offered insight into how they actually performed and the consequences of their actions [5]. Providing feedback can help learners maximize their performance at different stages of training, and it can assist learners in recognizing their strengths and areas for improvement and identifying actions that can be taken to improve performance. Since the early 1980s, feedback in medical education has been recognized as being important, and giving feedback is far from simple. Preceptors have concerns about giving negative feedback, and each student has their own comfort level and needs when receiving feedback [5]. An integrative review of the content of teacher-learner feedback found that preceptors were reluctant to give critical feedback, preceptors provided low-quality feedback, and feedback sessions were dominated by the preceptors [6]. These results indicate that providing feedback has remained a challenge over the last 3 decades.

One of the early approaches to giving feedback featured a unidirectional approach wherein a preceptor surrounds a piece of criticism with 2 pieces of praise—the so-called *feedback sandwich* [7]. In some instances, this approach resulted in dissatisfaction as the preceptor initiated the feedback process, leaving the receiver without enough quality feedback. Some workshops were created to alleviate this problem and help students elicit feedback from their preceptors. This approach had benefits but placed the onus of obtaining feedback on the receiver [8]. In response, an educational alliance framework for improving feedback effectiveness was proposed. An educational alliance framework posits that feedback needs to be changed from an "information download" to a bidirectional conversation in an authentic partnership that includes mutually agreed upon performances and standards, a coconstructed action plan, teamwork, and the purposeful use of a feedback discussion in practice [9]. Using an educational alliance framework has been suggested as an effective way to promote a feedback culture in *Medical Teacher's* popular *Twelve Tips* section [10].

Research that uses an educational alliance to frame an intervention has had moderate success but suggests that one major barrier is the lack of interest from clinical teachers [11]. Another barrier is the challenge with establishing relationships [12].

One method that has been used and can work with an educational alliance framework is a coaching approach. Coaching involves observing a task and then using different actions, questioning tactics, or encouragement to improve performance [13]. Using a coaching approach might help with establishing stronger relationships by building mutual trust, promoting engagement with educational content, increasing reflection among both preceptors and students, and using failure as a catalyst for learning [14]. However, little research has been able to use these previous findings and suggestions to create a deeply meaningful intervention.

To overcome the limitations described in the literature and build on an educational alliance and coaching framework, a relational feedback approach can be utilized. *Relational feedback* is a term rooted in relational pedagogy—a teaching philosophy that aims to create a trusting and caring relationship that supports students throughout their educational journey [15]. Using this bidirectional caring relationship as a basis to give and receive feedback may improve the feedback process and forms the basis for this intervention.

Research Purpose and Questions

To date, few studies have examined a relational feedback intervention for preceptors and students that focuses on their shared responsibilities and skills in the feedback process. This type of intervention brings medical students (feedback receivers) and preceptors (feedback givers) into the same room, with participants learning about feedback giving and receiving skills with and from each other through collaborative educational activities. They will be provided with educational tools for giving and receiving feedback within a coaching-like relationship wherein the feedback process is a 2-way conversation.

In this study, the following subquestions and objectives will be explored. First, what is the impact of a relational feedback intervention on the quality of feedback between preceptors and students during a longitudinal integrated clerkship (LIC)? We will explore up to 6 key elements of quality feedback conversations that were previously identified and validated by the Center for Medical Simulation [16]—(i) the establishment of an engaging learning environment, (ii) the maintenance of an engaging learning environment, (iii) feedback conversations organized in a structured way, (iv) the provocation of an engaging discussion, (v) the identification and exploration of

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performance gaps, and (vi) assistance in achieving or sustaining good future performance.

Second, what are the relational attributes that influence feedback incorporation and engagement with learning? We will investigate this from both learners' and preceptors' points of view. Through the presurveys, postsurveys, and follow-up surveys, we will examine the extent to which preceptors in LIC communities see positive attributes (eg, enthusiasm, openness, and collaboration) in their relationships with and supervision of their learners.

Third, in what ways does a relational feedback and professional development educational intervention influence the educational experiences of preceptors and students within the clinical settings of an LIC? As part of the intervention, we will explore this through facilitated discussion and developmental evaluation. We will also explore changes in both individual behaviors and community cultural patterns through presurveys, postsurveys, and follow-up surveys.

Fourth, what are the system-based factors that contribute to the impact of a relational feedback and professional development educational intervention? Again, we will explore this through both facilitated discussions during the relational feedback intervention and follow-ups with students and preceptors at the end of the LIC. This question and approach acknowledge that the wider context plays a crucial role in developing successful feedback relationships. They will allow us to understand the limits of a student-preceptor intervention and identify the enablers and barriers that intersect with knowledge and skills in the real-world context of clerkships in Northern Ontario.

We hypothesize that by creating awareness of the relationship context for both preceptors (feedback givers) and students (feedback receivers) and by providing tools for navigating that relationship, the intervention will be more successful. We also hypothesize that both student participants and preceptor participants will receive more effective feedback (quality) and additional feedback (quantity), thereby providing them with more opportunities to improve.

By answering these questions, we aim to improve medical students' educational and clinical experiences by further developing preceptors' and students' feedback skills and optimizing their relationships.

Methods

Context

The Northern Ontario School of Medicine (NOSM) was founded with a social accountability mandate to address physician shortages in Northern Ontario. The school aims to reach this goal by recruiting students who are interested in rural practice and giving these students positive rural educational experiences [17]. In its undergraduate curriculum, the NOSM uses a distributed model of learning, which is embedded with experiential learning experiences, wherein students undertake several placements in rural and remote communities [17]. In the third year, the core curriculum includes an 8-month LIC. During the clerkship, learners spend extended time in a community clinical setting where they have frequent and consistent interactions with their preceptors [18]. Within this educational context, it is of the utmost importance that students and preceptors develop relationships in which feedback can be given and received in a safe and effective manner.

Sample

The project was scheduled to last for 3 years (2019-2022) but has been extended to the end of 2023 due to the impact of COVID-19. Based on the geographic distribution of the clerkship communities, a regional approach will be utilized, and clerkship communities will be divided into 3 regions. Each year, 1 region, which includes 4 to 6 of the clerkship communities, will be visited until all 3 regions and 15 communities have participated. Communities range in size from 5000 to 76,000 people and include rural, semirural, and urban environments. There are between 2 and 9 medical students and between 5 and 70 preceptors in each clerkship community, as shown in Figure 1. JG will work with the site liaison clinician (academic lead) and site administrative coordinator to set up the educational intervention. The site administrative coordinator will send preceptors and students an invitation for participating in the research. Therefore, potential participants will be students and preceptors in each of the communities where the relational feedback intervention will be held. Since the study uses a pre- and posttest design, the participants who are interested in the study will form the intervention group. We will also invite other professionals who support teaching in the community, such as site educational administrators. Each research participant will be sent a letter of information and detailed consent forms before the project relational feedback intervention is performed. Participants will be notified about any potential risks and benefits and (for preceptors only) their responsibilities if they choose to participate by releasing their anonymized learner evaluations for analysis.

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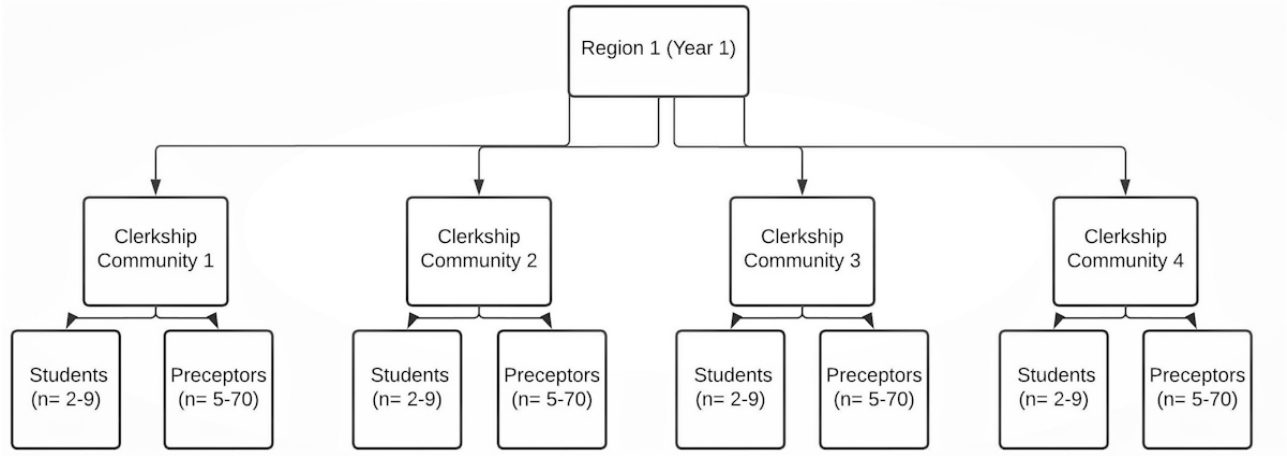
Figure 1. A visual representation of a sample year of interventions with clerkship communities and the range of the number of students and preceptors in each community.



Ethics Approval

This project has received approval from the Lakehead University Research Ethics Board (reference number: 8777) and Laurentian University Research Ethics Board (reference number: 6020466). To mitigate risk during COVID-19 outbreaks, sessions may be held over the internet via WebEx (Cisco Webex), depending on local risk and public health guidelines.

Intervention

The intervention was designed by a group of community physicians, medical educators, and researchers at the NOSM, and to date, we have not found any comparable feedback professional development initiatives. Throughout this paper, the phrase *relational feedback intervention* is used to refer to the student-only, 1-hour orientation session; the 2.5-hour combined preceptor and student professional development session; and the 1-hour, student-only debrief/focus group.

Before the combined professional development session, students will be asked to participate in a 1-hour session that will provide an orientation on their role in receiving feedback and their participation in the combined session; they will discuss what makes feedback effective or difficult and how preceptors can make giving and receiving feedback more effective and safer for students.

Students and their preceptors will then participate in a 2.5-hour combined professional development session with the following learning objectives: (i) implement strategies for building preceptor-learner trust and rapport during feedback conversations within a clinical setting, (ii) provide feedback through coaching conversations to support the improvement of learners' future performance, and (iii) use the Ask/Tell/Ask feedback framework to facilitate 2-way feedback conversations and assess the results. This will be accomplished through a 4-part outline.

For part 1, the concept of feedback and its impact on learners' performance within a clinical setting will be introduced. Participants will describe successful examples of when they gave or received feedback during a clinical placement and identified factors that contributed to the success of the feedback. Participants will also describe difficult interactions in which they gave or received feedback during a clinical placement and factors that contributed to the difficulty. A facilitated discussion will be conducted to explore the conditions that make it safe for participants to both give and receive critical feedback on their performance.

For part 2, the Ask/Tell/Ask framework will be introduced. The Ask/Tell/Ask framework is a collaborative communication approach that allows a learner to explain their perceptions of their performance, receive feedback on their performance, and create a plan for improvement [19]. This framework will be introduced by using a 3-minute video that describes the cons of the feedback sandwich ("good/bad/good"); presents the purpose of feedback; provides an explanation of the Ask/Tell/Ask framework, which includes specific questions that can be asked (ie, what went well and what could have gone better in that patient encounter); and shows an example of the framework. The facilitators will use a video from the Virginia Apgar Academy of Medical Educators to spark discussions between preceptors and students [20].

For part 3, coaching techniques for linking feedback conversations with the development of opportunities for improving future performance will be discussed. Large groups will be divided into groups of 3 to 5 participants, who will work through 3 simulated/practice feedback examples. Each group will typically have 1 student and 2 to 3 preceptors. Each preceptor participant will be the preceptor, or observer, for one of the examples, while students will be the learners. Practice examples will provide opportunities to apply the Ask/Tell/Ask framework.

For part 4, following a large group debrief of 3 simulated/practice feedback examples, a discussion of strategies or next steps for supporting the development of preceptor-learner trust and rapport for future feedback conversations in a clinical setting will conclude the session.

The relational feedback intervention will be delivered by 2 members of the research team. EC is a professionally trained teacher with years of experience in facilitating workshops, an educational scholar, and an associate professor at the NOSM. JG is a clinician-scientist and the associate dean of Continuing Education and Professional Development, and one of the

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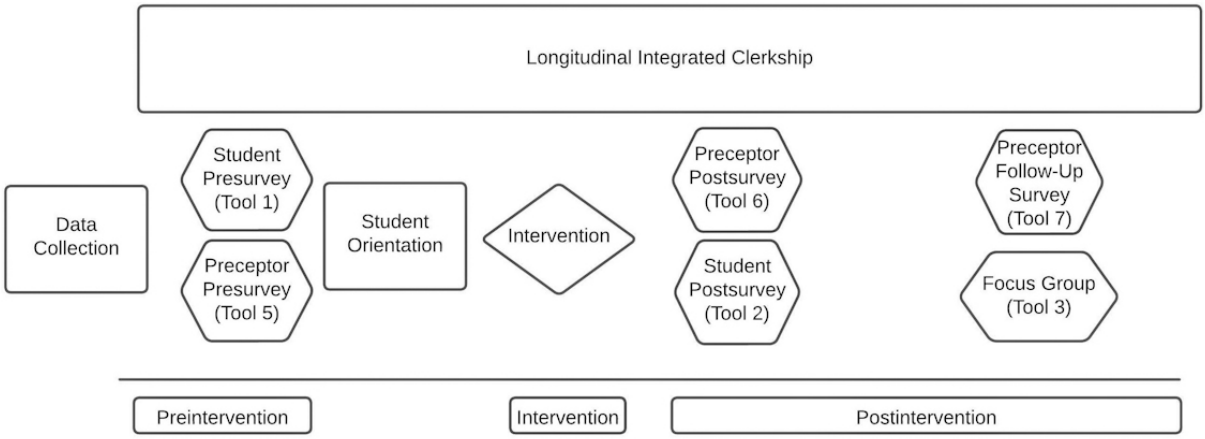
primary focuses of his research program is optimizing feedback conversations.

Data Collection

To evaluate the relational feedback intervention, multiple tools were developed by the research team based on current literature in the field of medical education to answer the specified research questions. Standardized NOSM evaluations will also be used in the study. These tools are based on face validity and a data collection policy whereby information about the exact tools cannot be made available. The general timing and use of the data collection tools are shown in Figure 2.

Figure 2. A visual representation of the data collection procedure.



Research Tools

Student Precombined Professional Development Session Survey (Tool 1)

The student precombined professional development session survey includes a series of 4 open-ended questions on what makes preceptor feedback effective for improving performance, what aspects of receiving feedback are the most difficult for students, how preceptors can make it safe for students to receive critical feedback, and how preceptors can make it safe for students to provide feedback on their teaching or supervision.

Student Postcombined Professional Development Session Survey (Tool 2)

The student postcombined professional development session survey is a series of 7 open-ended questions regarding students' perspectives on the combined professional development session and on attending it with preceptors, the strategies they learned to enhance both the giving and receiving of feedback, and how the NOSM can further assist with improving their skills for receiving and giving feedback.

Student Postcombined Professional Development Session Focus Group (Tool 3)

Students will participate in a debrief focus group wherein a semistructured guide will be used that asks questions on the lessons learned from the combined professional development session; how a relational approach supports teaching and learning, influences educational environments, and supports clinical practice; how the combined professional development session influenced competence and confidence in giving feedback; how the combined professional development session challenges previously held ideas; and whether students will be able to incorporate the material into their practice.

Student Program Evaluation Surveys (Tool 4)

During the 8-month LIC, students will complete an anonymous program evaluation survey 3 times. At the end of the clerkship, students will also be asked to complete an anonymous final program evaluation. These program surveys were not specifically designed for our study, but through a secondary analysis, useful information can be extracted to help us answer the project's research questions. Both the end-of-year survey and program evaluation survey comprise a combination of open- and close-ended questions. The close-ended questions are typically yes-no questions or 4-point or 5-point Likert scale questions. Project-relevant questions from the program surveys include questions on how the clerkship experience can be enhanced (open ended), questions that ask students to comment on the usefulness of the feedback they have received (open ended), and questions on the learning environment (4-point Likert scale).

Preceptor Precombined Professional Development Session Survey (Tool 5)

The preceptor precombined professional development session survey asks a total of 4 open-ended questions on the successful provision of feedback, a difficult interaction in which preceptors provided feedback, what preceptors would like to learn about preceptor-learner feedback interactions, and what skills related to giving or receiving feedback are important to develop.

Preceptor Postcombined Professional Development Session Survey (Tool 6)

Like the student survey, the preceptors will be asked a series of 7 open-ended questions on general feedback about the combined professional development session and their thoughts on attending it with students. The questions ask about the strategies they learned to enhance both the giving and receiving of feedback and how the NOSM can further assist them in improving their skills for receiving and giving feedback.

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Preceptor Follow-up Survey (Tool 7)

Approximately 6 to 8 weeks after the combined professional development session, preceptors will be sent a survey with 4 open-ended questions. The questions utilize previously gathered information and ask about the steps that were taken to make changes in giving feedback and whether these changes have led to any results. A series of probative questions about the last time preceptors gave feedback and further program development questions are also included in the survey.

Student Evaluations of Preceptors (Tool 8)

The research will also use secondary data from clinical faculty evaluations, which will be completed by NOSM learners. Preceptors will be asked to consent to the release of their completed evaluations, and only evaluations from consenting preceptors will be used. All NOSM undergraduate and postgraduate learners will be asked to complete clinical faculty evaluations on preceptors. Faculty evaluations include a combination of open- and close-ended Likert scale questions. The open-ended questions ask about areas of strengths and weaknesses, while close-ended questions ask about supervision, feedback, teamwork, and learning supportiveness. Information on students who complete the evaluations will not be recorded when the evaluations are submitted (ie, the evaluations will be anonymized at the time of submission).

Analysis

The qualitative data from the surveys, interviews, focus groups, and preceptor evaluation forms will be transcribed verbatim, anonymized, and uploaded into ATLAS.ti (Scientific Software Development GmbH). To help protect anonymity and aid the analysis, each of the 4 to 6 communities will be treated as 1 cohort. Data will be coded by using grounded theory approaches and thematic coding. The grounded theory approaches will include open, axial, and selective coding, which will involve breaking data up into smaller sections, deeply analyzing these sections, developing codes, and drawing connections between codes [21]. The thematic coding process will follow the 6-step process described by Braun and Clark [22] (data familiarization, the generation of initial codes, the search for themes, the review of themes, the defining of themes, and the write-up). Depending on the specifics of the research questions, appropriate steps for ensuring quality will be included. These may include triangulation, the involvement of multiple researchers, audit trails, reflexivity, and accurate transcriptions [23]. Most analyses will focus on the qualitative data, but quantitative data will be analyzed by using descriptive statistics. Since the study involves more than 1 cohort, as well as data from preceptors and students, analyses will be performed within and across groups.

Results

Participant recruitment began in January 2019. As of April 2021, a total of 29 students and 66 preceptors have completed the premeasures, postmeasures, and follow-up measures in 7 sites. We aim to finish the study in December 2023 and make the results available in 2024.

Discussion

The relational feedback intervention will provide further knowledge on and promote growth in the conceptualization of feedback dialogues wherein learners and preceptors develop conversations and are equal participants in the feedback process. As both the students and the preceptors will be included in a combined professional development session where they learn with and from each other, there is the potential to amplify learning, enhance professional relationships, create a safer educational space for both students and preceptors, and improve feedback dialogues.

On the basis of the use of data from the pre– and post–professional development session surveys for both preceptors and students, we hypothesize that within the community clinical site, preceptors and students will learn new skills for giving and receiving feedback in a coaching relationship. Previous literature has noted problems with a lack of engagement from preceptors and difficulties with establishing relationships [11,12]. Having both the students and preceptors, along with other preceptors in the clerkship community, attend the combined session will increase its potential impact, as it will demonstrate the commitment to the feedback process in the clerkship community, help with creating coconstructed feedback guidelines, and build relationships through the educational activities.

On the basis of the postsession follow-up surveys, we hypothesize that in the medium term, preceptors will be able to incorporate feedback strategies within their clinical educational contexts, resulting in feedback that students are able to recognize, identify as useful, and effectively process. This finding will be interpreted by using social learning theory. Social learning looks at learning that takes place in a social context and how people learn from each other, and it has been used in medical education [24-26]. Preceptors in each clinical site function as a community of practice. As all preceptors will be invited to and given study credits for their attendance in the combined 2.5-hour professional development session, the lessons learned from the innovative intervention will diffuse throughout each community of practice, in part due to the participants learning from one another.

In the long term, there will be increased competence in relational feedback skills that students will apply in future clinical placements and preceptors will incorporate into their supervision of future learners. At the institutional level, the design of the study (ie, the inclusion of all community clinical sites) will help with creating a safer place for giving and receiving feedback. The results of the study will be of interest to the medical education community and other health care professionals, as feedback is an integral part of career training. Implementing the relational feedback intervention will allow for improvements in learners' and preceptors' relationships, which will enhance their learning environments.

Our study will have some potential limitations. First, the study will use secondary data from student evaluations of preceptors. As interventions will occur at different times in the year, there is potential for recency bias in the student evaluations. Students

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that have the intervention closer to a teaching evaluation might report more favorable outcomes related to feedback. Another limitation of the study and other educational studies is the system's noted complexities. There is a chance that we may miss some of the system-level variables that influence the feedback relationship.

At the conclusion of the project, the research team will be uniquely positioned to disseminate the results of the project within the institution and beyond. The team includes practicing health professionals who can disseminate the findings to other health professionals, individuals who work in continuing professional development and can share the results with their administrations, and academics who can help with presenting the results at academic conferences and publishing the results in peer-reviewed journals. The findings will also be presented in 1-page infographics that will be distributed over social media.

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Conflicts of Interest

This scholarly project is receiving special funding from the Northern Ontario School of Medicine. We are all employees of the Northern Ontario School of Medicine.

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Abbreviations

LIC: longitudinal integrated clerkship
NOSM: Northern Ontario School of Medicine

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Protocol

Evaluation of a Collaborative Care Program for Patients With Treatment-Resistant Schizophrenia: Protocol for a Multiple Case Study

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Abstract

Background: Approximately one-third of all patients with schizophrenia are treatment resistant. Worldwide, undertreatment with clozapine and other effective treatment options exist for people with treatment-resistant schizophrenia (TRS). In this respect, it appears that regular health care models do not optimally fit this patient group. The Collaborative Care (CC) model has proven to be effective for patients with severe mental illness, both in primary care and in specialized mental health care facilities. The key principles of the CC model are that both patients and informal caregivers are part of the treatment team, that a structured treatment plan is put in place with planned evaluations by the team, and that the treatment approach is multidisciplinary in nature and uses evidence-based interventions. We developed a tailored CC program for patients with TRS.

Objective: In this paper, we provide an overview of the research design for a potential study that seeks to gain insight into both the process of implementation and the preliminary effects of the CC program for patients with TRS. Moreover, we aim to gain insight into the experiences of professionals, patients, and informal caregivers with the program.

Methods: This study will be underpinned by a multiple case study design (N=20) that uses a mixed methods approach. These case studies will focus on an Early Psychosis Intervention Team and 2 Flexible Assertive Community treatment teams in the Netherlands. Data will be collected from patient records as well as through questionnaires, individual interviews, and focus groups. Patient recruitment commenced from October 2020.

Results: Recruitment of participants commenced from October 2020, with the aim of enrolling 20 patients over 2 years. Data collection will be completed by the end of 2023, and the results will be published once all data are available for reporting.

Conclusions: The research design, framed within the process of developing and testing innovative interventions, is discussed in line with the aims of the study. The limitations in clinical practice and specific consequences of this study are explained.

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KEYWORDS

treatment-resistant schizophrenia; collaborative care; recovery; personalized care; clozapine; lifestyle; peer support; shared decision-making; motivational interviewing; nurse-led intervention

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Introduction

Background

Approximately 20% to 30% of patients with schizophrenia appear to be resistant to treatment. This means that current antipsychotics insufficiently affect this patient group, despite adequate dosage and duration of treatment with antipsychotics [1]. Compared with patients with schizophrenia who are not treatment resistant, those with treatment-resistant schizophrenia (TRS) display more social, functional, and economic problems [2] and poorer cognitive functioning, in addition to being at a higher risk of metabolic syndrome and other health-related problems due to their unhealthy lifestyle [3]. For example, these patients consume more drugs, nicotine, and alcohol [2]. Suicidal behavior is more prevalent [2], and it also causes a higher burden of disease [4] than patients who are not treatment resistant. Finally, studies have also shown that treatment adherence often proves challenging owing to cognitive problems, low motivation, side effects of sedative use, and psychiatric symptoms such as hallucinations and delusions [5].

Despite the denotation *treatment resistant*, there is still an evidence-based treatment option available for this patient group, namely clozapine treatment or optimizing treatment with clozapine if patients are already using it. Several treatment options are available for clozapine resistance, such as pharmacological additions to clozapine, physical exercise, cognitive behavioral therapy, music therapy, and electroconvulsive therapy [1,6,7].

Resistance can be considered as incomplete recovery [8]. Within clinical practice, the mentioned treatment options are often not optimally offered [1]. For example, the suboptimal prescription of clozapine constitutes a serious problem in the treatment of patients with TRS, because both prior use of clozapine and fewer pre–clozapine antipsychotic trials have been associated with better treatment outcomes for people with TRS [9]. The effectiveness of clozapine is superior and unique to TRS [10]. Clinical practice guidelines are typically not followed by prescribers, and, as such, clozapine remains underused in patients [11]. More than half of all individuals with schizophrenia receive either no treatment or suboptimal treatment [11], whereas approximately 95% of people with schizophrenia do not receive an appropriate combination of evidence-based services [12].

Evidently, there is a notable gap between the available treatment options and their uptake in daily practice. In some cases, care professionals simply feel that patients should not be burdened by further treatment after having previously undergone unsuccessful treatment. Demoralization among both patients and professionals can occur, thus leading to both sides having little hope for improvement [13]. Psychiatrists are often reluctant to prescribe clozapine, in part, owing to problems in regulating its side effects, which often leads patients to discontinue clozapine. Other reasons for underprescribing clozapine include the inconvenience of therapeutic blood monitoring [6], lack of knowledge and training regarding clozapine among care professionals [14], lack of clarity over diagnosis, difficulty in correctly identifying patients for this treatment, service fragmentation, and lack of adequate training of health care professionals in clozapine use [15]. Another reason for non–guideline-compliant treatment is that patients with TRS either refuse treatment or display poor adherence [16].

This paper introduces the Collaborative Care (CC) model as a means to improve the quality of care among patients with TRS. CC has proven to be effective for other serious mental illnesses, such as depressive, bipolar, and personality disorders [17-20]. The CC model is predicated on the principles that both patients and their informal caregivers should form part of the treatment team, that a structured personalized treatment plan should be put in place with planned evaluations by the team, and that the approach should be multidisciplinary in nature and make use of evidence-based interventions. In CC, the patient is in a position to manage their own treatment. Within the team, a personalized treatment plan is set up along with clear recovery goals that will be evaluated every 3 months. Important treatment decisions are jointly made within the team based on shared decision-making (SDM) principles. In CC, medical, psychological, and social interventions are integrated, which means that it is a holistic approach that incorporates treatments that have been shown to be effective on their own, within a coherent longitudinal treatment framework.

Given that a CC program for patients with TRS (CC-TRS) was not yet available, we developed such a program ourselves. Previous research provides evidence of the value of treatment programs that combine medications with a range of psychosocial services in the treatment of people with schizophrenia [21]. The evidence-based interventions provided in the CC-TRS comprise optimal medical treatment (including the use of clozapine), lifestyle interventions, peer support, SDM, and motivational interviewing for informal caregivers. CC-TRS is consistent with the idea that a combination of psychological and psychosocial care with medication treatment is the key factor in maximizing the effectiveness of the treatment of patients with TRS [8,22] and is not only about treating positive psychotic symptoms and responses to antipsychotic medications. We expect that this program will improve quality of care and promote patients' symptomatic recovery, psychosocial functioning, and quality of life.

However, the implementation of scientific knowledge in daily practice is problematic worldwide. Indeed, there remains a gap in how implementation strategies might improve patient outcomes and health services [23]. Moreover, clozapine use varies widely across settings and countries, whereas patient factors remain relatively consistent. Therefore, not to mention the fact that patients who use clozapine report that its advantages outweigh its disadvantages, it appears that the impact of patient factors is smaller compared with both organizational and clinician-related factors [24].

In this paper, we delineate the research design of a study that aims to gain insight into both the implementation process and preliminary effects of CC-TRS as well as professionals, patients, and informal caregivers' experiences with the program.

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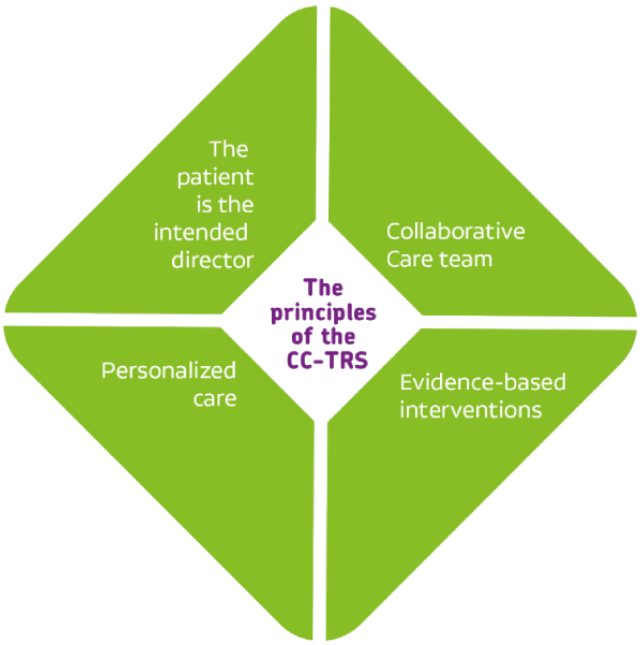
Intervention: Principles of the CC-TRS

There are four key principles that guide the CC-TRS intervention program (Figure 1):

Figure 1. Key principles of the Collaborative Care program for patients with treatment-resistant schizophrenia (CC-TRS).



1. To optimize both the continuity and coordination of care, intensive collaboration will be established in a CC team. The CC team will comprise the patient, informal caregiver or caregivers, a care manager, a mental health nurse who will administer the CC-TRS interventions (CC nurse), and a clinical nurse specialist (CNS) who will be responsible for the overall treatment. At all times, the CNS will consult a psychiatrist. There will also be an option to expand the CC team to include other health care professionals to effectively execute the treatment plan.
2. The patient is the intended manager of their own treatment. Other members of the CC team (including informal caregivers) will assist the patient in strengthening their self-management skills and empowerment. Considerations and decisions regarding treatment will be made in collaboration with the CC team according to the principles of SDM [25]. If the patients are not able to manage their own treatment, then other members of the CC team will (temporarily) take over.
3. A personalized treatment plan with clear recovery goals will be developed within the CC team and will be evaluated by the CC team every 3 months. To encourage patient engagement, we have created practical documents for patients, which include a format for a treatment plan and a format for preparing the evaluations of the treatment.
4. Evidence-based interventions are integrated into the treatment plan (see the following sections and Figure 2). These interventions have been proven to be effective in reducing psychotic symptoms and improving social functioning and self-management among patients with persistent psychosis. The caregiver will inform both the patient and informal caregivers about effective treatment options for TRS, such as those included in the CC-TRS. Given the principles of personalized care, the precise trajectory that treatment can take varies among patients, which is why no specific intervention is included as a default in the treatment plan. Moreover, the order and pace at which interventions are delivered can vary. In CC-TRS, the caregiver will continue to both hold out hope for recovery and search for possibilities to improve symptoms and functioning.

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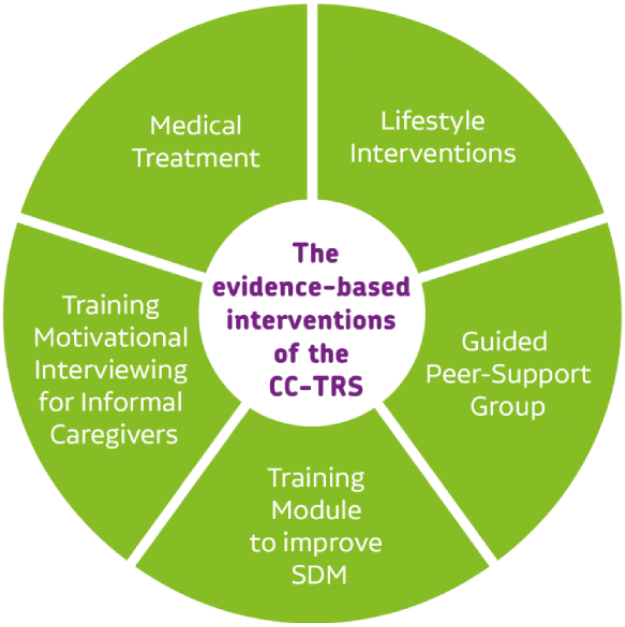
Figure 2. Evidence-based interventions for the Collaborative Care program for patients with treatment-resistant schizophrenia (CC-TRS). SDM: shared decision-making.



Evidence-Based Interventions Within the CC-TRS

Medical Treatment

Given that clozapine is the only effective drug for treating psychotic symptoms in patients with TRS [1,9,26-28], patients in the CC-TRS will be comprehensively informed about the added value of clozapine as part of their recovery. Once patients decide to start clozapine, every effort will be made to ensure that the clozapine treatment is successful. For instance, the psychiatrist will assess both the indications and contraindications for clozapine. If the psychiatrist indicates clozapine and the patient is willing to start, the CNS will prescribe and carry out further treatment with clozapine. The CNS is trained to provide protocol-based clozapine treatment and is legally authorized to carry it out. Clozapine treatment under the care of the CNS is as safe as that under the care of a psychiatrist. Previous research has shown that patients who are monitored by a CNS tend to use clozapine for longer than those monitored by a psychiatrist [29]. Treatment by nurses as opposed to physicians also generally leads to longer consultation times, either more or the same amount of information being provided to patients, and higher patient satisfaction with care [30]. This is because the CNS generally has more available time than the psychiatrist to provide psychoeducation, support the use of eHealth, and carry out motivational interventions [31,32]. The assumption here is that this will encourage adherence to medical treatment, while simultaneously preventing or reducing the common side effects of clozapine (eg, excessive weight gain).

The CNS will prepare for treatment with clozapine by performing the necessary pretreatment checks, as delineated in the guidelines of the Dutch Clozapine Collaboration Group [1]. These checks will also be systematically recorded once again through recourse to the checklist from the Dutch Clozapine Collaboration Group.

We developed an eHealth module for clozapine treatment for patients. This eHealth module provides information about the effects and side effects of clozapine, the course of treatment, and information on the safe use of clozapine. It also provides a diary for patients to monitor their own side effects and a form to evaluate the effects of clozapine.

Lifestyle Interventions

The program *Traffic Light Method for Somatic Screening and Lifestyle* [33] will be delivered by a CC nurse who will adopt the role of a lifestyle coach. Weight gain is a common side effect of clozapine [34-36], which is perceived very negatively by patients and, indeed, is commonly cited as a reason to either not start using clozapine in the first place or to discontinue its use [37]. Exercise improves positive and negative symptoms in patients with schizophrenia [38,39]. Hence, with the support of the CC nurse, the patient will develop a lifestyle plan consisting of individual lifestyle goals, with particular attention being paid to exercise and nutrition. By applying the principles of motivational interviewing and SDM, the CC nurse will encourage the patient to adopt a healthy lifestyle. Adoption of a healthy lifestyle will also be encouraged by organizing pleasant lifestyle activities for a group of patients, which can help patients live healthier and produce positive effects on social interaction, mood, and stress [40].

Guided Peer-Support Group

A guided peer-support group will be delivered to groups of approximately 8 patients and will involve 90-minute biweekly sessions. We will use a peer-support intervention that was investigated in a randomized clinical trial and found to induce positive effects on social support, self-efficacy, quality of life, negative symptoms, and reduction of distress from symptoms [41]. The patient has the option of joining the group for as long as they want. Each session will follow the same structure, namely, discussing daily experiences in pairs and within the group as a whole. The patients themselves will decide what topics they want to discuss in each session. The CC nurses will

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guide the groups with minimal professional involvement to stimulate peer-to-peer interaction.

Training Module to Improve SDM

A special training was developed by the first author (AJ) in collaboration with care professionals and (former) patients to improve patients' skills in SDM. Although SDM is mainly advocated to preserve patients' autonomy, it has also been found to lead to better affective-cognitive outcomes, increased satisfaction, less decisional conflict, and, as such, appears expedient for self-reported health-related patient outcomes [42]. The principles of SDM between patients and professionals are central to this training and should enable patients to be more actively involved in their treatment [25]. A group interview was held with (former) patients about their experiences with SDM during treatment and the specific needs that they felt the training should address. A preliminary version of the training was evaluated by (former) patients and trainers. On the basis of their suggestions for improvement, adjustments were made to the training program. The modified version of the training was again provided to (former) patients by the trainers, after which the final version of the training was formalized. The training consists of psychoeducation and various exercises that seek to build patients' assertiveness skills, such as asking questions, speaking up, and asking for a second opinion. The training will consist of 4 sessions lasting 2 hours each and will be provided by the CC nurse and a peer-support worker.

Training Motivational Interviewing for Informal Caregivers

This training is based on *Family Motivational Intervention* (FMI), which is a form of motivational interviewing training for parents of patients with psychotic vulnerabilities and who engage in cannabis use. This training aims to reduce or stop cannabis use among patients by training parents using motivational interviewing techniques. In our version of the training, informal caregivers will learn communication skills to reduce stress and conflicts and motivate patients to engage in behavior change. FMI training leads to behavioral change in patients, an improvement in patients' quality of life, and a reduction in both the stress and burden placed on informal caregivers [43]. We modified the original version of the FMI to make it applicable to all informal caregivers of patients with psychosis. Most importantly, the modified FMI does not focus on a predetermined behavioral component such as cannabis use but encompasses all health-promoting behaviors. Our modified FMI training will consist of 7 weekly meetings of 3 hours each, which will be provided by 2 CC nurses.

Implementation Plan and Training

Overview

To implement CC-TRS, an implementation plan will be developed for each participating team [44]. This implementation plan will describe the strategies and responsibilities of each team member during the implementation of CC-TRS. This implementation plan will be developed in collaboration with all team members. Quality consultants will then assist the teams in implementing the CC-TRS.

All team members will have to attend a 60-minute meeting in which the principal investigator will inform them about the study, CC-TRS intervention, and implementation plan. The CNS and CC nurse who will deliver evidence-based CC-TRS interventions will take part in a comprehensive 4-day training course. The CNS and CC nurses will also be supervised and supported by the principal investigator during the implementation of the intervention through at least monthly (telephone) meetings.

Research Questions

The study will be underpinned by the following research questions:

1. What course did the implementation process of CC-TRS take, and to what extent was the intervention implemented as originally planned?
2. What barriers and facilitators (ie, factors at the patient, caregiver, and organization levels) influenced its implementation?
3. What treatment options did patients receive during the intervention period?
4. What are the experiences of patients, informal caregivers, and care professionals with the CC-TRS?
5. What are the preliminary effects of CC-TRS on psychosocial functioning, symptoms, quality of life, empowerment, recovery, SDM, self-management, and somatic comorbidities? How can these effects be explained by both the implementation process and the experiences of patients, caregivers, and professionals?

Objectives

The purpose of our study is to describe the implementation process of the CC-TRS program in clinical practice and to gain insight into the factors that influence the success of the implementation. We also aim to explicate the relationship between the implementation process (also considering the experiences of participants) and the realized effects at the patient level. This will provide preliminary insights into the effects of such an intervention, both in a variety of circumstances and with respect to different patient variables. The aim of this study is not to quantitatively generalize the results of the sample to the general population but rather to conduct an in-depth analysis of the process of implementation and its attendant outcomes. On the basis of the results of this study, we will subsequently seek to further optimize the CC-TRS intervention.

Methods

Design

Overview

We will use a multiple case study design that uses a mixed methods approach [45]. The multiple case study design is suitable for research that seeks to gain detailed insight into both the implementation process and preliminary effects of an intervention, as well as the relationship between the implementation process and outcomes. Different perspectives are integrated into the study: the perspective of patients, their informal caregivers, and care professionals. Implementation of

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the intervention in relation to the outcomes will initially be studied at the individual case level (a single-case analysis). Subsequently, the findings of all cases will be aggregated via a cross-case analysis [45]. Participating patients will be followed up for 1 year during the course of their treatment. The inclusion process was initiated in October 2020.

Setting

The study will be carried out in a specialized mental health organization in the Netherlands, with the inclusion of 2 Flexible Assertive Community treatment (FACT) teams and an Early Psychosis Intervention Team (EIT). FACT teams are based on the Assertive Community Treatment model that specifically focuses on patients with serious mental illness who are reluctant to keep appointments at a clinic where outreach care is recommended [46]. Alongside these difficult-to-reach patients, FACT teams are also responsible for the treatment of all patients with severe mental illness in a specific region, with the possibility of intensifying treatment if and when patients experience a crisis. A FACT team treats approximately 200 to 250 outpatients. EITs specialize in the treatment of outpatients in the initial years after the onset of psychosis. Although EITs work in the same way as FACT teams, they spend more time on diagnostics and psychoeducation. Their caseloads are generally smaller and their patients are younger. The EIT, which is part of this study, offers treatment to patients who have presented with a first episode of psychosis and are sometimes treated in this team for several years. The patients included in our study from this EIT met the criteria for TRS.

Inclusion Criteria

Patients will be included in the study if they meet the inclusion criteria presented in Textbox 1.

To assess patients' decisional capacity to consent while taking part in our study, the principal investigator will use the *Brief Assessment of Capacity to Consent* [47]. Patients with impaired capacity will be excluded from this study.

If patients consent to participate, an informal caregiver will also be asked to participate in the study, based on the inclusion criteria presented in Textbox 2.

Textbox 1. Inclusion criteria for patients.

Inclusion criteria

- Aged ≥18 years.
- Have a sufficient command of the Dutch language.
- Diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, as having schizophrenia, schizophreniform disorder, schizoaffective disorder, another specified schizophrenia spectrum disorder, other psychotic disorder, unspecified schizophrenia spectrum disorder, or other psychotic disorder.
- Was defined as treatment resistant. In our study, we will determine treatment resistance for each symptom domain (positive and negative domains) using scores on the Positive and Negative Syndrome Scale (PANSS) [48]. Following the remission criteria proposed by Andreasen et al [49], symptoms must be (1) at least moderately severe, that is, a PANSS score of 5 on at least two items or a PANSS score of 6 on 1 item or (2) mildly severe, that is, a PANSS score of at least 4 on one of the items P1, P2, P3, N1, N4, N6, G5, and G9. Moreover, the patient must show impaired psychosocial functioning, with a score of <60 on the Social and Occupational Functioning Assessment Scale [50]. Concerning medical treatment, there must have been 2 adequate treatment episodes in the past with different antipsychotic drugs. The duration of this antipsychotic treatment needs to have been for at least six weeks at the therapeutic dosage. We will use the minimum maintenance dose from the Dutch Summary of Product Characteristics from the Rules Governing Medicinal Products in the European Union to determine the therapeutic dosage criterion. We will also determine medication adherence using data from the electronic prescription system in patients' files and reports. This will enable us to see whether medication is still being held for patients at a pharmacy that they have not yet picked up.

Textbox 2. Inclusion criteria for informal caregivers.

Inclusion criteria

- The informal caregiver is assigned by the patient.
- The informal caregiver is aged ≥18 years.
- The informal caregiver has a sufficient command of the Dutch language.
- The informal caregiver is able and willing to give informed consent.

Sample Size

To gain insight into the implementation process of the CC-TRS, the factors influencing this implementation and preliminary effects at the patient level, sufficient variation in patient characteristics, caregiver characteristics, and the context of implementation are needed. Within the context of the 2 FACT teams and an EIT, we believe that it will be sufficient to include 20 patients in our study to achieve the desired variation. If patients decide to stop the CC-TRS interventions, they will be asked to remain in the study purely for the purpose of carrying out a follow-up analysis.

Modifications Due to the COVID-19 Pandemic

Owing to the COVID-19 pandemic, face-to-face contact with participants is no longer self-evident. Therefore, we will have to make modifications to the treatment and measurements of the study depending on the applicable COVID-19 guidelines at

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that juncture. All modifications will, of course, be in accordance with the advice and guidelines of the mental health organization where the study will be conducted as well as the National Institute for Public Health and the Environment in the Netherlands.

Treatment-based contact will be face-to-face as much as possible. When face-to-face contact is not possible or the patient feels uncomfortable with face-to-face contact and refuses to do so, video calling will be the preferred form of contact, followed by telephone calling.

Team members will preferably engage in contact through video calling. This also applies to feedback meetings with all team members. Measurements with patients will preferably take place face-to-face. Interviews will be conducted via video calling when face-to-face contact is not possible. We will adhere to the recommendations of Opler [51] for conducting Positive and Negative Syndrome Scale interviews via video calling. These recommendations relate to—among other things—video connectivity, high-bandwidth connections, and the webcam's field of view. Research assistants will also receive additional training on how to conduct interviews via video calling.

Group interviews with caregivers and care professionals will take place 1 year after the start of the first inclusion, which means that it will be conducted in October 2022. If there are still restrictions on face-to-face contact at that juncture, group interviews will be conducted by video calling.

Recruitment of Patients

Patients who receive treatment in the participating teams will be screened for eligibility for the study. This screening process will divide participants into 3 categories. First, patients who met the inclusion criteria will be invited to participate in the study. Second, patients who do not meet all the inclusion criteria at the time of screening might be potential participants in the future. Third, patients who meet exclusion criteria are excluded. Every 3 months, we will reassess both the patients within the second group and those who are new to the team.

The care manager will screen selected patients supervised by the quality consultants. Patients who meet the inclusion criteria and agree to contact the principal investigator will receive verbal and written information about the study and CC-TRS intervention. The patient will have at least 7 days to consider participation. In the case of consent to participate, the principal investigator will determine the patient's decisional capacity using the Brief Assessment of Capacity to Consent, over telephone. The patients will be then asked to sign an informed consent form. The reasons for refusal to participate will be registered. The patients will sign an informed consent form before they are included in the study. At T0, we will determine whether a patient is eligible for inclusion in the study.

In the informed consent procedure, patients will be asked to point out an informal caregiver. The informal caregivers will also receive verbal and written information about the study and CC-TRS from the principal investigator. After at least 7 days to consider participation, informal caregivers will be asked for consent for participation in the study. In the case of a positive response, the informal caregiver will sign an informed consent form.

As part of the informed consent procedure, patients will be asked to name an informal caregiver, who will subsequently be asked to give their consent to participate in the study.

Research Assistants

Trained research assistants will perform the measurements required for this study. These assistants will not be involved in either the implementation or execution of the CC-TRS. Interrater reliability will be assessed using a simulated interview.

Data Collection

Patients

We will perform document analysis 3 (T3), 6 (T6), 9 (T9), and 12 (T12) months after a patient is included in the study. As part of these document analyses, we will conduct an intervention check to ascertain whether the CC-TRS is being carried out in adherence to the intervention protocol. Therefore, it will be possible to quantify the care received by patients. As part of the intervention, both patients and informal caregivers will discuss their experiences with the CC-TRS as part of their treatment plan evaluations with the CC team. This will be reported in patient files, thus offering the opportunity to gain insight into their experiences with the CC-TRS by conducting document analysis. We expect the CC-TRS to produce positive effects on somatic outcomes such as metabolic syndrome, cardiovascular risks, and (risk of) diabetes mellitus. Therefore, the following somatic outcomes of patients will be extracted from their medical files at baseline (T0) and after 12 months (T12): height, weight, BMI, waist circumference, systolic and diastolic blood pressure, lipid profile, and fasting blood glucose levels. Moreover, the presence of cardiovascular disease, diabetes mellitus, or hypertension will be registered, including the use of medications for these disorders.

There will be 3 face-to-face measurements: when patients are included in the study (T0), after 6 months (T6), and after 12 months (T12). The questionnaires used for quantitative data collection at T0, T6, and T12 are summarized in Table 1. The questionnaires *Consumer Quality Index* and *Experiences with CC-TRS* will only be administered at T12. At T12, after completion of all quantitative measurements, a 60-minute interview will be conducted with the patients. In this interview, a topic list will be used to discuss the results of the quantitative data, the course of the treatment, the implementation of the various treatment components, and the experiences of patients with the CC-TRS. Furthermore, patients will be asked which factors and specific aspects of the CC-TRS influenced the outcomes and whether the desired effects were achieved. All the interviews will be audiotaped and transcribed verbatim.

Patients will receive €7.50 (US $8.02) for each of the first 3 face-to-face measurements and €15 (US $16.04) for the fourth face-to-face measurement in the form of gift vouchers. In addition, their travel expenses will be reimbursed.

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Table 1. Quantitative measurements of patients at T0, T6, and T12.

Instrument	Description	Validity and reliability
CGI[a]	This is a 3-item scale and the most widely used brief assessment tool in psychiatry for measuring illness severity, global improvement or change, and therapeutic response [52,53].	The psychometric properties of CGI have not yet been established, but clinicians' ratings of psychiatric symptoms correlate significantly with self-rated and other valid scales of symptom severity [54]. Rating scales are an appropriate clinical technique for the measurement of change in antidepressant trials. Global improvement scales would be sufficiently sensitive toto distinguish between responders and nonresponders in clinical [55].
CQi[b]	This is a 15-item questionnaire that allows for the evaluation of outpatient treatment from patients' perspectives [56].	Research has shown sufficient reliability (Cronbach α between .69 and .95) [57]. The CQi provides valid and reliable results in short-term care for patients in mental health care [58].
DES[c]	This is the Dutch version of the MHRM[d], a 26-item questionnaire that measures recovery [59].	The Dutch version of the MHRM is a reliable measure (in terms of internal consistency) with a generally acceptable convergent and divergent validity. Cronbach α ranged from .86 to .94 [59].
Dutch PIH[e]	This is a Dutch translation 12-item questionnaire developed in Australia to measure self-management behavior and knowledge among patients with chronic diseases [60].	The PIH exhibits construct validity and internal consistency. Cronbach α is .82 [61]. The PIH has been translated and validated for use among Dutch patients with chronic obstructive pulmonary disease [60].
HoNOS[f]	The HoNOS is a structured interview measuring behavior, impairments, symptoms, and social functioning via the use of 12 items. The instrument has 3 addendums that measure manic symptoms, treatment motivation, and compliance with medication [62].	The Dutch version of the HoNOS has reasonably good psychometric qualities (intraclass correlation coefficient=0.92), can be administrated in a short period, is neither dependent on psychiatric diagnosis nor language, and is regarded as useful by both clinicians and patients [62].
MANSA[g]	This is a 16-item questionnaire that measures the quality of life, with a particular focus on satisfaction with life as a whole and with different life domains [63]. In addition to the MANSA, we will also ask patients to give a score between 0 and 10 to describe their quality of life in general.	The MANSA is a brief instrument for assessing quality of life focusing on satisfaction with life as a whole and with life domains. Its psychometric properties appear satisfactory (Cronbach α=.74 for the satisfaction rating) [63].
PANSS[h]	This is one of the most widely used instruments for measuring the presence and severity of positive, negative, and general psychopathological symptoms of schizophrenia. The PANSS is a 30-item structured interview [48].	The PANSS has good interrater reliability, adequate construct validity, high internal reliability, appropriate test-retest reliability, and external validity [48,64-66].
SDM-Q-9[i]	This is a self-report instrument comprising 9 items that was developed to measure patients' perceptions of the shared decision-making process (SDM-Q-9) [67].	The SDM-Q-9 has a good acceptance, internal consistency, and acceptable to good convergent validity (Cronbach α=.88) [67].
SOFAS[j]	This is a 1-item rating (0-100) that assesses social and occupational functioning (independently of the severity of psychological symptoms) [50].	To our knowledge, the SOFAS has not yet been tested for psychometric quality. We will use this questionnaire to assess the criteria for treatment-resistant schizophrenia as established by the Working Group of the Treatment Response and Resistance in Psychosis. They use SOFAS to operationalize functional limitations [68].
Questionnaire experiences with treatment	This is a self-developed questionnaire containing 11 items about satisfaction with treatment in general and 4 items about satisfaction with treatment via the Collaborative Care program for patients with treatment-resistant schizophrenia.	The questionnaire has not been examined for psychometric quality.

[a]CGI: Clinical Global Impression.

[b]CQi: Consumer Quality Index (Geestelijke Gezondheidszorg en Verslavingszorg Ambulant).

[c]DES: Dutch Empowerment Scale.

[d]MHRM: Mental Health Recovery Measure.

[e]PIH: Partners in Health scale.

[f]HoNOS: Health of the Nation Outcome Scale.

[g]MANSA: Manchester Short Assessment of Quality of Life.

[h]PANSS: Positive and Negative Syndrome Scale.

[i]SDM-Q-9: Shared Decision-Making Questionnaire 9-item.

[j]SOFAS: Social and Occupational Functioning Assessment Scale.

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Informal Caregivers

After 12 months (T12), informal caregivers' experiences regarding both their role in the treatment and the degree of cooperation with the CC team will be measured via a Dutch translation of the *Family Perceptions of Caregiving Role* (FPCR) [69]. The FPCR is a 15-item questionnaire that measures collaboration between informal caregivers and care professionals. To the best of our knowledge, FPCR has not yet been examined for its psychometric quality. However, we consider this questionnaire to be suitable for measuring both the perceived collaboration between informal caregivers and the CC team and the former's involvement in care. To measure the experiences of informal caregivers with respect to specific elements of CC-TRS, we will use a self-developed 15-item questionnaire called *Evaluation informal caregivers CC-TRS*.

Two 90-minute-long focus group interviews with informal caregivers will be conducted at T12. Given that patients could be enrolled at different points of the study, we plan to conduct focus group interviews as soon as possible after a sufficient number of patients have completed a full year of treatment with the CC-TRS. The focus group interviews will preferably take place with 6 to 12 informal caregivers, with a minimum of 4 people. In these focus group interviews, a topic list will be used, with topics referring to the overall experiences of the informal caregivers with the CC-TRS, its various components, and aspects of collaboration with the CC team. In the interviews, informal caregivers will also be asked to reflect on the perceived effects of the CC-TRS on the patients. The underlying principles of the CC-TRS will be discussed in conjunction with the specific features of CC-TRS that contribute to positive treatment outcomes. All interviews will be audiotaped and transcribed verbatim.

Care Professionals

To compare team characteristics, we will describe the standard of care provided by the participating teams as well as the composition of staff before the start of the intervention period. To measure experiences with the training program, care professionals will complete an evaluation form after completing the training.

During the implementation of the CC-TRS, 90-minute feedback meetings will be held every 3 months with all care professionals in the team as well as the team manager. During these meetings, concrete information about the implementation achievements of the team will be discussed to promote the implementation and execution of the CC-TRS. In addition, factors that either promoted or hindered the implementation of the CC-TRS at the patient level will be discussed in an endeavor to both identify practical solutions to the barriers experienced and learn from each other by sharing successful applications of the CC-TRS. All these feedback meetings will be audiotaped and summarized, with notable quotes being transcribed verbatim.

For each patient, there will be a group interview with involved care professionals at T12. Within this 1-hour group interview, the individual case will be discussed in detail with care professionals. A quantitative measure will form the input for this interview. In addition, a topic list will be drawn to discuss the process of implementation of the CC-TRS within that specific case and to explore associations between the implementation process and patient outcomes. All interviews will be audiotaped and transcribed verbatim.

The quantitative data will be entered into SPSS Statistics (version 26; IBM Corp). The transcribed texts from the qualitative interviews and feedback meetings will be entered into MAXQDA (version 2020).

Analyses

We will perform a combination of qualitative and quantitative analyses in accordance with the method described by Stake [45]. In this multiple case study, the analysis of data will occur at 2 different levels: the individual case level (single-case analysis) and group level (cross-case analysis).

In the single-case analysis, data from different sources and perspectives will be analyzed for each individual case. On the basis of the document analysis; quantitative measurements; and interviews with patients, informal caregivers, and care professionals, we will draw up a comprehensive description of each case in order to gain insight into how the CC-TRS was offered to each individual patient, how this was experienced by different people (patients, informal caregivers, and professionals), the course of the treatment over time, and individual patient' outcomes over time. For each case, we will examine which factors (CC-TRS-related and other) contribute to both positive and negative treatment outcomes. By integrating data at the case level, we can examine the factors that influence the effective application of the CC-TRS at the following levels: (1) treatment-related variables, (2) patient variables, (3) caregiver variables, (4) informal caregiver variables, (5) interactional variables, (6) organizational variables, and (7) other contextual variables. The single-case analysis will result in a detailed description of the relevant case, including tables with a summary of the findings in relation to our aforementioned research questions.

In the cross-case analyses, the findings from the 20 single-case analyses will be analyzed at the group level. In 3 ways, we will investigate the extent to which the implementation plans were successfully carried out. First, we will conduct an intervention check through document analysis. In this way, we systematically identify if and to what extent the interventions have been implemented. Second, we will discuss, through feedback meetings with team members, which components of the CC-TRS are implemented as planned and which components are not, whether all preconditions are met sufficiently, and discuss the teams' needs to overcome experienced barriers regarding implementation. Feedback meetings will be audiotaped and summarized, with notable quotes being transcribed verbatim. Third, in supervision meetings, CNS and CC nurses will discuss their own considerations and explanations for the extent and manner in which interventions are implemented at the patient level. Noteworthy findings and considerations will be noted. We will quantitatively analyze the overall effects of CC-TRS on different outcome measures. To this end, exploratory analyses will be performed on patients (n=20) using the Friedman Test (nonparametric variant of the repeated measures analysis of variance). Next, we will descriptively analyze the quantitative

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data related to patients' satisfaction with the CC-TRS program, by using the *Consumer Quality Index* and the questionnaire *Experiences with CC-TRS*. Following this, an overall analysis of individual interviews with patients will be conducted. Descriptive qualitative analyses will then be performed to explore the experiences of patients in the CC-TRS intervention program. Subsequently, the data from informal caregivers will be analyzed, first quantitatively (FPCR and the questionnaire *Evaluation informal caregivers CC-TRS*), followed by a qualitative descriptive analysis of the data generated in the focus group interviews. The next step will be to analyze the data pertaining to care professionals. The first quantitative analysis will be conducted on caregivers' satisfaction with the training program. This will be followed by a qualitative analysis of the data generated through feedback meetings. Finally, data from the caregivers' interviews will be descriptively analyzed. Through recourse to the method of content analysis [70], patient records will be analyzed to investigate the implementation of the CC-TRS.

The final step in the cross-case analysis will involve the integration of both qualitative and quantitative findings through the use of summary descriptions and tables drawn up in previous stages of the data analysis. In addition, the experiences of the patients, informal caregivers, and professionals will be presented at the group level. On the basis of our analyses, we will be able to describe the extent to which the CC-TRS was implemented and the factors determining its successful implementation. At both the individual and group levels, we will provide insight into the preliminary effects of the intervention, including the factors that contributed to these effects.

Ethics Approval

The protocol was approved by the scientific committee of Reinier van Arkel (ID CWO1803) and the Medical Ethical Committee of the Vrije Universiteit University Medical Centre (ID A2019.475, 2018.071 and NL number NL64469.029.18). The procedures in this study are in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki (1975) as revised in 2013 [71].

Results

Recruitment commenced in October 2020, with the aim of enrolling 20 patients over 2 years. Data collection will be completed by the end of 2023, and the results will be published once all data are available for reporting.

Discussion

Strengths and Limitations

A strength of this study is, as undertreatment of TRS is a common problem [1,11,12], extensive attention was paid to the recruitment procedure by screening all patients every 3 months supervised by the quality consultants to evaluate if they are eligible for participation in the study. Therefore, we expect it to be feasible to include 20 patients within 3 teams in an inclusion period of 2 years.

There are several strengths in the study regarding the factors that are crucial for effective implementation [72]. This study will consider both the facilitating factors and barriers to implementation. For example, the CC-TRS is a bottom-up initiative carried out by the CNS in clinical practice. This is expected to enhance support among other care professionals in the implementation of the CC program. Both the board and management support the implementation of the CC-TRS, which creates favorable conditions in terms of financial support, commitment, and the availability of staff. Moreover, the CC-TRS includes an extensive training program for care professionals. To build support among care professionals and secure the division of tasks, a tailored implementation plan will be drawn up for each team in close collaboration with team members. Quality managers will be appointed to support the implementation process. Feedback meetings will be organized regularly to discuss and streamline the implementation process. We expect the implementation of the CC-TRS to be promoted because of this comprehensive strategy.

A special feature of the CC-TRS intervention and the multiple case study is that they are initiated and developed by mental health nurses. In the CC-TRS, the CNS will be the supervising practitioner and CC nurses will carry out the CC-TRS in close cooperation with the other members of the multidisciplinary treatment team. The PhD candidate is a CNS, and mental health nurses will perform measurements in the role of researchers. Thus, the CC-TRS might also have a positive effect on the professionalization of the nursing profession as a whole.

This study had some limitations. The first limitation is that this study has faced delays in execution owing to suboptimal conditions in the teams that needed to be resolved before the start of the study, such as the completion of other projects that required significant time from care professionals and the availability of a CNS on the team. In addition, the outbreak of the COVID-19 pandemic has caused a delay. As a result, there will be a considerable amount of time between the training of professionals and the start of the intervention. To solve this problem, we will provide a refresher course before the inclusion of patients. A second limitation of this study concerns the establishment of treatment adherence and treatment resistance. It is important to know whether a patient is taking antipsychotics. We assess medication adherence as best as possible in a way that we considered appropriate for our pragmatic study, namely by using data from the electronic prescription system in patients' files and reports. In clinical practice, it is difficult to quantify the actual intake of medications. Our participants belong to an outpatient population, which means that it is not easy to reliably observe the intake of medication or count pills. With our inclusion criteria, we aimed to align with the consensus criteria for assessment and definition of TRS as described by the Treatment Response and Resistance in Psychosis Working Group [60]. A final limitation is that the self-developed questionnaires, that is, *Questionnaire Experiences with Treatment* and *Evaluation informal caregivers CC-TRS* are not validated and pilot-tested. For interested readers, the questionnaires are available in Dutch by contacting the first author.

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Several other issues were carefully considered in this study. First, we consider the inclusion strategy of participants. In clinical practice, and also noticed by other researchers [73], besides the Diagnostic and Statistical Manual of Mental Disorders diagnoses of schizophrenia or schizoaffective disorder, other schizophrenia spectrum disorders are also diagnosed in cases of persistent psychotic symptoms. To avoid the risk of excluding patients who meet the criteria for TRS, we will include a broader range of Diagnostic and Statistical Manual of Mental Disorders diagnoses. At T0, we will determine whether a patient is eligible for inclusion in the study. The second consideration is the exclusion of inpatient treatment settings. We expect the CC-TRS to be important in inpatient long-term care units given the presence of (undertreated) patients with TRS in such units. However, for practical reasons and to limit the scope of our study, we now focus exclusively on outpatient settings. To determine the effectiveness of the intervention in both outpatient and inpatient treatment settings unambiguously, it is desirable to conduct an experimental study on the effects of the intervention. If our study shows that the CC-TRS has positive effects on the outpatient population, future research should determine whether these effects can also be achieved in the inpatient population.

Future Directions

One of the goals of our study is improved recovery (symptomatic, functional, and personal) by offering integrated treatment opportunities for patients with TRS. It also addresses treatment pessimism among mental health professionals regarding our target group of patients. On the basis of the results of this study, we will be able to formulate recommendations for clinical practice regarding preconditions and factors that influence the optimization of treatment of patients with TRS.

Conclusions

Although the interventions in the CC-TRS are all established evidence-based interventions, they have hitherto not been consistently delivered to patients using the framework of the CC model. We expect this study to gain insight into the process of implementation, preliminary outcomes, and experiences of care professionals, patients, and informal caregivers with the CC-TRS and to contribute to the optimization of treatment for patients with TRS.

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Conflicts of Interest

None declared.

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Abbreviations

CC: Collaborative Care
CC-TRS: Collaborative Care program for patients with treatment-resistant schizophrenia
CNS: clinical nurse specialist
EIT: Early Psychosis Intervention Team
FACT: Flexible Assertive Community treatment
FMI: Family Motivational Intervention
FPCR: Family Perceptions of Caregiving Role
SDM: shared decision-making
TRS: treatment-resistant schizophrenia

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Protocol

Antimicrobial Use in Pediatric Oncology and Hematology: Protocol for a Multicenter Point-Prevalence Study With Qualitative Expert Panel Assessment

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Abstract

Background: Because infections are a major driver of morbidity and mortality in children with hematologic or oncologic diseases, antimicrobials are frequently prescribed in pediatric oncology practice. However, excess or inappropriate use of antimicrobials is directly linked to the emergence of antimicrobial resistance. Although point-prevalence studies have examined the extent of antimicrobial use, a comprehensive qualitative evaluation of individual antimicrobial prescriptions remains lacking.

Objective: The aim of this study is to identify appropriate versus inappropriate antimicrobial use among pediatric cancer patients in a point-prevalence study, followed by an expert panel adjudication process and a subsequent report of these findings to participating centers. This study also aims to improve the quality of patient care by informing centers about discrepancies between internal standards of care and national guidelines.

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Methods: Our point-prevalence study is performed at pediatric cancer centers in Germany and Austria. All patients under 18 years old who are hospitalized at the time of the study are included. As a supplement to the point-prevalence study, an expert panel is qualitatively assessing each of the antimicrobial prescriptions at the participating centers to review local guidelines and compare them with national guidelines.

Results: As of December 2021, the point-prevalence survey has been conducted at 30 sites and expert panel adjudication for qualitative assessment of each antimicrobial use is ongoing. Results of the study are expected in 2022.

Conclusions: This is the first point-prevalence study conducted among pediatric cancer centers with an integrated, multistep, qualitative approach that assesses each antimicrobial prescription. The results of this study will inform possible interventions for internal guidelines and antimicrobial stewardship programs implemented at pediatric cancer centers. In addition, local guidelines will be compared with national guidelines. Furthermore, this study will contribute to the overall integration of antimicrobial stewardship principles and initiatives in pediatric oncology and hematology, thereby improving safety and quality of care for children and adolescents with cancer and blood disorders.

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KEYWORDS

point-prevalence study; antimicrobial stewardship; pediatric oncology; pediatric hematology; expert panel; antimicrobial resistance; oncology; cancer; pediatrics

Introduction

Children with oncologic or hematologic diseases are at particularly high risk for severe infections, especially while on chemotherapeutic treatment, radiation, or stem cell transplantation [1,2]. This vulnerability can be attributed to the immunodeficient state caused by the underlying disease as well as by the anticancer treatment. Among children treated in pediatric cancer centers, the high prevalence of and risk for adverse outcomes related to severe bacterial and fungal infections lead to a high level of antimicrobial prescribing [3,4], both for treatment and prophylaxis [5]. These levels are comparable to those in pediatric intensive care units.

Ill-advised, excess use of antimicrobials has been associated with the epidemiological increase of antimicrobial resistance, an imminent global health care threat. Similarly, at the individual level, severe adverse events such as allergic reactions, acute organ toxicity, or *Clostridioides difficile*–related enterocolitis can result from antimicrobial use [6-8].

In general terms, point-prevalence studies (PPSs) are used to monitor the prescription of antimicrobials in a cross-sectional design in a given setting or across different centers. This allows for benchmarking, as well as for the identification of potential targets for antimicrobial stewardship programs (ASPs) [9-12]. Although a PPS may provide a first impression about local antimicrobial use patterns, a critical appraisal of individual indications, choice of antimicrobials, combination therapy, dosing, deescalation, and therapeutic drug monitoring (TDM) issues (ie, an in-depth qualitative assessment) is often hampered by limitations in the PPS data set or by the lack of available time for discussion of individual cases. Consequently, most published PPSs only contain little or no qualitative data and are rather limited to quantitative assessments of antimicrobial use in broader terms. Another limitation of qualitative assessments is the lack of a gold standard in defining treatment approaches in many infectious disease etiologies (with the exception of febrile neutropenia [FN]) in pediatric oncology and hematology [13,14]. One way to address the issue of this missing gold standard is to assemble an expert panel who employ a set of peer-blind adjudicators to determine the most probable etiology based on the available data [15,16]. However, there are scarce data pertaining to the use of expert panels in the determination of infectious disease etiology in pediatric oncology and hematology.

In our study, we will perform a PPS among pediatric oncology and hematology units in Germany and Austria. Specifically, the study employs external expert panels to conduct an incorporated, extensive, qualitative assessment of internal local guidelines and case-based antibacterial and antifungal use. This unique approach may pave the way for the identification of ASP targets in the participating pediatric cancer centers. The aims of the study are to assess antimicrobial prescribing and suitability of antimicrobial treatment at the patient level in pediatric oncology and hematology units, to investigate the extent to which local guidelines may be in line with national guidelines, and to identify potential quality improvement measures for the participating centers.

Methods

Study Design

This is a prospective, multicenter, observational PPS of hospitalized children and adolescents from pediatric cancer centers across Germany and Austria. The study assesses antimicrobial prescribing and the suitability of antimicrobial treatment at the patient level, and also investigates the extent to which local guidelines are in line with national guidelines. The study's goal is to identify potential quality improvement measures for the participating centers.

Study Population

All university and district hospitals represented within the German Society for Pediatric Oncology and Hematology (Gesellschaft für Pädiatrische Onkologie und Hämatologie [GPOH]) and the German Society for Pediatric Infectious

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Diseases (Deutsche Gesellschaft für Pädiatrische Infektiologie [DGPI]) were invited to participate. Invitation announcements were communicated via a society newsletter or conveyed by the principal investigators to department heads. Only centers with an existing internal guideline pertinent to antimicrobial treatment in FN were eligible. Inclusion to the study was irrespective of the level of health care and the presence of or affiliation to a university hospital. Only patients hospitalized at the time of the PPS were included.

Point-Prevalence Survey

The point-prevalence survey was conducted on a select weekday between November 30 and December 4, 2020, or between December 7 and December 11, 2020.

The following general data pertaining to the respective pediatric oncology/hematology unit on the day of the point-prevalence survey were collected: numbers of total beds, hospitalized patients, patients on source isolation (eg, due to colonization or infection with a multidrug-resistant pathogen), patients on protective isolation, and patients on antibacterial and/or antifungal therapy.

In addition, the following data for each patient receiving antibacterial and/or antifungal therapy on the point-prevalence day were collected: age and age group, body weight, height, underlying oncologic/hematologic disease, state of disease (first diagnosis vs relapse), trimethoprim/sulfamethoxazole prophylaxis (yes/no), granulocytopenia (ie, $<0.5\times10^9$/L), mucositis grade III (according to the World Health Organization oral mucositis grading scale), severe graft-versus-host disease (grade III to IV), subcutaneously tunneled or implanted long-term central venous access device (Broviac, Hickman, or Port), creatinine clearance <50 mL/min per 1.73 m^2, high risk for fungal infections (defined as acute myeloid leukemia undergoing induction therapy, leukemia relapse/not in remission, allogeneic stem cell transplantation, prolonged neutropenia for ≥10 days and steroid therapy, or graft-versus-host-disease grade III-IV), and colonization with multidrug-resistant organisms (eg, methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant enterococci; multidrug-resistant gram-negative bacteria, including extended-spectrum beta-lactamase producers and carbapenem-resistant bacteria according to the German classification system of multidrug-resistant gram-negative bacteria [17]).

Furthermore, for each antibacterial or antifungal drug, the following data were recorded: type of infectious disease diagnosis (fever without source, skin and soft tissue infection, respiratory tract infection, urinary tract infection, intra-abdominal infection, *C. difficile*–associated disease, postoperative wound infection, bloodstream infection/sepsis, infection of the central nervous system, osteomyelitis/arthritis, other infectious disease diagnosis); generic name of antibacterial or antifungal drug; start date of treatment; route of administration (intravenous vs oral), dosage, number of doses per day versus continuous infusion, indication (therapy, prophylaxis, perioperative prophylaxis, indeterminate); empiric therapy (no known source, no pathogen), calculated therapy (source, no pathogen), or directed therapy (pathogen detected); TDM for aminoglycosides, glycopeptides, triazole antifungals; and if TDM performed, the trough and/or peak levels (choice without additional detail).

Participating centers were asked to provide their center-specific standard-of-care guidelines regarding antimicrobial treatment, with particular attention to the management of FN. The rationale for this approach is to not solely rely on the centers' purported adherence to guidelines of patient management but rather to verify and scrutinize the content of internal guidance documents concerning their alignment with national guidelines.

Modified Expert Panel Process

In previous studies, an expert panel approach using three independent, blinded adjudicators with field-specific expertise yielded reproducible, consistent results in the determination of infectious disease etiology [15,16]. For this study, we designed a multistep approach to be conducted throughout the year (2021). Before initiating the adjudication process, all data obtained from the point-prevalence survey were deidentified with respect to the participating center. A total of 15 experts from the field of pediatric oncology/hematology and infectious diseases formed five panels with three adjudicators each (Figure 1). Of note, cases from a given center were not assigned to panels that included an adjudicator from that same center. In a first step, while blinded to their panel peers' adjudications, experts were asked to independently adjudicate each patient's antimicrobial therapy regarding the suitability of each antimicrobial used. In this process, the adjudicators used both the center-specific local guidelines and the national guidelines for reference in deciding whether the respective therapy was appropriate, inappropriate, or whether appropriateness was indeterminable. When labeled inappropriate, the adjudicators specified the reason for inappropriateness (Table 1). When all three adjudicators unanimously and congruently labeled the antimicrobial use as either appropriate or inappropriate, the case was considered closed. When the adjudicators had differences of opinion, a video conference among the three adjudicators and a moderator was scheduled to reach a consensus by discussing differing perspectives. When consensus could not be reached (eg, because of missing information), the case was classified as "indeterminate."

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Figure 1. Flow diagram of the point-prevalence study conducted among 30 pediatric cancer centers in Germany and Austria, 2020/2021, and the consecutive multistep adjudication process to define appropriateness of antimicrobial therapy in all reported patients.

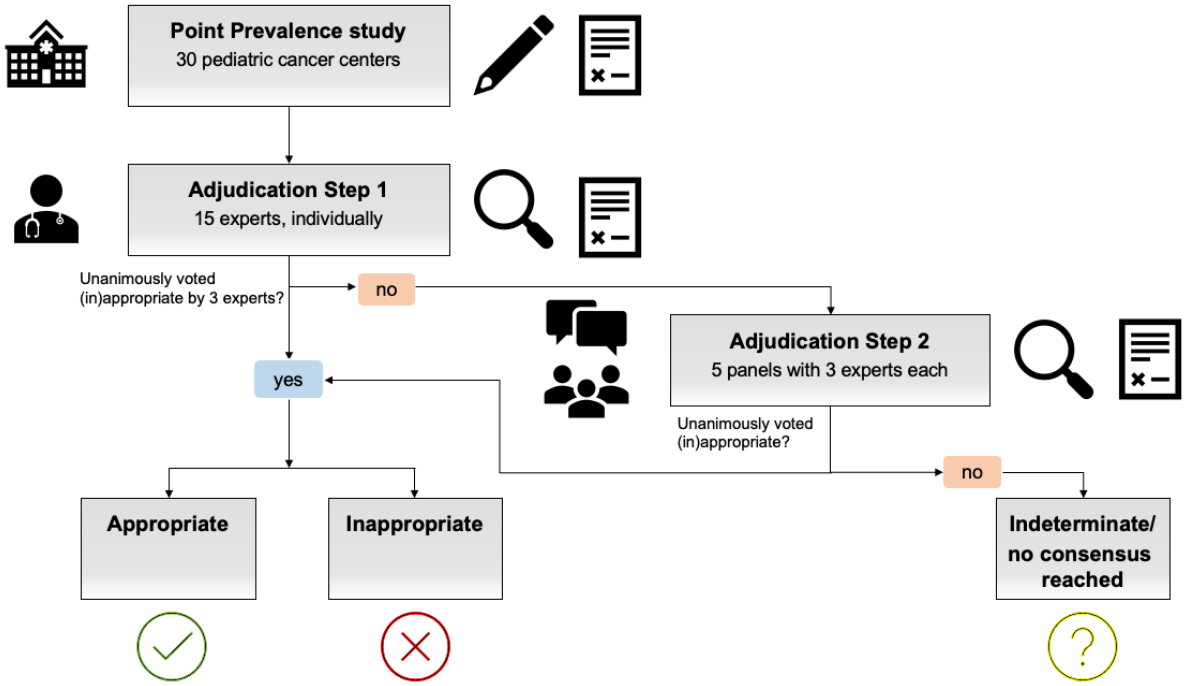

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Table 1. Nonredundant list of items to specify inappropriate therapy as adjudicated by the expert panelists in the point-prevalence study conducted among 30 pediatric cancer centers in Germany and Austria, 2020-2021.

Code	Item	Notes
1	Unnecessary therapy (1)	(Prolonged) antibacterial therapy in patients with respiratory tract infection with viral detection
2	Unnecessary therapy (2)	Prolonged antibacterial therapy (>72 h) in newly diagnosed ALL[a] with fever without signs of a bacterial infection
3	Inappropriate therapy (1)	No deescalation when pathogen is known
4	Inappropriate therapy (2)	Early escalation (before 48h) without clinical deterioration
5	Dosage	>20% above or below the range for an antimicrobial agent as indicated in the internal guideline
6	Lack of *Pseudomonas aeruginosa* coverage	—[b]
7	Empirical combination therapy	Upfront combination therapy in febrile neutropenia without being founded in the local guideline
8	Primary empirical treatment with meropenem or imipenem	In patients without known colonization with multidrug-resistant organisms
9	Primary empirical treatment with vancomycin or teicoplanin	Exceptions: AML[c] induction therapy with high-dose cytarabine; extensive skin/soft tissue infection; central line–associated infection; known colonization with MRSA[d]
10	Double coverage (1)	Piperacillin/tazobactam or meropenem, each combined with metronidazole (exception: systemic infection in addition to *Clostridioides difficile* enterocolitis)
11	Double coverage (2)	Meropenem plus aminoglycoside (exceptions: multidrug-resistant *P. aeruginosa*)
12	*C. difficile* (1)	Intravenous treatment with vancomycin or teicoplanin in *C. difficile*–related enterocolitis
13	*C. difficile* (2)	Primary oral treatment with metronidazole instead of vancomycin
14	Surgical antibiotic prophylaxis (1)	>24h without a comprehensible rationale
15	Surgical antibiotic prophylaxis (2)	Drugs of choice: cefazolin, cefuroxime, or ampicillin-sulbactam; in penicillin allergy: clindamycin
16	Bug-drug mismatch	—
17	Aminoglycosides (1)	Application twice or thrice per day instead of once
18	Aminoglycosides (2)	No TDM[e] performed
19	Aminoglycosides (3)	Contraindications (eg, renal insufficiency)
20	Vancomycin	No TDM performed
21	Linezolid	Twice per day instead of thrice per day in children ≤12 years of age
22	Lack of dosage adjustment in renal insufficiency (creatinine clearance <50 $mL \cdot min^{-1} \cdot 1.72\ m^{-2}$)	for example: ceftazidime, cefepime, ciprofloxacin, imipenem/cilastatin, meropenem, metronidazole, vancomycin
23	Other	Indicated in an open-text format

[a]ALL: acute lymphocytic leukemia.

[b]Not applicable.

[c]AML: acute myeloid leukemia.

[d]MRSA: methicillin-resistant *Staphylococcus aureus*.

[e]TDM: therapeutic drug monitoring.

Feedback to Centers

A further objective of the study is to improve quality of patient care at the participating centers. This is achieved by reporting back to the centers regarding the panel adjudications, as well as by highlighting discrepancies between local and national guidelines, especially with regard to the center's internal standards for management of FN and any case-related antimicrobial use deemed to have been inappropriate.

Outcome Measures

In addition to descriptive data pertaining to the centers and patients receiving antimicrobial therapy, the following outcome parameters are analyzed: antimicrobial prevalence rate per center (number of patients treated with antibacterial and/or antifungal drugs divided by the number of hospitalized patients for a given center on the day of the point-prevalence survey), antimicrobial prevalence rate overall (total number of patients treated with antibacterial and/or antifungal drugs divided by the total number of hospitalized patients for all centers on the day of the point-prevalence survey), rate of appropriate antimicrobial

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therapies per center and overall, rate of inappropriate antimicrobial therapies with regard to the center-specific standard of care per center and overall, rate of inappropriate antimicrobial therapies with regard to the national guidelines [13,18] per center and overall, rate of indeterminate antimicrobial therapies per center and overall, and rate of antimicrobial therapies without consensus per center and overall.

Statistical Analysis

Baseline characteristics will be reported descriptively, with counts and percentages used as appropriate. Means with SDs are given for normally distributed data and medians with IQRs are reported for nonnormally distributed data. The primary outcome parameters are reported as point estimates including 95% CIs. Statistical analyses will be performed using SPSS (version 26.0).

Patient and Public Involvement

No patients are involved in this study protocol.

Ethics Approval

This study has been approved by the local ethics committee (Ärztekammer des Saarlandes, number 33/20). The need for informed patient consent was waived, since only routinely available data are included in the study, and all patient data were pseudonymized per center.

Dissemination

The findings of this study will be presented at national and international conferences. Results will be published in international peer-reviewed journals. Reporting will adhere to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for cross-sectional studies [19].

Results

As of December 2021, the point-prevalence survey has been conducted at 30 sites and expert panel adjudication for qualitative assessment of each antimicrobial use is ongoing. Results of the study are expected for 2022.

Discussion

To our knowledge, this is the first study to apply a qualitative assessment of antimicrobial use by combining a multistep expert panel approach with a PPS in the context of pediatric oncology and hematology. The aim of this study is to identify appropriate versus inappropriate antimicrobial use, and to subsequently report these findings to the participating centers. In addition, by informing centers about potential discrepancies between internal standards of care and national guidelines [13], the authors of this study also hope to improve quality of patient care.

In contrast to previous studies using expert panel adjudication as a reference standard [16], we provide a modified approach, whereby the blinded panel adjudication is supplemented by a panel discussion with the aim of reaching consensus.

We expect the results of our study to be largely in line with the generally high antimicrobial consumption in pediatric oncology/hematology, given the ample evidence in the existing literature [20,21]. There are limitations to the study design that deserve mentioning. First, while we were able to include many German centers, outreach toward Swiss centers was unsuccessful. However, the study itself remains scalable, and more centers, especially from more countries, could be aimed for in a follow-up study. Another limitation pertains to the patients who were under no antimicrobial treatment, but inappropriately so. The study design did not allow for including these patients who may have been subject to “undertreatment,” which in turn is generally regarded as being less prevalent than overtreatment [15,22]. Moreover, a certain degree of participation bias may have been introduced by centers with an existing ASP who are eager to take part in contrast to centers with little appreciation for the topic, which may coincide with the level of case mix and case complexity. Related to this, an inclusion criterion was the existence of an internal guidance document, which may also raise the possibility of a selection bias. An expert panel should be regarded as an approximation, as imperfect as any other, toward the true etiology of infection in the absence of a gold standard. Some of the known drawbacks of this approach are possible adjudicator fatigue, which may influence outcome classification. In addition, the consensus approach in the second step of the expert panel adjudication, during which adjudicators are no longer blinded but openly discuss each case, may give rise to reciprocal influencing and may favor dominant over reserved adjudicators.

Finally, although the study will inform the participating centers about their guideline adherence and the accuracy of their internal guidance documents, no statements can be made about the sustainability of any change that may be induced by feedback given to the centers.

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Authors' Contributions

CP, MH, and AS conceived and designed the study, and wrote the first draft of the study protocol. All authors contributed to the development and the revision of the study protocol.

Conflicts of Interest

None declared.

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Abbreviations

ASP: antimicrobial stewardship program
DGKH: Deutsche Gesellschaft für Krankenhaushygiene
DGPI: Deutsche Gesellschaft für Pädiatrische Infektiologie
ESCMID: European Society of Clinical Microbiology and Infectious Diseases
FN: febrile neutropenia
GPOH: Gesellschaft für Pädiatrische Onkologie und Hämatologie
PPS: point-prevalence study
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TDM: therapeutic drug monitoring

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Protocol

Neural Activity During Audiovisual Speech Processing: Protocol For a Functional Neuroimaging Study

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Related Article:

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Abstract

Background: Functional near-infrared spectroscopy (fNIRS) studies have demonstrated associations between hearing outcomes after cochlear implantation and plastic brain changes. However, inconsistent results make it difficult to draw conclusions. A major problem is that many variables need to be controlled. To gain further understanding, a careful preparation and planning of such a functional neuroimaging task is key.

Objective: Using fNIRS, our main objective is to develop a well-controlled audiovisual speech comprehension task to study brain activation in individuals with normal hearing and hearing impairment (including cochlear implant users). The task should be deductible from clinically established tests, induce maximal cortical activation, use optimal coverage of relevant brain regions, and be reproducible by other research groups.

Methods: The protocol will consist of a 5-minute resting state and 2 stimulation periods that are 12 minutes each. During the stimulation periods, 13-second video recordings of the clinically established Oldenburg Sentence Test (OLSA) will be presented. Stimuli will be presented in 4 different modalities: (1) speech in quiet, (2) speech in noise, (3) visual only (ie, lipreading), and (4) audiovisual speech. Each stimulus type will be repeated 10 times in a counterbalanced block design. Interactive question windows will monitor speech comprehension during the task. After the measurement, we will perform a 3D scan to digitize optode positions and verify the covered anatomical locations.

Results: This paper reports the study protocol. Enrollment for the study started in August 2021. We expect to publish our first results by the end of 2022.

Conclusions: The proposed audiovisual speech comprehension task will help elucidate neural correlates to speech understanding. The comprehensive study will have the potential to provide additional information beyond the conventional clinical standards about the underlying plastic brain changes of a hearing-impaired person. It will facilitate more precise indication criteria for cochlear implantation and better planning of rehabilitation.

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KEYWORDS

hearing loss; brain plasticity; functional near-infrared spectroscopy (fNIRS); cochlear implant; neuroimaging; speech understanding; comprehension; speech; brain activation; brain activity; hearing impairment; cortical activation; neural; brain; protocol; spectroscopy; cochlear; hearing

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Introduction

Background

Disabling hearing loss is a major communication and health problem that affects over 6% of the overall population and over 50% of adults above the age of 65. For adults, deafness leads to social isolation, unemployment, and reliance on social services. This problem will increase with demographic change. It is estimated that by 2050, 10% of the global population will be living with disabling hearing loss [1]. In patients with severe to profound hearing loss, a cochlear implant (CI) offers an effective treatment [2]. A CI is a neuroprosthetic device that electrically stimulates the auditory nerve in response to acoustic stimulation. CIs enable deaf patients to regain their speech understanding [3,4], improve sound localization [5], and increase their quality of life [6]. However, hearing outcomes after implantation surgery vary widely in both prelingually and postlingually deafened patients. About 20%-30% of postlingually deafened patients who receive a CI do not gain the expected benefit from the implant. Nowadays, over 75% of the variance in CI outcomes remains unclear [7-9]. Consequently, it is not possible to predict preoperatively how well a CI candidate will perform with the implant. Therefore, there is an urgent need to better understand this variability and find ways to improve outcomes for people with poor language comprehension.

In the absence of auditory input, the sensory deprivation induces reallocation of cortical areas (so-called brain plasticity). This leads to functional reorganization within the auditory and auditory-related brain cortex, with new functions being assigned to these brain regions [10]. As an example, the visual takeover (also referred as cross-modal reorganization) in the impaired auditory brain areas has been demonstrated. It means that visual information, for instance, during a lipreading task, can be processed partially in former auditory associated brain areas [11-14]. A CI can counteract these hearing loss–induced plastic changes, and the success of the rehabilitation depends on them. It has been shown that different hearing outcomes after implantation correlate with these reorganization processes [3,15-17].

We use functional imaging to study these described plastic brain changes. However, in CI recipients, there are important considerations to make. Despite the efforts of CI manufacturers to allow structural magnetic resonance imaging (MRI) with a surgically implanted device, the technique has limitations. The outer speech processor cannot be worn during MRI scanning and thus cannot be used to assess evoked auditory responses associated with functional MRI. Furthermore, the implanted magnet and electrode array of the CI cause imaging artifacts in MRI and stimulation artifacts in electroencephalography (EEG) [18-20].

Functional near-infrared spectroscopy (fNIRS), on the other hand, is ideal for this patient population [21]. The technique uses near-infrared light to measure the blood oxygen saturation of the cerebral cortex. This allows indirect conclusions to be drawn about neuronal activation. Other advantages of fNIRS are that the measurements are not affected by electrical pulses, do not interfere with the CI, are quiet (which is important in auditory tasks), are noninvasive, suitable for all ages, and enable the evaluation of responses to spoken words and whole sentences.

Previous fNIRS studies with implanted adults showed evidence of cortical reorganization. However, when comparing study findings, there are contradictory results. For example, some studies suggest that strong activation of the auditory cortex during lipreading tasks is a negative predictor of speech understanding with the implant [22,23]. Other publications describe an opposite effect or no effect [24,25].

According to a recent review on fNIRS measurements in CI patients, at the current stage, it is difficult to draw a general conclusion about the potential positive or negative effects of cortical reorganization. Instead, methodological aspects must first be clarified [26]. The effect of cross-modal plasticity may be more complex than suggested in previous studies. One problem with measuring functional brain activation is that many variables need to be controlled. For example, it makes a remarkable difference how patients are selected (pre- or postlingually deafened) [24], whether a study participant is actively engaged in the experiment (otherwise mind wandering might occur) [27], how the stimuli are presented, and whether the task performance is monitored [28]. Poorly controlled variables during an fNIRS experiment can lead to misinterpretations and mistakes in data analysis.

The aim of our study protocol is to develop a well-controlled and reproducible fNIRS task to evaluate brain activation in response to speech comprehension in individuals with normal hearing, those with hearing impairments, and CI users. Our hypothesis is that through such a task, we can identify cortical networks that are clearly correlated to hearing performance with the implant. Identified brain activation patterns may later be used preoperatively as biomarkers of speech understanding with the implant.

Objectives

Using fNIRS, our main objective is to develop an audiovisual speech comprehension task to measure functional brain activity regarding speech understanding. The task should comply with the following criteria: it should (1) be deducible from clinically established hearing tests; (2) induce maximal cortical activation (and thus allow reproducible recognition of activation patterns); (3) align with the international 10-10 system of electrode placement, using optimally spaced optode positions with maximal coverage over the responsible brain regions. Short separation channels should allow noise reduction; (4) be time-efficient (to avoid fatigue due to experiment duration; (5) be suitable for normal hearing, hearing impaired, and cochlear implant users; and (6) be reproducible by other research groups.

We will correlate the fNIRS recordings with (1) data from patients' history, (2) clinically validated questionnaires, and (3) performance during the fNIRS measurements (eg, speech comprehension during the fNIRS task).

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Methods

Study Design

This research project is a prospective single-center study and will be conducted at the Department of Otolaryngology, Head and Neck Surgery at the Bern University Hospital, Inselspital, Bern, Switzerland.

Ethics Approval

The protocol was designed in accordance with the ethical principles of the Declaration of Helsinki. The study setup was approved by the local ethical committee (reference number 2020-02978) and fulfils all the patient data regulations of Switzerland.

Participants and Eligibility Criteria

All study participants must (1) be at least 18 years old, (2) be native German speakers, and (3) have preferably light and thin hair [29,30]. Participants with a severe cardiac, psychiatric, or neurological disease (eg, epilepsy) or brain injury will be excluded from the study (refer to Multimedia Appendix 1 for details). CI users must be bilaterally and postlingually deafened, with an unaided pure-tone average (PTA) hearing threshold exceeding a hearing level (HL) of 80 dB.

The ear through which the acoustic stimulation will be presented needs to be implanted for at least 1 year. This will ensure that hearing rehabilitation after implantation is completed.

Participants will be allocated to one of 3 groups: (1) normal hearing "control" cohort, (2) CI users with good speech understanding ("overperformer"), or (3) CI users with poor speech understanding ("underperformer"). CI users with moderate speech perception (ie, between 40% and 70% aided monosyllabic word recognition score) will not be recruited because we want to investigate the functional mechanisms specifically for good and poor outcomes. Table 1 provides an overview of the categorization criteria for each subgroup.

Table 1. Overview of categorization according to participants' hearing performance[a].

Criterion	Normal hearing	CI[b] "overperformer"	CI "underperformer"
Unaided PTA[c] hearing threshold	≤20 dB HL[d]	≥80 dB HL	≥80 dB HL
Word recognition score	100%	≥70%	≤40%

[a]Word recognition score will be measured using Freiburg monosyllabic test lists at a 65 dB sound pressure level.

[b]CI: cochlear implant.

[c]PTA: pure-tone average.

[d]HL: hearing level.

Sample Size

Pilot measurements were performed on 10 participants to estimate an appropriate sample size. We compared the median relative change in the concentration of oxygenated hemoglobin in the auditory cortex. After acoustic stimulation (speech in quiet), an increase of 1.315 (SD 1.275) µMolar*cm was measured, while during the resting state, the value fluctuated close to 0. A power analysis to test a 2-sided hypothesis at 95% significance and 80% power showed that we need at least 15 participants with normal hearing to detect auditory activations. In addition, we considered previous findings from auditory fNIRS studies [26,28,31,32]. We compared the size of their study cohorts, the fNIRS systems used, the optode arrangements used, and the reliability of their results. To allow for a possibly larger variation, we propose including 60 individuals in this study (20 listeners with normal hearing, 20 CI overperformers, and 20 CI underperformers).

Recruitment

Recruitment will be done through the CI center of our department. Potential study candidates will be screened based on their medical records and will be subsequently informed verbally or in writing about the study procedure. Candidates who are willing to participate and able to complete all tests required for the study will be asked to sign an informed consent form.

Study Procedure

Table 2 shows the time schedule for participants. The enrollment and the data collection sessions are described in more detail in the subsequent subsections.

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Table 2. Overview of the study procedure.

Item	Enrollment session	Data collection session
Information sheet	√	
Medical history	√	
Questionnaires	√	
Hearing tests	√	
fNIRS[a] recording		√
Behavioral assessment		√
Optode position registration		√
Total duration	30 min	90-120 min

[a]fNIRS: functional near-infrared spectroscopy.

Enrollment Session

Potential study candidates will be invited to an enrollment session. First, we will hand out the information sheet and answer any questions the candidates may have. To assess full eligibility, the candidates will have to fill in questionnaires and perform additional hearing tests before data collection. Bilateral CI users will be asked to turn off and remove the audio processor of the worse hearing ear to limit acoustic stimulation exclusively to the better ear. The worse hearing ear will be covered using an ear plug. The full enrollment session will take a maximum of 30 minutes.

Questionnaires

Questions on medical history will target the candidates' handedness (Edinburgh Handedness Inventory) and the presence of diseases, which are among the exclusion criteria [33-35]. Additional questions on health status will inquire about the presence of influences that could alter the brain activity of interest, such as the use of stimulants [36]. CI users will receive questions about the duration of their hearing loss, and if they have tinnitus, about the objectivity and laterality of their tinnitus [37]. The Hearing Ability Questionnaires will investigate lipreading experience and hearing-associated factors, including the Speech, Spatial, and Qualities (SSQ-12) questions [38]. The question sheet should cover the subjective assessment of hearing ability in the last 6 months.

Hearing Tests

The audiometric measurements and the fNIRS recordings will take place in an acoustic chamber (6 m × 4 m × 2 m) with a separate ventilation system and electromagnetic shielding. The broadband reverberation time is ~200 ms.

In normal hearing participants, we will assess pure tone air-conduction hearing thresholds with a clinical audiometer (GSI 61, Grason-Stadler). The findings must confirm that participants have no hidden or undetected hearing loss (Table 1). For CI users, audiograms are available from clinical routine measurements.

In all participants, we will measure the word recognition score for Freiburg monosyllabic word lists at a sound pressure level (SPL) of 65 dB [39]. Additionally, we will perform the widely used Oldenburg Sentence Test (OLSA) [40-42]. The sentences will be played with 65 dB SPL background noise, using an adaptive version of the female OLSA test [43-45]. The OLSA sentences will also be used as a stimulus during the fNIRS measurement. Speech material will be presented from a loudspeaker (Control 1 Pro) placed in front of the participants at a distance of 1 m.

Data Collection Session

Experimental Setup

During fNIRS recording, each study participant will sit in a comfortable chair with an armrest, headrest, and lumbar support (Figure 1). A desk will be placed in front of the participant with the electrical equipment. Visual stimuli will be presented through a computer screen (P2210, Dell) placed on the table at a distance of 120 cm in front of the participant. The acoustic stimuli will be played through a loudspeaker (8040B, Genelec) placed above the monitor at a distance of 130 cm from the ears. The loudspeaker will receive input from an external ASIO sound card (Scarlett 2i2, FocusRite) connected to the control laptop (XPS 13, Dell) via USB. The system will be calibrated to 65 dB SPL with the OLSA calibration noise and an acoustic analyzer (XL2, NTi Audio).

The stimulation protocol will be controlled by a custom-written script (Python 3.8.8) using Tkinter and python-vlc libraries. The script will send triggers via the serial interface to a trigger-box (MMBT-S Interface Box, NEUROSPEC AG), which converts the signals to transistor-transistor Logic (TTL) levels. The TTL-encoded signals will then be received by the fNIRS machine (FOIRE-3000, Shimadzu).

Participants will interact with the control laptop using the buttons of a mouse (WM527, Dell). The pointing function of the mouse will be disabled to ensure that participants control the experiment only by clicking and rolling. During the fNIRS measurement, the participants will be able to press an alarm button (Switchbox, Delock) positioned in a reachable distance on the table.

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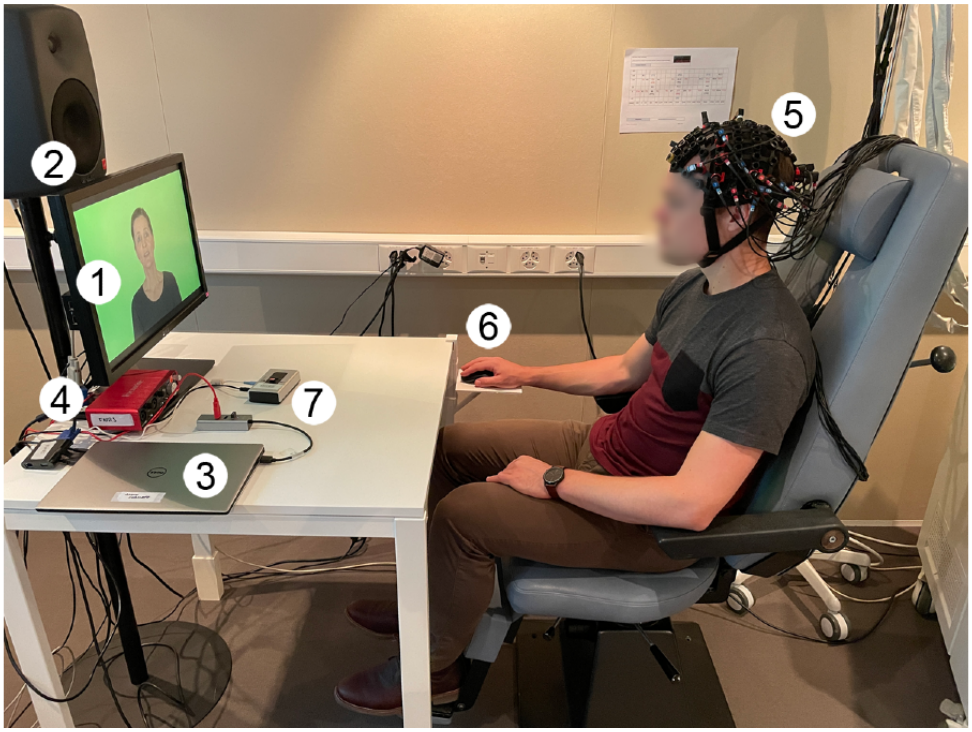
Figure 1. Experimental setup during functional near-infrared spectroscopy (fNIRS) recording. The participant will receive the stimulation via the computer screen (1) and the loudspeaker (2). The loudspeaker will be connected to the control laptop (3) via an external soundcard (4). The fNIRS cap (5) will be fitted on the participant's head, and the subject will interact using a response mouse (6). The alarm button (7) will be positioned in front of the subject.



Optode Placement

We will select the regions of interest (ROIs) for the placement of the optodes considering previous studies. We expect responses related to audiovisual speech comprehension in the auditory and visual cortex, more specifically in the following ROIs: superior temporal gyrus (STG), primary visual cortex (V1), and visual association cortex (V2) [28,31,46-50]. Additionally, during similar conditions, the left inferior frontal gyrus (LIFG) has been associated with effortful listening [27,51], and elevated cortical responses have been reported in the middle temporal gyrus (MTG) and middle frontal gyrus (MFG) [52]. Based on the defined ROIs, we will determine the optimal selection of EEG coordinates using the fNIRS optode's location decider (fOLD) toolbox [53]. We will further consider the position of the audio processor and receiver coil in CI participants to avoid interference with optodes.

The montage will consist of 16 sources and 16 detectors placed on the surface of the skull according to the international 10-10 system of electrode placement (Figure 2A) [54]. The source-detector pairs will result in a total of 43 channels in a multidistance setup: 3 of them are short-separation channels with a 15-mm interoptode distance, 4 are extra-long channels with a distance of 36-37 mm, and 36 are normal length channels that are approximately 30 mm apart. In a multidistance approach, shorter channels (15 mm) provide information about the interfering systemic signals in the outer cortex and longer channels (36+ mm) about brain activation in deep regions [55,56]. Practically, however, the signal-to-noise ratio may be poor in long distances, so in many cases we will not be able to use those channels. The Monte Carlo sensitivity simulation of all source-detector pairs is shown in Figure 2B and indicates a uniform sensitivity profile across the temporal, visual, and prefrontal cortical regions [57]. The sampling rate will be set to 14 Hz.

The optode holder cap will be assembled using the manufacturer's components (Holder kit, Shimadzu) and custom 3D printed parts (colored optode markers and stabilizers for different head sizes). The parts will be designed in a solid modelling software (SolidWorks 2019, Dassault Systemes) and printed using a 3D printer (Prusa i3 MK3S+, Prusa Research).

At the end of the experiment, we will digitize the position of all optodes with a depth sensing camera (Structure Sensor Pro, Occipital Inc) connected to an iPad (iPad Pro 2020, Apple Inc). The depth sensing camera will be set up for optimized scanning of dark objects with low ambient infrared light. The infrared exposure time, gain, and depth resolution will be set to the highest available settings so that the colored optode markers can be easily identified on the 3D scan.

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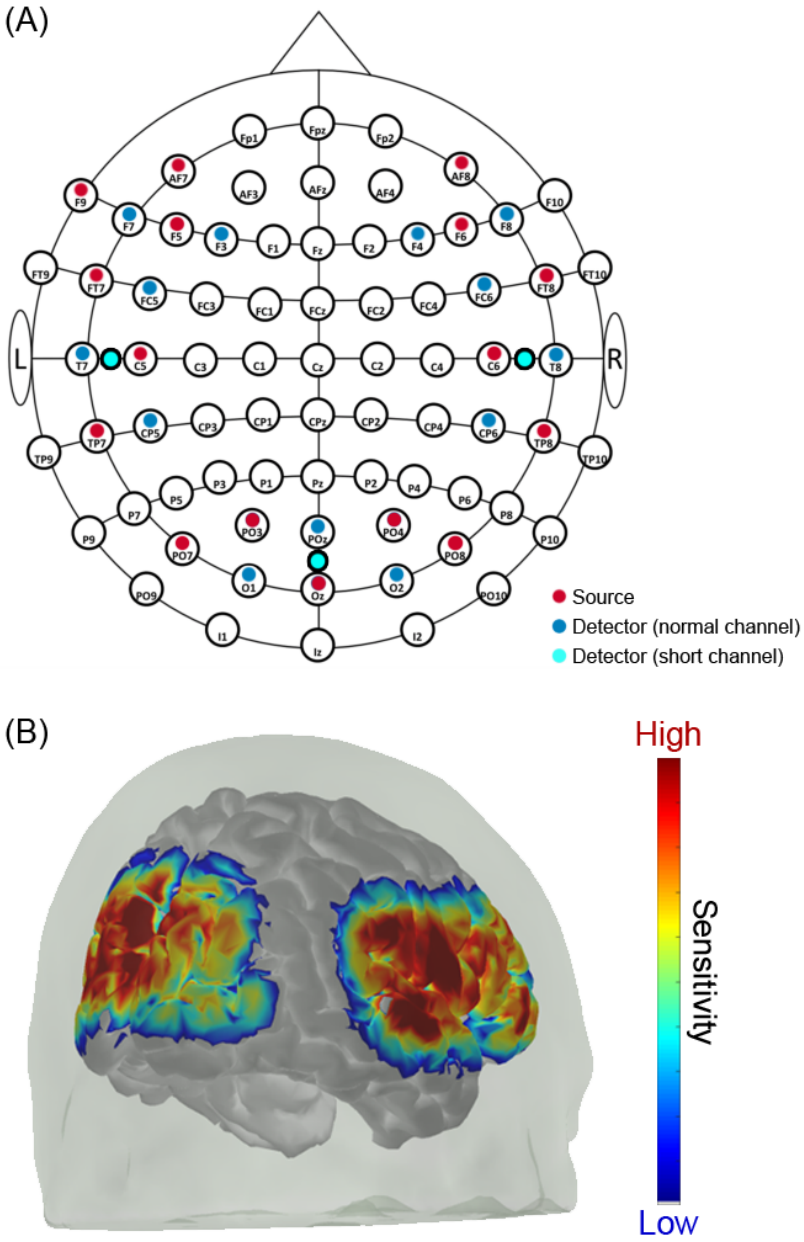
Figure 2. Functional near-infrared spectroscopy (fNIRS) montage. (A) Optode arrangement on the head. Sixteen sources (red circles) and 16 detectors (blue and cyan circles) will be placed on the scalp, forming a total of 43 channels. Three of the detectors (cyan circles) will be forming short-separation channels. (B) Sensitivity map of the optode arrangement.



Functional Near-Infrared Spectroscopy

During fNIRS recordings, we will instruct the participants to concentrate on the screen, follow the instructions, and reduce head movements. If the participants feel uncomfortable, an emergency button in front of them will be made available to stop the experiment. We will give all instructions both verbally and in writing. Before the recordings, the participants will conduct a short familiarization session with 4 example stimulations. Once the participant confirms that the task is understood, we will start the definitive recording. The functional recordings will begin with a 5-minute resting state period (Figure 3A). We will instruct the participant to sit still, close their eyes, and relax but try not to fall asleep. Then 2 stimulation sessions approximately 12 minutes each will follow. Between the 3 sessions (ie, the resting and the 2 stimulation sessions), the participants can take a break of their chosen duration.

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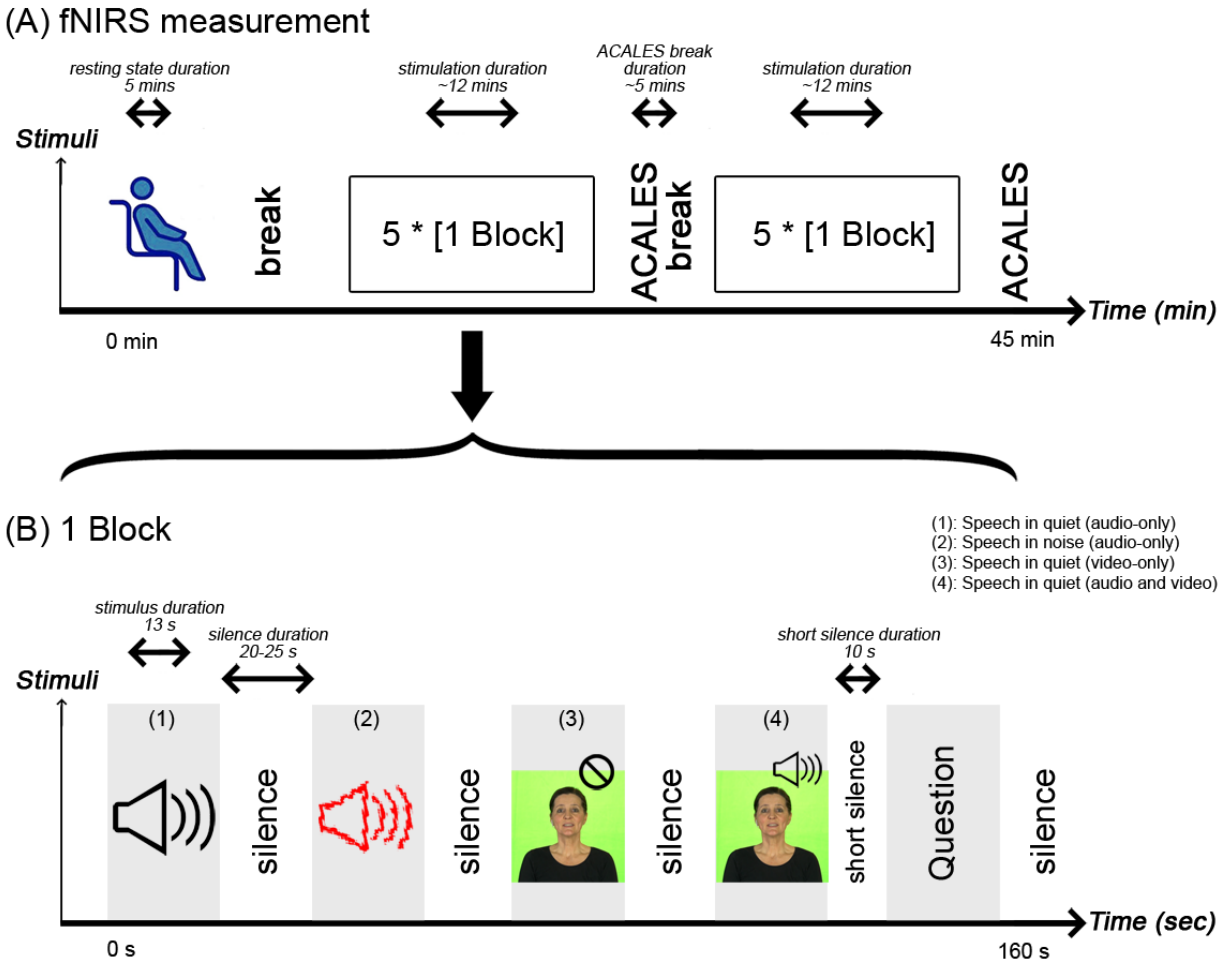
Figure 3. Functional near-infrared spectroscopy (fNIRS) measurement overview. (A) Following the resting state measurement, 2 x 5 counterbalanced blocks will be presented, with breaks in between. (A) A single block consists of a (1) speech in quiet (audio only), (2) speech in noise (audio only), (3) speech in quiet (video only), (4) speech in quiet (audio and video) stimulation, and an additional question.



Stimuli

As stimulus material, we will use a video version of the female OLSA test [40,58]. A single stimulus will consist of one sentence (eg, “Nina gives twelve red flowers”) which will be repeated 3 times. The duration of one stimulus will be 13 seconds, comparable to hemodynamic responses [59].

A single stimulation block will contain 4 different stimuli, presented in one of the following modalities in a counterbalanced order (Figure 3B): (1) speech in quiet (audio only), (2) speech in noise (audio only), (3) speech in quiet (video only, ie, lipreading), and (4) speech in quiet (audio and video). The stimulation will be followed by 20-25 seconds of nonstimulus interval, during which a white fixation point will be presented on a black screen. During the audio-only conditions, the same black screen will be displayed so that the participant will have no indication other than hearing whether the stimulation has already started or not.

At random points, participants will be asked to answer questions to ensure attention and monitor speech comprehension during the test. The questions will be displayed in the nonstimulus epoch, for which the nonstimulus interval will be shortened to 10 seconds. The questions will ask to repeat the correct name or number of the last sentence from 4 possible answers. For example, if the sentence is “Nina gives 12 red flowers,” the question is either ”How many red flowers?“ or ”Who gives 12 red flowers?“ To answer the question, the participant will have to select 1 of 4 choices: 2 randomly selected numbers/names from the OLSA sentence matrix (wrong answers), an option if the respondent is not sure of the answer (skipped answer), and the correct answer. For the previous question, a possible combination could be (1) ”Britta,” (2) “Nina,” (3) “Peter,” and (4) “I cannot decide.” The participant will select an option with the roller on the computer mouse and confirm the answer with a double click. In the previous example, the participant must select the second option (”Nina“). The questions and the answers will be randomly generated, and the position of the question within the blocks will also be randomly chosen.

The shortened nonstimulus interval of 10 seconds prior to the question window will allow us to evaluate the fNIRS responses. Therefore, the interleaved questions will not harm the overall effectiveness of the measurement. After the question is answered, the regular 20-25 second relaxation time will be applied to ensure that the brain responses return to baseline. Overall, 2 questions per modality will be asked, resulting in 8 questions throughout the entire fNIRS measurement.

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Following the breaks, before the first stimulation, there will be a stimulus-free interval of 20 seconds. This will ensure homogeneity of responses, meaning that all stimuli are perceived under similar circumstances. Overall, 10 blocks will be presented, resulting in 10 responses per stimulation modality, and the total fNIRS measurement time will be around 45 minutes. At the beginning of every event (start/stop of a block, resting state, stimulation, question, answer), a trigger will be sent from the control computer to the fNIRS machine through the trigger-box and stored as an extra channel in the fNIRS raw data.

Listening Effort

Following 5 stimulation blocks, we will ask every participant to rate their listening effort to the different stimuli, their rating of fatigue and their level of mind-wandering (Figure 3A) [60-64]. To evaluate the listening effort, we will use Adaptive Categorical Listening Effort Scaling (ACALES) [65].

Data Management

All written source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. For each participant, a case report form (CRF) will be maintained, including the participant number. In CRFs and other project-specific documents, participants are only identified by a unique participant number. fNIRS measurements will be stored in a closed research environment (REDCap, Vanderbilt University, Nashville, United States). The secure web application is running on a local server maintained and backed up by the University of Bern. All documents related to the study, including the CRFs will be considered as source data, and these will be stored at the measurement site in accordance with relevant standards.

Data Analysis

fNIRS Preprocessing

Data preprocessing will be performed in MATLAB (MathWorks) using the Homer2 (v2.3) [66] and NIRS [67] toolboxes. The signal quality will be checked based on the heart rate content of the signal, using a sliding window approach [68-71]. Channels and time points with insufficient signal quality will be removed. Short channel correction will be applied to the absorbance data, using short separation regression [56,72]. The motion artifacts will be removed with a WaveletFilter module of the NIRS toolbox [67]. The signal will be bandpass filtered between 0.01 and 0.12 Hz with the BandpassFilter function from the Homer toolbox [66]. Then, the absorbance data will be converted to concentration changes of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in mMolar*cm using the following equations, as specified by the manufacturer based on the modified Beer-Lambert law [73]:

$$\Delta HbO = (-1.4887) * Abs[780nm] + 0.5970 * Abs[805nm] + 1.4878 * Abs[830nm]$$

$$\Delta HbR = 1.8545 * Abs[780nm] - 0.2394 * Abs[805nm] - 1.0947 * Abs[830nm]$$

A further correction step will be performed to reduce noise based on the principle that the concentration changes of oxygenated and deoxygenated hemoglobin should be negatively correlated [74].

Optode Positions

We will perform the postprocessing of the scans with a 3D mesh processing tool (MeshLab) and custom-written scripts (MathWorks) [75].

We will manually select the coordinates of the optodes and anatomical landmarks with MeshLab on the obtained 3D scans. The list of coordinates will then be exported and projected into Montreal Neurological Institute (MNI) space. The MNI coordinates will be displayed on the preoperative MRI scan of every CI-user participant, and the exact source of measured hemodynamic activation will be determined. Additionally, the mean and the standard deviation of optode coordinates will be calculated and reported as quality measure for optode fittings [55,76].

fNIRS Recordings

Data analysis will be performed in Python using the MNE-Toolbox [77] and MNE-NIRS package [78]. Individual epochs will be subtracted from the channel data, from t=0 seconds to *t*=24 seconds relative to the stimulus onset. The epochs will be baseline-corrected by subtracting the mean of the signal between t =−5 seconds and t=0 seconds. Using the Glover canonical hemodynamic response function [79] a design matrix for the general linear model (GLM) will be constructed [80,81]. After GLM fitting, the regression results will be stored. Following this, temporal and spatial features will be extracted from each epoch (amplitude, area under curve, peak latency, laterality, power). The regression results and the extracted features will be weight-averaged over ROIs by taking the inverse of the standard error of the GLM fit for each channel [67]. The data will be averaged over the participants, and group-level statistics will be calculated using correlation analysis and linear mixed-effects models.

Behavioral Data

The answers from the questionnaires will be digitized, and correlation analysis will be performed to reveal relations between the measured brain activation patterns and the evaluated questionnaires. Additionally, further behavioral data will be obtained from the triggers, such as reaction time to questions across the measurement as a measure of fatigue or response accuracy for each stimulation type as a measure of speech understanding.

Results

The enrollment for the study described in this protocol started in August 2021. The first results are expected at the end of 2022.

Discussion

The postoperative adaptive or maladaptive effect of existing cross-modal reorganization in CI candidates is a complex question. The available studies show contradictory findings. A recent review states that it is important to discuss the methodological aspects of such functional neuroimaging examinations [22-26,46,47,50]. One problem with measuring

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functional brain activation is that many variables must be considered. To better control these variables, we present hereby an audiovisual speech comprehension task that fulfills the 6 points outlined below.

First, the test should be deducible from clinically established hearing tests. We used the video version of a widely used clinical test (Oldenburg Sentence Test) [58]. Functional brain activation patterns can therefore be correlated with clinical findings. These results are easier to interpret than custom-made speech materials [23,46,47,50]. Our employed stimulation design consists of complete sentences, which reflect everyday life and real language comprehension much better than nonspeech auditory stimuli or speech snippets [13,23,25,28,46,47]. Before conducting the fNIRS experiment, we will repeat clinical speech comprehension tests (ie, Freiburg monosyllabic test, Oldenburg Sentence Test). This enables a clear grouping of the CI participants into good and poor performers. During the fNIRS experiment, we will continue to assess speech comprehension in 4 different situations (ie, speech in quiet, speech in noise, visual-speech, audiovisual speech) with interleaved comprehension questions. This allows us to maintain attention and monitor speech comprehension while measuring brain activity. This advantage has only been applied by one research group [22,24]. To assess listening effort during the fNIRS task, we will use a validated questionnaire (ie, ACALES) [65]. Listening effort in CI users is an active topic of discussion [82]; its possible influence on the measured cortical activation, to the best of our knowledge, has never been reported before. To describe the subjective hearing perception in their daily lives, participants will complete validated questionnaires (ie, SSQ-12) on the day of the test [38]. We will conduct our tests in a validated audio chamber (as used in clinically performed hearing tests).

Second, the task should induce maximal cortical activation (and thus allow reproducible recognition of activation patterns). We use an optimized counterbalanced block design. The duration of 1 stimulus will be 13 seconds, and the interstimulus break will be between 20 and 25 seconds, comparable to hemodynamic responses [49,59]. Our task requires the active participation of the participants. Previous studies have shown that this can significantly increase brain activation [63,64]. Furthermore, we mitigate mind wandering and fatigue by filling out validated questionnaires [60-62]. As far as we know, in persons with hearing impairments, this has never been reported in the context of fNIRS measurements. To avoid fatigue (which can lead to decreased brain activation), we keep the fNIRS task as short as possible. Additionally, participants can take 2 breaks of self-selected duration.

Third, it should be in alignment with the international 10-10 system of electrode placement, using optimally spaced optode positions with maximal coverage over the responsible brain regions. Short separation channels should allow noise reduction. Our optode placement covers the following brain regions: superior temporal gyrus (STG), primary visual cortex (V1), visual association cortex (V2), left inferior frontal gyrus (LIFG), middle temporal gyrus (MTG), and middle frontal gyrus (MFG). This allows us to study not only audiovisual activations but also speech perception in noise, the effects of fatigue, and activity related to higher-order cortical processing. Many other studies have not had the opportunity to cover such a wide range of cortical regions, mostly due to hardware limitations [22-25,50]. We use the Edinburgh Handedness Inventory to control for handedness, which might affect the laterality of brain activation [33-35]. We also perform a spatial registration of optode positions to increase reproducibility. Furthermore, these measured positions can be projected into MNI space and displayed on MRI images. In the diagnostic workup, MRI are routinely performed prior to CI surgery. The method will allow a more accurate localization of hemodynamic responses compared to atlas-based approaches [55,76].

Additionally, we use a multidistance channel setup. The optodes of the regular channels are ~30 mm apart from each other. Additional short channels with a 15-mm interoptode distance over the auditory and visual cortex provide extracerebral information to remove confounding systemic signals. It is recommended to use a systemic physiology controlled fNIRS approach, although this has rarely been applied in previous studies [55].

Fourth, it should be time efficient to avoid fatigue due to experiment duration. The longest task the participants will be required to complete will last 12 minutes, and the total measurement time will be around 45 minutes. Regular breaks will be provided, and the total duration of the experiment is expected to be around 120-150 minutes.

Fifth, it should be suitable for participants with normal hearing, hearing impairments, and those using CIs. The audio material is presented through a loudspeaker, so the task is suitable for people with normal hearing as well as for hearing aid and CI users. Alternatively, an insert earphone or a direct CI audio input simulation would be feasible. However, these 2 approaches have the disadvantage that the 3 aforementioned groups cannot not be stimulated identically. Our optode placement was chosen to allow for easy attachment of the implant coil.

Sixth, it should be reproducible by other research groups. The audiovisual version of the OLSA was published in 2021 and is now accessible [58]. Moreover, we are happy to share our setup upon request.

In summary, the proposed audiovisual speech comprehension task will help us understand neural correlates to speech understanding. In the first stage, we will perform these measurements postoperatively to better understand the corresponding neuronal networks with an activated implant. In the subsequent stage, we will perform the measurements pre- and postoperatively to make prognostic calculations. The comprehensive study will have the potential to provide additional prognostic information beyond the conventional clinical standards regarding the underlying plastic brain changes of a person with hearing impairment. Our study will facilitate more precise indication criteria for cochlear implantation and a better planning of rehabilitation.

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Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Neurological, cardiac, psychiatric, or other major diseases used as exclusion criteria.
[PDF File (Adobe PDF File), 50 KB - resprot_v11i6e38407_app1.pdf]

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Abbreviations

ACALES: Adaptive Categorical Listening Effort Scaling
CI: cochlear implant

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CRF: case report form
EEG: electroencephalography
fNIRS: functional near-infrared spectroscopy
GLM: general linear model
HbO: oxygenated hemoglobin
HbR: deoxygenated hemoglobin
HL: hearing level
LIFG: left inferior frontal gyrus
MFG: and middle frontal gyrus
MNI: Montreal Neurological Institute
MRI: magnetic resonance imaging
MTG: middle temporal gyrus
OLSA: Oldenburg Sentence Test
PTA: pure-tone average
ROI: region of interest
SPL: sound pressure level
SSQ-12: Speech, Spatial, and Qualities
STG: superior temporal gyrus
TTL: Transistor-Transistor Logic
V1: primary visual cortex
V2: visual association cortex

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Protocol

The First National Remote Emergency System for Malignant Hyperthermia (MH-NRES) in China: Protocol for the Design, Development, and Evaluation of a WeChat Applet

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Abstract

Background: Malignant hyperthermia (MH) is a rare life-threatening anesthetic emergency. With respect to the high fatality rate, difficulty in early recognition, and the lack of disease-specific drug (ie, dantrolene) in China, more effort is needed to strengthen early diagnosis and effective treatment of MH emergencies. Nowadays, mobile health (mHealth) apps are changing the way of medical practice; they can serve as an accessible tool to help anesthesiologists deal with MH crises. However, no related mHealth-based emergency system is available currently.

Objective: The aim of this study is to outline the protocol for the development of a WeChat applet used to design a National Remote Emergency System for Malignant Hyperthermia (MH-NRES) in China, as well as the protocol for the evaluation of the user experience and perception of the system.

Methods: The system adopts the client-server architecture, with a custom user interface operating as clients and the back-end system operating as the server. The client-side software was developed using uni-app technology with Vue.js-based framework, which consists of 6 modules: Quick Diagnosis, Dantrolene Mobilization, Instruction on Dantrolene Use, MH Treatment, Recovery Period Treatment, and DNA Test and Biopsy. The back-end system was developed based on the Spring framework. The system will be evaluated by administrating a modified user version of the Mobile App Rating Scale. Pilot testing will be conducted in Sichuan Province, China, and a subsequent evaluation on a national scale is planned.

Results: The theoretical framework design of this system was completed in August 2021. The development of the system was completed in February 2022, and the refinement is currently ongoing. Pilot testing after the implementation of the system in Sichuan Province is planned to take 2 months, and the subsequent evaluation on a national scale is planned to take 2 months.

Conclusions: We have described a novel approach using the WeChat applet to develop the MH-NRES. Findings from the usability testing process in the current study may lead to refinements and is expected to suggest that this system is both feasible and welcomed by anesthesiologists. Depending on the availability of research funding, this system will be extended nationally across China.

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KEYWORDS

malignant hyperthermia; hyperthermia; anesthetic; anesthesia; anesthesiology; anesthesiologist; mHealth; mobile health; health app; evaluation; user experience; perception; development; uni-app; digital health; national remote emergency system; WeChat; emergency; WeChat applet; dantrolene; China; Chinese; applet; messaging app; calling app; diagnosis; diagnostic service

Introduction

Malignant hyperthermia (MH) is a progressive life-threatening pharmacogenetic disorder of skeletal muscle occurring during general anesthesia. MH is usually triggered by exposure to any of the potent inhalational anesthetics or succinylcholine [1,2]. It is manifested by sustained skeletal muscle hypermetabolism related to altered calcium homeostasis [3]. MH is a rare anesthetic emergency. The incidence of MH reactions has been estimated to range from 1 per 10,000 to 1 per 150,000 general anesthetic procedures [4,5]. Nevertheless, MH should not be neglected as it is a fatal medical emergency in the operating room. However, the diagnosis of an acute MH reaction can be difficult because of the nonspecific nature and variable incidence of many of the clinical signs and laboratory findings [6]. Anesthesiologists need to recognize it in its early stages and begin appropriate management without any delay [7]. In China, there has been increased recognition and publication of MH cases in recent years [8-10]. Over the past 35 years, a reported total of 136 MH events occurred in mainland China according to data from the nonprofit academic organization China MH Emergency Assistance Group [11]. However, knowledge about the recognition and management of MH is still lacking among anesthesiologists [8]. The mortality rate of MH was as high as 55.9% [11], which was similar to the range reported in the pre-dantrolene era in the United States [2]. More effort is needed to strengthen early diagnosis and effective treatment of MH cases in the Chinese medical community, especially among anesthesiologists.

Furthermore, the lack of intravenous (IV) dantrolene in most Chinese hospitals is the major limitation in MH treatment [8]. Dantrolene is the only disease-specific drug available for MH. The fatality rate of MH has dropped from 70% in the 1970s to 9.5% after IV dantrolene became commercially available in the United State in 1981, according to a report from the Malignant Hyperthermia Association of the United States (MHAUS) [2]. Nevertheless, few hospitals in China stored IV dantrolene because the imported IV dantrolene was not on the list of government-approved drugs in China in the past. To address this problem, domestic IV dantrolene was produced by a Chinese pharmaceutical company (Livzon Pharmaceutical Group Co) and approved by the Chinese Food and Drug Administration in 2020. However, it is difficult for IV dantrolene to be stocked in all Chinese hospitals where general anesthesia is performed because of the low incidence and poor awareness of MH and the high cost of dantrolene. A more realistic solution would be that IV dantrolene is stored in a portion of the major hospitals within a reasonable distance and mobilized as soon as possible when an MH emergency occurs.

In recent years, as smartphones have become widely used in China, mobile health (mHealth) apps are changing the way of medical practice. Given the high fatality rate of MH and lack of information among anesthesiologists in China, it is necessary to implement a national remote emergency system for MH. However, no mHealth apps that can help anesthesiologists deal with MH crises were available until now. We planned to develop this system as an applet of the WeChat app. This would have several benefits. First, WeChat is an extremely popular social app in China [12]. By 2016, WeChat was installed in more than 94% of smartphones in China. When needed, anesthesiologists could find this system quickly by searching for this applet in WeChat without taking time to download a new app. Second, the applet in WeChat is easy to operate and can offer multiple functions, such as text and voice messages, free voice and video calls, group chats, and subscription to public accounts. Therefore, this WeChat applet might have the potential to help anesthesiologists improve the management of MH in emergency situations.

The primary aim of this paper is to outline the protocol for the development of a WeChat applet used to design the National Remote Emergency System for Malignant Hyperthermia (MH-NRES), a free mHealth WeChat applet providing a paperless, user-friendly solution for quick diagnosis, the rapid initiation of MH treatment, and dantrolene mobilization. The secondary aim of the paper is to describe the protocol for the evaluation of the user experience and perception of the system.

Methods

Software System Development

Basic Applet Conception

We built the MH-NRES as an applet of WeChat. We took into account several important considerations of the design. First, the applet should ensure quick access without the hindrances of registration and authorization (not exceeding >1 minute). Second, the system needs to be user friendly with ease for quick data entry (not exceeding >2 minutes). Third, the accuracy of all MH-related medical knowledge should be ensured. Fourth, there needs to be a back-end server that stores the data for future analysis. Finally, all information related to MH must be presented in a way that is easily read and interpreted.

Technical Specifications

The system adopts the client-server architecture, with a custom user interface (UI) operating as clients (service requesters) and the back-end system operating as the server (service provider) to securely store the data.

The client-side software was developed using uni-app technology. Uni-app is a Vue.js-based framework for software developers, with good cross-platform compatibility (ability to work on multiple operating systems; eg, it supports Android, iOS, H5, and multiple applet formats). The Vue.js-based framework features application programming interfaces, which only focuses on view layers. It simplifies the integration with third-party databases or existing projects. The interactive UI of

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the system uses ColorUI (version 2.1.6; Xiaogang Wen). ColorUI is a highly customizable Cascading Style Sheets styles gallery, providing common elements and components that can be integrated into other elements or components.

The back-end system was developed based on the Spring framework. Spring is an open-source app framework on the Java platform that includes containers with the inversion of control characteristics and provides a series of solutions for development. The app server follows the hierarchical structure of SpringBoot—Data Access Object, Service, and Controller. The Controller layer allows the client side to implement logic task by accessing the application programming interfaces. We used a widely used database management system called Oracle database to capture, query, and administer the data collected by the applet. As a general database system, it has complete data management functions.

UI Design

Design Overview

The theoretical framework design of UI used MindMaster Software (version 9.0.4; Yitu Software). The UI was designed to be user friendly with little-to-no training time. The content is written in Chinese. The UI provides forms with checkboxes, radio buttons, text-input boxes, and numeric sliders to make data input quick and simple. This system permits access to all anesthesiologists (and is not limited to anesthesiologists). When opening the applet, the user is asked to log in with their smartphone number and dynamic certification code and provide the purpose of this log-in (review or an encounter with a suspected MH patient). The back-end server will store this information which would facilitate the data tracking of suspected MH cases and subsequently the establishment of the database. There are 6 major modules visibly placed on the home page including Quick Diagnosis, Dantrolene Mobilization, Instruction on Dantrolene Use, MH Treatment, Recovery Period Treatment, and DNA Test and Biopsy (Figure 1A).

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Figure 1. The user interface design of the National Remote Emergency System for Malignant Hyperthermia (MH-NRES), including (A) the Home Page, (B) the Quick Diagnosis forum, (C) an example of Malignant Hyperthermia (MH) rank and the corresponding recommendation in the Quick Diagnosis forum, (D) the Dantrolene Mobilization forum, (E) the Instruction on Dantrolene Use forum, and (F) the MH Treatment forum.

Quick Diagnosis

The Quick Diagnosis forum is the most prominent part on the home page, which can be quickly seen by users. Users can make a quick diagnosis by self-diagnosing according to the Scoring Rule for the MH Clinical Grading Scale [6,13] (Figure 1B). The Clinical Grading Scale provides the qualitative likelihood of an MH event, which consists of 7 categories: rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, family history, and other indicators. Each category corresponds to several clinical indicators. Users can use the checkboxes to select each present clinical indicator, and all inputs are stored on the server and accessible to the user for re-evaluation. Points are assigned for each present clinical indicator—if more than 1 indicator represents a single category, only the indicator with the highest score is counted; these points are then added to produce a raw score. The raw score was designed to be translated into an MH rank designating the risk of MH occurring, from 1 (almost never) to 6 (almost certain; Multimedia Appendix 1). Different MH ranks corresponds to different intervention recommendations (an example of MH rank 5 and the corresponding recommendation is shown in Figure 1C). For MH ranks 1 and 2, the recommendation is "Re-evaluation" or "Differential Diagnosis"; for MH rank 3, the recommendation is "Re-evaluation" and to observe the patients closely; for MH ranks 4 to 6, a sparkling "SOS" will emerge to alert the anesthesiologists of a highly likely MH crisis, and "MH Treatment," "Dantrolene Mobilization," and "Dantrolene Use" are recommended. The texts of "Re-evaluation," "Differential Diagnosis," "MH Treatment," "Dantrolene Mobilization," and "Dantrolene Use" were designed as tabs hyperlinked to new UIs to give the users detailed information. After self-diagnosing, alternatively, anesthesiologists can ask for help from experts either through

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the experts' hotline or by contacting the administrator (LT) to join the China MH Emergency Assistance WeChat Group.

Dantrolene Mobilization

If the likelihood of an MH event is graded at ranks 4-6, then dantrolene administration is the most important intervention. Users could use the function of Dantrolene Mobilization when dantrolene is not available in their hospital. In this forum, dantrolene could be mobilized in 3 steps (Figure 1D). Step 1 involves calculating the minimum number of dantrolene vials needed according to the formula. The minimum dose corresponds to the initial dose administrated (1 mg/kg for Asian people based on actual bodyweight) [13]. Step 2 involves finding the appropriate drug suppliers. A list of the nationwide drug suppliers (hospitals or pharmaceutical companies) with available preparations was established. The information of the suppliers' name and location, the distance away from the user's hospital, the amount of the drug in stock, and contact telephone number were collected and presented. We established the following rules to order the drug suppliers displayed in the UI: (1) the shortest distance away from the users' hospital, and (2) the amount of the drug in stock exceeding the minimum initial dosage. According to the geographical location of the users and the quantity of dantrolene needed, the institutions that can provide dantrolene are intelligently selected and displayed in order. Step 3 involves selecting an institution and dialing the contact number to start dantrolene mobilization.

Instruction on Dantrolene Use

This forum provides information on how to use dantrolene. The instruction on dantrolene use is based on the Malignant hyperthermia 2020 Guideline from the Association of Anesthetists [7] and the drug direction of the domestic dantrolene sodium injection produced by Livzon Pharmaceutical Group Co. The UI consists of 5 parts: Preparation of Dantrolene, Dantrolene for Acute MH Reaction, Dantrolene for MH Recurrence, Treatment Goals, and Side Effects (Figure 1E). Each part is hyperlinked to the corresponding text description when clicked by the users [14] (Multimedia Appendix 2).

MH Treatment

According to the principles of treatment, this forum lists the management protocol of an MH emergency (eg, administer dantrolene, notify the surgeon, discontinue triggering agents, optimize oxygenation and ventilation, etc; Figure 1F). Each intervention is a tab hyperlinked to a new UI to give the users detailed information [7] (Multimedia Appendix 3).

Recovery Period Treatment

This forum consists of 3 parts: Monitoring, Clinical Signs for Recurrence, and Dantrolene for MH Recurrence. Each part is a tab hyperlinked to a new UI to give the users detailed information [7] (Multimedia Appendix 4).

DNA Test and Biopsy

This forum provides diagnostic services for suspected MH patients and their family. There are 2 options for the investigation of MH susceptibility [15]. The first option is DNA screening, which is relatively cheap, minimally invasive, and convenient for the patients. The "DNA Test" part provides users with the information of the available centers for DNA testing and instructions for blood sampling. Notably, DNA screening only has approximately 50% sensitivity for detecting MH susceptibility [16]. A definitive diagnosis of MH susceptibility relies on specialized tests carried out on freshly excised muscle strips taken from open biopsy (the in vitro contracture test) [15]. Unfortunately, the muscle biopsy test is not conducted in China, so the "Biopsy" part only provides users with some theoretical knowledge about biopsy.

Evaluation of the MH-NRES

Modified User Version of the Mobile App Rating Scale

After the development of a fully functional smartphone-based prototype, usability testing of this system will be conducted with a modified user version of the Mobile App Rating Scale (uMARS) in 2 stages. The app interface designs will be trialed with anesthesiologists. The first stage is a pilot test that will be conducted by informal user reviews from 20 members of the Anesthesiology Committee of Sichuan Medical Association in Sichuan Province. The second stage is a nationwide sample survey. The target participants are 20 anesthesiologists working in the top 10 Chinese university–affiliated hospitals of anesthesiology. The uMARS is derived from the Mobile App Rating Scale and is a validated mobile app evaluation tool that has been used extensively to rate the quality of medical apps [17]. The original version of uMARS comprises the following 3 domains to evaluate an app using a Likert-type rating scale: (1) quality score, which examines engagement, functionality, aesthetics, and content information; (2) subjective quality, which questions the likelihood of recommending the app to others, use in the future, overall rating, etc; and (3) behavior change, which assesses the perceived impacts on knowledge, attitude, awareness, and behavior [17]. The modified uMARS comprises 25 questions by retaining those questions that are relevant to the current applet. Since the applet was designed to be used as an aid when an adverse anesthetic event (clinical MH) occurs, we excluded the items evaluating entertainment and interest in the engagement domain. As the applet is free and a nonprofit property, we excluded the question "Would you pay for this applet?" Moreover, user perceptions will be collected with 2 open-ended questions: (1) If you decide to use or not use this app, what are the possible reasons for it? and (2) What improvements do you want to see in future versions of the app? (Multimedia Appendix 5)

Data Analysis

SPSS statistical software (version 23.0; IBM Corp) will be used for all quantitative data analysis including participant demographic data and the subscales and total scores of the uMARS. Descriptive statistics will be used to show continuous variables as mean (SD) and categorical variables as frequency and percentage. The open-ended questions will be reviewed by 2 researchers (HY and LT) independently. Qualitative data will be organized into meaningful groups by combining similar patterns into themes.

Quality Control

Quality control strategies are being implemented. The principal investigator (XD) works closely with research staff in the applet

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design, development, and evaluation process. Team meetings are conducted every 1 or 2 weeks for progress updates and problem-solving. Discussion and debriefing are conducted promptly if needed. All the knowledge about MH in this system is derived from the Malignant hyperthermia 2020 Guideline from the Association of Anesthetists [7] in China and the UpToDate website [18].

Ethics Approval

The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This trial was approved by the Institutional Review Board of West China Hospital of Sichuan University on November 11, 2021 (Ethical number: 2021-1446). All data will be treated anonymously to protect personal privacy. Private information such as patients' name and ID number will not be input during any operating steps. If the experts' hotline is initiated, only the patient's hospital will be disclosed. Informed consent will be sought from patients before subsequent gene diagnosis, family counseling, and MH database construction.

Results

The theoretical framework design of this system was completed in August 2021. The development of the system was completed in February 2022, and the refinement is currently ongoing. Pilot testing after the implementation of the system in Sichuan Province is planned to take 2 months, and the subsequent survey on a national scale is planned to take 2 months. The project is supported by the National Natural Science Foundation of China (72074162).

Discussion

Comparison With Prior Work

MH is a rare life-threatening anesthetic emergency, which has been found to occur worldwide including in China. The current status of MH in mainland China is still not optimistic as problems regarding the underestimation of the incidence, poor recognition and diagnosis, and the lack of specific treatment still exist [19]. This study will provide valuable information on the development and evaluation of the MH-NRES, which is aimed at providing a real-time and effective emergency system to help Chinese anesthesiologists deal with MH crises.

In the United States, a nonprofit organization, MHAUS, provides a 24-hour MH hotline to give real-time advice to professionals in handling MH crises. However, this approach may not be suitable for Chinese users. First, the language barrier cannot be ignored. Second, a hotline is not as readily available in the operating room as smartphone apps. Third, it cannot support the dantrolene mobilization that is practical and necessary in China. Nevertheless, Chinese experts have made a lot of efforts to improve the management of MH. A WeChat chat group (China MH Emergency Assistance Group) was established in 2015. This chat group is composed of MH experts from large academic medical centers and anesthesiologists from different levels of hospitals in China. However, it has some limitations. First, this group can only accommodate 500 members from 300 hospitals with many grassroots hospitals excluded. Second, the system highly relies on real-time direction from experts, but the help-seeking message might be obscured by other irrelevant messages. Third, anesthesiologists need to filter the suitable information from a large number of expert suggestions, which may be time-consuming and beyond their ability. Compared to the MHAUS and China MH Emergency Assistance Group, the MH-NRES might be a more effective real-time emergency system for MH in China. The MH-NRES is available for free and can be accessed quickly by all anesthesiologists. The system provides standard and evidence-based knowledge of MH and updated, real-world information of the amount of dantrolene in stock. The use of this system can assist anesthesiologists in China to make rapid diagnosis, implement effective management, initiate dantrolene mobilization in real time when MH cases occur, and provide subsequent gene diagnostic services and family counseling. The results from the user evaluation in this study will improve future versions of the system. The long-term impact of this system is expected to be beneficial, as it could increase anesthesiologists' ability to deal with MH crises, increase dantrolene use, and consequently improve the prognosis of MH patients.

Strengths and Limitations

The WeChat applet–based MH-NRES is different from other mHealth-based emergency system of MH (ie, the WeChat help groups) in China. First, besides providing direction to the experts' hotline, this system can guide anesthesiologists to conduct self-diagnosis and manage MH. Second, it displays all service types without requiring specific user identification, and there is no limitation to the number of people online. Third, this study provides a guide to the architecture and framework for developing a national remote emergency system, which can be applied to design similar systems for other clinical emergencies. Fourth, the data collected by the system are helpful to building the first national MH database and obtaining a better estimate of the incidence of MH in China. With respect to the limitations, we expect that the results from the evaluation of user experience and perception could help us improve future versions of the system.

Conclusions

We have described a novel approach using the WeChat applet to develop the MH-NRES. Findings from the usability testing process in this study may lead to refinements and is expected to suggest that this system is both feasible and welcomed by anesthesiologists. Depending on the availability of research funding, this system will be extended nationally across China.

Acknowledgments

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Authors' Contributions

XD is the principal investigator and responsible for the overall management of this study. XD, HY, LT, YT, YZ, and TZ conceived the study and were involved in the initial study design. KX and JY contributed to the development of the WeChat applet. HY completed the first draft of the manuscript. XD and ZX revised the manuscript. All authors contributed to reviewing the protocol and approving the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinical indicators for use in determining the Malignant Hyperthermia (MH) raw score and the corresponding MH rank.
[DOCX File , 19 KB - resprot_v11i6e37084_app1.docx]

Multimedia Appendix 2
Mapping of the Instruction on Dantrolene Use forum.
[DOCX File , 15 KB - resprot_v11i6e37084_app2.docx]

Multimedia Appendix 3
Mapping of the Malignant Hyperthermia Treatment forum.
[DOCX File , 18 KB - resprot_v11i6e37084_app3.docx]

Multimedia Appendix 4
Mapping of the Recovery Period Treatment forum.
[DOCX File , 15 KB - resprot_v11i6e37084_app4.docx]

Multimedia Appendix 5
Modified user version of the Mobile Application Rating Scale (uMARS).
[DOCX File , 27 KB - resprot_v11i6e37084_app5.docx]

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Abbreviations

IV: intravenous
MH: malignant hyperthermia
MH-NRES: National Remote Emergency System for Malignant Hyperthermia
MHAUS: Malignant Hyperthermia Association of the United States
mHealth: mobile health
UI: user interface
uMARS: user version of the Mobile App Rating Scale

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Protocol

Immersive Virtual Reality Exergames to Promote the Well-being of Community-Dwelling Older Adults: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: Despite the proven benefits of exercise in older adults, challenges such as access and motivation can deter their engagement. Interactive virtual reality (VR) games combined with exercise (exergames) are a plausible strategy to encourage physical activity among this population. However, there has been little research on the feasibility, acceptability, and potential benefits of deploying at-home VR exergames among community-dwelling older adults.

Objective: The objectives of this study are to estimate the feasibility, usability, and acceptability of a co-designed VR exergame in community-dwelling older adults; examine intervention feasibility and assessment protocols for a future large-scale trial; and provide pilot data on outcomes of interest (physical activity, exercise self-efficacy, mood, cognition, perception, and gameplay metrics).

Methods: The study will be a remote, 6-week intervention comprising an experimental and a control group. A sample of at least 12 community-dwelling older adults (with no or mild cognitive impairment) will be recruited for each group. Both groups will follow the same study procedures and assessment methods. However, the experimental group will engage with a co-designed VR exergame (*Seas The Day*) thrice weekly for approximately 20 minutes using the Oculus Quest 2 (Facebook Reality Labs) VR headset. The control group will read (instead of playing *Seas The Day*) thrice weekly for approximately 20 minutes over the 6-week period. A mixed methods evaluation will be used. Changes in physical activity, exercise self-efficacy, mood, cognition, and perception will be compared before and after acute data as well as before and after the 6 weeks between the experimental (exergaming) and control (reading) groups. Qualitative data from postintervention focus groups or interviews and informal notes and reports from all participants will be analyzed to assess the feasibility of the study protocol. Qualitative data from the experimental group will also be analyzed to assess the feasibility, usability, and acceptability of at-home VR exergames and explore perceived facilitators of and barriers to uptaking VR systems among community-dwelling older adults.

Results: The screening and recruitment process for the experimental group started in May 2021, and the data collection process will be completed by September 2021. The timeline of the recruitment process for the control group is September 2021 to December 2021. We anticipate an estimated adherence rate of ≥80%. Challenges associated with VR technology and the complexity of remote assessments are expected.

Conclusions: This pilot study will provide important information on the feasibility, acceptability, and usability of a custom-made VR exergaming intervention to promote older adults' well-being. Findings from this study will be useful to inform the methodology, design, study procedures, and assessment protocol for future large-scale trials of VR exergames with older adults as well as deepen the understanding of remote deployment and at-home use of VR for exercise in older adults.

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KEYWORDS

virtual reality; exergames; community-dwelling older adults; pilot protocol; feasibility; well-being; physical activity; cognition; perception; mood; COVID-19

Introduction

Background

Population aging is a global phenomenon. With the increase in global life expectancy (average of 73.4 years in 2019) and all baby boomers reaching >65 years of age in 2031 [1], the proportion of older adults (aged ≥60 years) is estimated to nearly double (from 12% to 22%) and increase to upwards of 2 billion individuals by 2050 worldwide [2]. The number of *oldest-old* individuals (aged ≥80 years) is increasing even faster and is expected to triple by 2050 [3]. With such a drastic shift in global population demographics, the incidence of chronic conditions and cognitive impairment is also expected to increase exponentially, leading to higher rates of disability and dependency worldwide [4-6]. In addition to decreased functional ability, cognitive changes, specifically in executive function, pose significant health and social challenges to older adults' everyday lives and independence [7-9]. This warrants research focused on strategies to foster healthy aging and reduce the impact of age-related changes in older adults' functional and cognitive abilities.

Physical activity is an established predictor of healthy aging and is associated with numerous physical and psychological health benefits in older adults. Incorporating physical activity into daily life can improve older adults' motor function, mood, cognition, quality of life, and independence [10-12]. An extensive body of literature has highlighted the positive effects of physical activity on older adults' executive functions, including processing speed, attention, inhibition, and working memory [13,14]. In particular, both a single bout of aerobic exercise and a period of aerobic exercise training have been shown to promote brain health and executive function in the older population [12,15-17]. Physical activity has also been recognized as a valuable part of preventative and therapeutic strategies for older adults living with mild cognitive impairment and people living with dementia [12,18-21]. Despite strong evidence supporting the broad physical and mental benefits of physical activity, older adults tend to be the least physically active age group, and few older adults are sufficiently active to meet the physical activity guidelines [22]. Lack of motivation and enjoyment, limited access to exercise programs or equipment, and physical limitations are some of the main reasons cited for physical inactivity among older adults [23]. For those living with cognitive impairment, physical activity participation and adherence are particularly restricted because of health challenges associated with the condition as well as poor self-efficacy, apathy, and poor access to exercise opportunities that meet their needs and capabilities [24-26].

Physical Activity in the Era of the COVID-19 Pandemic

Barriers to physical activity have been exacerbated during the COVID-19 pandemic. Countries have implemented public health measures, including program and facility closures, to contain COVID-19 infection and reduce its health, social, and economic impacts. Older adults are considered a highly vulnerable population to the impact of the COVID-19 outbreak and have faced stricter restrictions than other age groups [27,28]. Staying physically active during the COVID-19 pandemic is more difficult but is particularly important as physical activity is a protective factor against viral infections [29,30]. In addition, engaging in physical activity can be a moderating factor for mental well-being [31-33].

However, with physical distancing measures and the closure of exercise programs and fitness facilities in response to the COVID-19 pandemic, physical activity and exercise opportunities are more restricted for many older adults [34,35]. More optimistically, restrictions and changes in lifestyle as a result of COVID-19 have increased technology adoption among older adults [36-39]. Various opportunities for using novel information and communication technologies (eg, mobile apps, activity trackers, and gamified exercises) have emerged aiming to complement remote exercise programs and potentially benefit older adults' health and well-being while mitigating social distancing [40,41]. From wearables to applied games, digitally connected technologies are now filling the gap in many in-person activities that cannot be conducted because of the COVID-19 pandemic [42].

When promoting at-home physical activity, exercise video games (also known as exergames) have been shown to be a viable supportive tool to enhance older adults' well-being during the current pandemic [43-46]. Systematic reviews have shown that exergames have been successfully used to foster improvements in health-related outcomes such as pain management, posture, cognitive functioning, and decreased risk of falls among community-dwelling older adults [47]. Specific physical outcomes such as muscle strength, balance, mobility (including upper and lower limb flexibility), and cardiorespiratory fitness also improved after exposing prefrail and frail older adults to exergaming interventions [48]. Similar results were found in active older adults using exergames with floor-projected features [49]. Although Nintendo Wii and Microsoft Kinect are among the most used interactive systems, the use of immersive virtual reality (VR)—which includes a head-mounted display—is still scarce [50]. Advancements in hardware development, distribution, and accessibility are essential to increase the use of VR applications. The creation of more immersive VR technologies, which are now accessible and commercially available, has allowed for the distribution of VR-based exergames to aid the immersion and interaction of

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players in virtual environments and potentially create an engaging experience to encourage physical activity participation [51]. The main difference of VR exergames compared with traditional exergames is the use of head-mounted displays to provide a more immersive experience, potentially leading to a more consistent feeling of presence and agency [52]. However, deploying VR exergaming technology for older adults' at-home exercise, especially during a pandemic, can be complex for various reasons, such as (1) technology access (eg, the cost is still similar to state-of-the-art video gaming consoles) [47], (2) technical complexities (eg, hardware calibration and launching the games as well as content appropriateness), (3) older adults' technology literacy, and (4) challenges of remote deployment and testing to capture potential physical and mental outcome measures [52]. Moreover, although the multisensory environment of VR exergames can be tailored to the participants' functional and cognitive abilities [53], research on preferences for VR activities and interactions among older adults and systematic evaluation of VR exergames is limited [54]. This makes the creation and deployment of home-based VR exergames for older adults challenging; and to our knowledge, it has not been done remotely before.

The long-term objective of our research is to develop and assess VR exergames that enable greater access to exercise opportunities for older adults. Therefore, the proposed pilot study aims to determine the feasibility, usability, and acceptability of a 6-week VR exergame intervention and the feasibility of the assessment protocol among community-dwelling older adults. Changes in potential outcomes for a larger-scale trial will also be explored, including physical activity, exercise self-efficacy, mood, cognition, and perception. The pilot gameplay data enable an exploration between game metrics and outcome performance, which will allow for the estimation of whether data from the game can be used for real-time assessments and other such applications.

Methods

Study Design

This is a 6-week pilot study to examine the feasibility, acceptability, and usefulness of a co-designed VR exergame intervention among older adults as well as the feasibility of the study procedures and assessment protocol. A control group will be used to account for practice and exposure effects and will follow the same protocol as that described for the experimental group without exposure to the exergame; they will read 3 times a week for 15 to 20 minutes instead of engaging with our exergames. To maintain consistency between the control and experimental conditions, the same questionnaires and surveys will be completed by all the participants in both groups, except for the *perceived enjoyment* and *rate of perceived exertion (RPE)* scales, which will be completed only by the experimental group. Both qualitative and quantitative methods will be used to provide pilot data on potential outcomes of interest. Although this study will evaluate the feasibility of both the study intervention and study control arms, we will not randomize the participants. Participants in the intervention arm will be recruited first, followed by a wave of participants recruited to the control group. The study is based in Waterloo but will be carried out remotely, so participants from across Canada will be eligible.

Study Sample and Recruitment

A combination of convenience and snowball sampling will be used for the purposes of this study. To be eligible, participants must be aged ≥60 years, living in a community setting in Canada, and able to communicate in English and provide consent on their own behalf. The participants must have access to a computing device (computer or tablet) and a reliable internet connection at their place of residence to complete the web-based assessments and tasks. Participants in both groups must be able to safely participate in light to moderate unsupervised activity without requiring a physician's approval as assessed using the Get Active Questionnaire (GAQ) [55,56]. Exclusion criteria include (1) diagnosis of moderate or severe dementia or a score <18 on the Montreal Cognitive Assessment (MoCA; version 8.1-Telemed) [57,58]; (2) self-reported severe motion sickness or commonly experienced motion sickness or nausea when driving or sitting in a car, train, or bus; (3) self-reported hearing impairment that may interfere with the participant's ability to hear and understand the auditory cues in the cognitive and perceptual tasks; (4) uncorrected visual impairment (eg, cataracts, glaucoma, or macular degeneration) that may interfere with the participant's ability to see and interact with the game and perform the cognitive and perceptual tasks; (5) ear infection in the previous 12 months or a diagnosis of a disease of the middle ear, such as Meniere disease; and (6) any preexisting conditions that would prevent them from engaging in exercise, including having a cardiac pacemaker. The same inclusion and exclusion criteria will be used for both the experimental and control groups to ensure internal validity.

VR Intervention

Software

For the VR exergame intervention in this study, the participants will play a custom-made VR exergame, *Seas The Day*, on an Oculus Quest 2 (Facebook Reality Labs) headset [59,60]. *Seas The Day* was designed using an extensive user-centered and participatory design process with various stakeholders, including older adults, exercise professionals, game designers, engineers in the field of human factors and assistive technologies, and a local VR studio [61]. The VR exergame simulates a remote tropical island with several different activities that are intended to encourage upper-body physical activity. The game is designed to be played seated so that fall risk is minimized. Each exergaming session lasts 15 to 20 minutes.

Seas The Day (Figure 1) includes 3 virtual locations with three different activities: (1) a tai chi warm-up, (2) a rowing conditioning exercise, and (3) a fishing cooldown. Recorded audio clips guide the participants on game activities alongside visuo-tactile cues to facilitate interaction. No buttons are needed to interact with the virtual elements. Players are automatically transported from one game stage to the next to prevent interaction errors.

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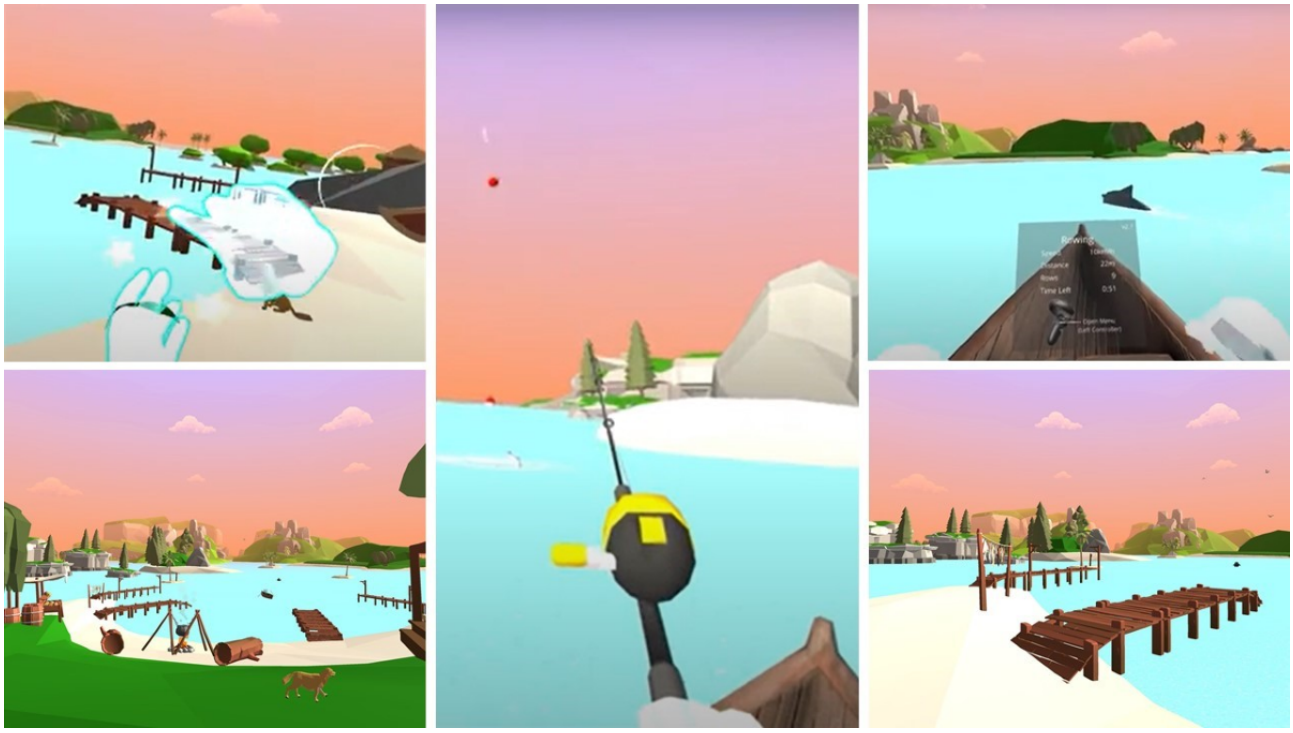
Figure 1. Screenshots of the *Seas The Day* exergame showing the tropical virtual environment and some of the activities.



Hardware

Seas The Day is designed to be played in stand-alone VR headsets. In this study, an Oculus Quest 2 will be used because of its widespread availability, relatively low weight (compared with other VR headsets), and performance when running the designed game. Two main hardware modifications will be made to the headset: (1) the conventional foam cover will be replaced with a silicon cover to facilitate cleaning and sanitization of the headset and (2) the conventional strap will be replaced with a more comfortable strap (ie, Elite Strap) [62], which allows for a more simplified way to adjust the headset (Figure 2 and Multimedia Appendix 1).

Figure 2. Participants playing the *Seas The Day* exergame using Oculus Quest 2 (Facebook Reality Labs).

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Procedure

The participants will be asked to play *Seas The Day* 3 times a week for 6 weeks. *Seas The Day* will be the only game that the participants will have access to in the provided VR headset. The participants will be encouraged to maintain consistency in engaging with the VR exergame by playing in the mornings and preferably on the same days every week. They will be notified that each exergame session will take approximately 15 to 20 minutes and encouraged to achieve a light to moderate intensity when playing the game. Setup and ongoing participation in the intervention will be supported in a number of ways. First, the participants will be provided with step-by-step software and hardware manuals (Multimedia Appendix 2). Second, each participant will meet with the study staff or trainees for a remote introductory session via a videoconference platform. The team member will show the participants how to use the system while sharing their screen so that the participants can see and become familiar with the visual information and the overall interaction with the system. The team member will also demonstrate how to calibrate the system and play the game, stage by stage, and answer any questions as they arise. The participants will then be encouraged to interact with the system and try playing the exergame in the presence of the team member and speaking aloud about what they are seeing and experiencing so they can be guided if facing any difficulties. Finally, the participants will be able to contact the study staff and trainees to troubleshoot the system via email, phone, SMS text message, or video calls at any time as most appropriate for the situation and the participant's comfort. To facilitate troubleshooting video calls, the participants will be offered screen-sharing options to facilitate the explanation as well as a view from the frontal camera of the computer to see how the team member is located and moving in the physical space.

Ethics Approval

This study has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Committee (experimental group 42908, control group 43379).

Data Collection and Assessments

Screening

The participants will complete a verbal informed consent agreement before taking part in the study and will be screened (via email or telephone) for eligibility using (1) a custom-made screening questionnaire and (2) the GAQ. The custom-made screening questionnaire is developed by the research team and includes questions on the study's inclusion and exclusion criteria. The GAQ, developed by the Canadian Society for Exercise Physiology [56], is a prescreening measure for physical activity to ensure the participants' safety when partaking in at-home exercise. The GAQ includes sections on preparing to become more physically active, assessing current physical activity, and general advice for becoming more active. A record of ineligible cases and those who did not provide consent to participate in the study will be kept in the screening log to inform the recruitment process. No further information will be collected from these cases.

Demographics

Background and demographic data will be obtained through (1) a demographic questionnaire, (2) the remote MoCA (version 8.1-Telemed) [58], and (3) the short version of the Geriatric Depression Scale-15 (GDS-15) [63]. The demographic questionnaire is developed by the research team and collects basic information of the participants (eg, age, sex, gender, and education), their health (eg, perceived physical and mental well-being, history of falls, and hearing and vision impairments), and previous experiences with gaming and motion sickness. The MoCA is a validated screening tool for cognitive impairment with high sensitivity and specificity for detecting mild cognitive impairment and dementia [57]. The MoCA will not be used for diagnostic purposes but will be used by the researchers to gain insight regarding the sample's baseline cognition (a MoCA score of <13 suggests severe cognitive impairment; this study will use a cutoff score of ≥18 for study inclusion). The remote audiovisual administration of the MoCA will be conducted by a trained researcher. The GDS-15 is a widely used depression assessment tool that is specifically designed for older adults. Similar to the MoCA, the purpose of using the GDS-15 is to gain insight into the sample's baseline depressive symptoms (if any). The GDS-15 consists of 15 questions about how the participant has felt over the previous week.

Outcomes and Measures

Overview

All participants will complete assessments at baseline and after the intervention (follow-up). Upon completion of the study (in a period of 8 weeks), semistructured focus groups or interviews will be conducted (with distinct questions for the control vs the experimental groups), and informal notes and reports will also be obtained from both the experimental and control groups. All participants will complete the exercise self-efficacy questionnaire; further acute changes in executive function, multisensory integration, and mood before and after gameplay or reading will also be assessed. In addition, the experimental group will complete the RPE [64] and perceived enjoyment scales upon completion of each exergaming session. All questionnaires except for RPE and perceived enjoyment for the experimental group will be completed on the web using Qualtrics survey software (Qualtrics International Inc) [65]. Refer to Table 1 for a summary of the outcomes and instruments used in this study and Table 2 for the study timeline.

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Table 1. Summary of outcome measures and instruments.

Outcome measures	Instrument
Primary outcome measures	
Background and demographic data	• Demographic questionnaire • MoCA[a] • GDS-15[b] • GAQ[c]
Feasibility, usability, and accessibility of at-home VR[d] exergaming	• Self-reported physical (eg, motion sickness, vertigo, or nausea) or emotional (eg, fear or anxiety) discomfort • Ad hoc usability and game user experience questionnaire • Perceived enjoyment • Exergaming session adherence rate • Informal notes and reports • Semistructured focus groups or interviews
Feasibility of the study protocol	• Consent and recruitment rate • Attrition and retention rate • Activity log • Rate of missing data • Semistructured focus groups or interviews
Secondary outcome measures	
Physical activity level	• PASE[e] • RPE[f]
Executive function	• Modified flanker task • OTMT[g] (part A and B) • VF[h] (animal naming)
Multisensory integration and temporal perception	• RT[i] task • SJ[j] task • SIFI[k] • TOJ[l] task
Affect	• PAAS[m]
Exercise self-efficacy	• Bandura exercise self-efficacy scale

[a]MoCA: Montreal Cognitive Assessment.
[b]GDS-15: Geriatric Depression Scale-15.
[c]GAQ: Get Active Questionnaire.
[d]VR: virtual reality.
[e]PASE: Physical Activity Scale for the Elderly.
[f]RPE: rate of perceived exertion.
[g]OTMT: Oral Trail Making Test.
[h]VF: verbal fluency.
[i]RT: response time.
[j]SJ: simultaneity judgment.
[k]SIFI: sound-induced flash illusion.
[l]TOJ: temporal-order judgment.
[m]PAAS: Physical Activity Affect Scale.

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Table 2. Summary of the study timeline.

Outcome measure and instrument	Time points													
	Baseline	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Follow-up
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	
Background and demographics														
Demographic questionnaire	✓													
MoCA[a]	✓													
GDS-15[b]	✓													
GAQ[c]	✓													
Executive function														
OTMT[d] (A and B)	✓	✓	✓			✓	✓			✓	✓			✓
VF[e]	✓	✓	✓			✓	✓			✓	✓			✓
Modified flanker task	✓	✓	✓			✓	✓			✓	✓			✓
Multisensory i ntegration and temporal perception														
SIFI[f] task	✓			✓	✓			✓	✓			✓	✓	✓
SJ[g] task	✓													✓
TOJ[h] task	✓													✓
RT[i] task	✓	✓	✓			✓	✓			✓	✓			✓
Physical activity, mood, and exercise self-efficacy														
PAAS[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PASE[k]	✓													✓
Exercise self-efficacy	✓				✓				✓				✓	
RPE[l]			✓		✓		✓		✓		✓		✓	
Perceived enjoyment			✓		✓		✓		✓		✓		✓	
Usability and game user experience questionnaire														✓

[a]MoCA: Montreal Cognitive Assessment.

[b]GDS-15: Geriatric Depression Scale-15.

[c]GAQ: Get Active Questionnaire.

[d]OTMT: Oral Trail Making Test (part A and B).

[e]VF: verbal fluency (animal naming).

[f]SIFI: sound-induced flash illusion.

[g]SJ: simultaneity judgment.

[h]TOJ: temporal-order judgment.

[i]RT: response time.

[j]PAAS: Physical Activity Affect Scale.

[k]PASE: Physical Activity Scale for the Elderly.

[l]RPE: rate of perceived exertion.

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Feasibility of the Study Protocol and VR Exergaming

The rates of recruitment, attrition, retention, and missing data will be used to assess the feasibility of the study protocol. The feasibility, usability, and accessibility of *Seas The Day* will be assessed using quantitative and qualitative data. Quantitative data will be collected from (1) an ad hoc usability and game user experience questionnaire, (2) the participants' adherence rate to the exergaming sessions, and (3) the participants' perceived enjoyment. Qualitative data will be obtained from (1) self-reported physical (eg, motion sickness, vertigo, or nausea) or emotional (eg, fear or anxiety) discomfort (if any), (2) the participants' informal notes and reports, and (3) semistructured focus groups or interviews.

The ad hoc usability and game user experience questionnaire is developed by the research team. Subscales of validated usability and acceptability models [66,67] are used in this questionnaire to explore users' attitudes and intentions of using VR exergame systems (eg, perceived usefulness, perceived ease of use, perceived enjoyment, and intention to use in the future). The participants will be asked to rank each question from 1 to 5 based on how much they agree with each statement. The participants' perceived enjoyment will be assessed using a paper-based, pictorial 5-point Likert scale ranging from *not enjoyable at all* to *extremely enjoyable*.

Semistructured focus groups or interviews (approximately 60 minutes) will be conducted to obtain in-depth information regarding each participant's experience of the study procedures and measures. For the experimental group in particular, focus groups or interviews will be used to gain more insight into the participants' perceived feasibility, acceptability, and usability of the VR exergaming system (eg, satisfaction, ease of use, engagement, safety, and motion sickness). Facilitators of and barriers to the adoption of and adherence to the VR exergaming system will also be explored in focus groups or interviews. For the control group, the focus groups or interviews will be used to gain insight regarding technology use and adoption and obtain feedback on the web-based tasks and assessments.

Executive Function

Measures of executive function will consist of a web-based modified flanker task, the Oral Trail Making Test (OTMT) parts A and B, and a verbal fluency (VF) test (animal naming). The modified flanker task includes a set of response inhibition tests to assess the ability of the participants to suppress responses that are inappropriate in a particular context [68,69]. In total, 3 types of stimuli—incongruent, congruent, and neutral—will be represented by arrowheads. In all sessions, the participants will be asked to complete 4 blocks: 1 practice block consisting of 30 mixed stimuli (10 experiments per flanker arrow type) to help familiarize the participants with the task, 2 blocks consisting of 100 trials (20 incongruent and 80 congruent flanker arrows [70]), and 1 block consisting of 100 trials (all neutral flanker arrows). The display duration of the flanker arrows will be 150 ms, and the intertrial interval duration (from a + sign to the next) will be 1500 ms (−100 to +100 ms). The participants will be asked to sit in a quiet room while directly facing their computing device. They will be instructed to keep their index fingers on the right and left arrow keys of their computer keyboard (to indicate the direction of the flanking arrow), look at a small white fixation cross in the middle of a black screen where the target stimuli will appear, and respond as quickly and accurately as possible. The task will take approximately 10 to 15 minutes to complete, and the participants will be able to take a break in between blocks if they wish. The OTMT is a neuropsychological test and can reflect a wide variety of cognitive processes [71-73]. The test consists of 2 conditions: condition A, in which the participants are instructed to count from 1 to 25, and condition B, in which the participants are instructed to count in an alternating numeric and alphabetic sequence (ie, 1-A-2-B). The goal of the test is for the participant to finish both parts as quickly as possible, and the time taken to complete the test will be used as the primary performance metric. The OTMT takes approximately 2 to 5 minutes to complete. VF is a widely used test of executive function in which the participants will be given 60 seconds to produce as many unique words as possible within a semantic category (ie, names of animals) [74,75]. The number of unique words will be the participant's score on this task. Both the OTMT and VF will be administered in an oral format via phone or an audio- and videoconferencing platform with the guidance of a trained researcher.

Multisensory Integration

Four web-based perceptual tasks will be performed: (1) the audiovisual response time (RT) task, (2) the sound-induced flash illusion (SIFI), (3) the simultaneity judgment (SJ) task, and (4) the temporal-order judgment (TOJ) task. The audiovisual RT, SJ, SIFI, and TOJ tasks have been specifically designed for web-based data collection. These tasks will be used to obtain various measures of sensory integration, including RT (to assess RT differences between uni- and multisensory cues), temporal binding window (TBW; the window of time during which stimuli from different modalities are bound together), and susceptibility to the SIFI (where the observer misperceives the number of visual flashes owing to the presentation of 2 auditory beeps in close temporal proximity).

The participants will be asked to sit in a quiet, dark room while directly facing their computing device, which will be placed at arm's length. The visual stimuli will be presented in the form of white circles, subtending approximately 2° of visual angle. The visual stimuli will appear approximately 8° below the fixation cross (visual angle=1.5°), which will appear at the center of the screen and will remain on display throughout the trial for 16 ms. The participants will be asked to fixate on the fixation cross throughout the duration of each task. Auditory stimuli will be presented in the form of beeps (16 ms) through speakers that are either connected to the participant's device or through external speakers placed beside the screen. To reduce temporal predictability, each trial will begin with the stimulus being presented after a delay of 1000 to 3000 ms. A computer keyboard will be used by the participants to input their responses for each trial; a response from the participant will initiate the next trial for each task. The participants will complete the RT, SJ, SIFI, and TOJ tasks in a randomized order where they will be explicitly asked to respond as accurately as possible as opposed to responding quickly for the SJ, SIFI, and TOJ tasks while responding as quickly as possible for the RT task. The

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participants will be presented with practice trials before the commencement of each of the experimental tasks. The following stimulus onset asynchronies (SOAs; the amount of time between the start of one stimulus, S1, and the start of another stimulus, S2) will be used for the multimodal conditions in the SJ, TOJ, and SIFI tasks: 0 ms, −70 to +70 ms, −150 to +150 ms, and −230 to +230 ms; here, + indicates vision-led trials, whereas − indicates auditory-led trials.

For the SIFI task, there will be 3 conditions: vision-only, auditory-only, and audiovisual. In the vision-only block, 2 flashes will be presented, and the participant's task will be to indicate the number of flashes they saw. In the auditory-only block, 2 beeps will be presented, and the participants will be asked to indicate the number of beeps they heard. There will be 30 trials in each of the unimodal conditions (SOAs: 70 ms, 150 ms, and 230 ms). The audiovisual trials will consist of 2 control conditions (1 beep and 1 flash and 2 beeps and 2 flashes) as well as the illusion condition (2 beeps and 1 flash). In the audiovisual control conditions, the auditory and visual stimuli will be presented simultaneously. In the 2 beeps and 1 flash (illusory condition) auditory-led trials, the auditory stimulus will be presented first, after which the auditory and visual stimuli will be presented simultaneously following a variable SOA. In the 2 beeps and 1 flash vision-led trials, the first auditory stimulus will be accompanied by a visual stimulus, and the second auditory beep will follow a variable SOA. The 3 audiovisual conditions will be randomly presented within the testing block to avoid response bias. The participants will be asked to fixate on the fixation cross for the duration of the task, report the number of flashes seen, and ignore the auditory stimuli. All conditions will be repeated 10 times for a total of 100 trials (including 10 repetitions for 0 SOAs, where a single beep and flash will be presented simultaneously). In total, 160 trials, as well as additional practice trials, will be presented for all 3 conditions (vision-only, auditory-only, and audiovisual). This task will take approximately 5 to 10 minutes to complete.

For the SJ task, the participants will be instructed to report, using the number *1* and *2* keys on their keyboard, whether they perceived the auditory and visual stimuli as occurring simultaneously (number *1* key) or not (number *2* key). A total of 10 trials will be presented in a randomized order for each SOA, and 6 practice trials will also be presented for a total of 76 trials. This task will take approximately 5 to 10 minutes to complete. The experimental design of the TOJ task will be identical to that of the SJ task with the exception of the task instructions. In this case, the participants will be asked to report, using the number *1* and *2* keys on their keyboard, whether they perceived the visual (number *1* key) or auditory (number *2* key) stimulus as appearing first.

For the RT task, the participants will be told that they will see a flash of light, hear a beep, or a combination of the 2, and they will be instructed to press the response button (space bar key) as soon as they detect any of the 3 experimental conditions. Each condition will be presented 50 times in a random order with 6 practice trials for a total of 156 trials. However, if a participant responds too quickly (<100 ms) or takes longer than 3 seconds to respond to a trial, that trial will be repeated. This task will take approximately 5 to 10 minutes to complete.

Both the multisensory integration and modified flanker tasks will be designed using PsychoPy (Open Science Tools Ltd) and distributed on the web using Pavlovia (Open Science Tools Ltd), wherein the participants will be provided with URLs to access the tasks. All instructions will be embedded within the tasks and will not require the presence of a researcher to be completed. However, a researcher will join the participants for the duration of the first session of these tasks to ensure that all inquiries and technical difficulties are resolved as soon as they arise. Furthermore, 1 to 2 members of the research team will check in with the participants every 2 weeks to answer any questions and ensure that they are following the protocol.

Physical Activity, Exercise Self-efficacy, and Mood

The Physical Activity Scale for the Elderly (PASE) [76] and RPE will be used to assess the participants' physical activity behavior. In the PASE, the participants will be asked to self-report the frequency with which they take part in leisure, household, and occupational activities (eg, outdoor walking; light, moderate, and strenuous sports and recreation; and muscle strengthening) by indicating never, 1 to 2 days per week (seldom), 3 to 4 days per week (sometimes), or 5 to 7 days per week (often). Activity duration will be indicated as <1 hour, between 1 and 2 hours, 2 to 4 hours, or >4 hours. RPE will be assessed through a paper-based pictorial omnibus scale wherein the participants will be asked to indicate how physically exhausting the VR exergaming was using a 10-point Likert scale ranging from *extremely easy* to *extremely hard* [64].

Mood will be assessed using the Physical Activity Affect Scale (PAAS) [77]. Affective states are thought to be highly influenced by exercise, thus leading to the development of the PAAS as a concise affect measurement tool [77-79]. The PAAS has 12 items, which can be further broken down into 4 subdomains, each further broken down into 3 mood states: positive affect (upbeat, energetic, and enthusiastic), negative affect (miserable, discouraged, and crummy), physical exhaustion (tired, worn-out, and fatigued), and tranquility (calm, peaceful, and relaxed). Exercise self-efficacy will be assessed using the Bandura exercise self-efficacy scale, which is a predictor of the adoption and maintenance of exercise behavior [80]. The Bandura scale includes 9 statements, and the participants will be asked to rank each statement from 1 to 4 indicating their belief in their ability to continue exercising in the future.

Automatic Data Logging System

Seas The Day includes a data logging system that allows for the capture of data related to game events and interactions inside the virtual environment during gameplay. In every session, the data logging system locally records data using a time series at 30 Hz combining game events, scores, achievements, and kinematic information from the VR equipment (controllers and headset). The data logging system records the following information: (1) tai chi (time to complete the activity and interactions with animals [when players were looking at them]), (2) rowing (boat speed, distance traveled, number of strokes [right or left], boat collisions, and interactions with the dolphin), and (3) fishing (number of fish caught, pulling out the fishing rod [number of repetitions], and RT after the fish is hooked).

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The kinematic information is captured through the inertial motor units embedded in the 2 VR controllers and the headset, recording 3-axis accelerometer information of the 3 points (head and right and left hand). Both game variables and kinematic information are locally stored in the headset and compressed in files of 15 MB.

Statistical Analysis Plan

Sample Size

Given that the primary purpose of the study is to assess the feasibility and usability of at-home VR exergaming over a 6-week period, no formal sample size calculation will be performed [81]. However, to explore data collection processes and also inform sample size calculations for a larger trial, the study will aim to recruit at least 12 participants for both the experimental and control groups [82].

Feasibility Analysis

Feasibility will be assessed through the recruitment rate (number of participants divided by the total number of potentially eligible participants), attrition rate (percentage of participants who did not complete the study), and adherence rate (number of completed exergaming or reading sessions divided by the total number of potential exergaming or reading sessions). Appropriate qualitative analyses will be carried out to provide further details regarding the feasibility, usability, and acceptability of the VR exergame as well as the study protocol. The focus group or semistructured interview script includes open-ended questions (Multimedia Appendix 3). These questions were refined through pretesting with a volunteer group of older adults (n=5) to ensure clarity and prompt discussion relevant to the issues of immediate interest [61]. Using a focus group allows the participants to exchange viewpoints and engage in conversations with peers to express general agreement or disagreement on various aspects of our study [83,84]. Individual interviews, by contrast, allow for a deeper understanding of the participants' experiences, beliefs, and attitudes through direct, one-on-one engagement [85]. Both methods will be considered in our study; however, deciding on whether to participate in a focus group or a one-on-one interview (or both) will be based on the participants' preferences and what would be the most feasible for them.

Focus groups or interviews will be digitally recorded (via videoconferencing platforms) and transcribed verbatim. All qualitative data (ie, focus groups or interviews, self-reported physical or emotional discomfort, and the participants' informal notes and reports) will be organized and coded using NVivo (version 12; QSR International) [86]. Inductive and deductive thematic analyses (informed by the feasibility, usability, and acceptability objectives of the study) will be performed after line-by-line coding to identify key topics and patterns of meaning across the data [87-89]. Open coding and axial coding will be conducted by multiple researchers independently to enhance the rigor of data analysis [89-91]. Researchers will use reflexive memos during the coding process to reflect on the emerging themes and patterns [87,92,93]. To create a robust codebook, researchers will regularly meet to resolve any coding challenges or discrepancies. The codebook will be refined by discussing the coding scheme (as different key topics emerge) and merging or deleting overlapping codes. After a consensus is reached, the codebook will include definitions and examples of each code, and the coding process will continue until data saturation (ie, no new data and no new themes are observed) [94,95]. Codes will then be categorized to detect overarching themes as well as subcategories to support themes [87].

Outcome Analyses

Descriptive statistics will be calculated for all demographic and baseline characteristics of the participants and presented as means and SDs or percentages (n), as appropriate. Assumptions underlying the statistical procedures will be checked, and corrective procedures will be used if necessary. Statistical analyses will be performed in R Studio (R Foundation for Statistical Computing) and SPSS (IBM Corporation). Data from the cognitive and perceptual tasks will be assessed for normality using *Q*-*Q* plots, the Shapiro-Wilk test, and histograms. Homogeneity of variance will also be tested using the Mauchly sphericity test, and Greenhouse-Geisser corrections will be applied if necessary. Potential deviations from a normal distribution will be identified in all cognitive and perceptual task data sets, and log transformations will be applied to the raw skewed data if deemed necessary to transform the data into a normal distribution. Paired and independent 2-tailed *t* tests will be used to compare the baseline, follow-up, and acute scores. Repeated-measure and mixed ANOVAs will be used to analyze before and after intervention data (exergaming or reading for 6 weeks) as well as acute data (before and after 1 bout of exergaming or reading) to understand changes by time (before and after), group (control vs experimental), and day (eg, weeks 2, 4, and 6 for SIFI) to compare baseline, follow-up, and acute scores.

Executive Function

Cognitive data from the OTMT (completion time [seconds] for parts A and B separately) and VF (the number of unique animal names) will be analyzed for within-participant and between-participant variables. For the modified flanker task, the participants' mean RT and proportion error (1-accuracy) for each block of flanker responses will be obtained and further separated by congruence (congruent, incongruent, and neutral). Incorrect responses, responses that occurred 1000 ms after stimulus onset, and double responses for a single stimulus will be considered as errors and excluded from the analysis. The rate of no response and gender will be included as covariates.

Multisensory Integration

SIFI Task

Analyses will be conducted to determine whether there are differences in before and after intervention (exergaming or reading for 6 weeks) data as well as for before and after acute (1 bout of exergaming or reading) data. Analyses will be conducted separately on the proportion correct for unimodal (modality: vision-only or auditory-only) and multimodal (audiovisual conditions: nonillusory, 1 flash and 1 beep or 2 flashes and 2 beeps; or illusory, 1 flash and 2 beeps) conditions. To examine changes in susceptibility to the SIFI, sensitivity (*d*)

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will be calculated (z[hits] − z[false alarms]) for each SOA, and appropriate analyses will be conducted [96-98].

SJ and TOJ Tasks

To estimate the accuracy (point of subjective simultaneity) and precision (TBW) with which the participants make their judgments for the SJ and TOJ tasks, psychometric functions will be fitted to each participant's responses as a function of SOA. To investigate the relationships between TBWs obtained from the 2 tasks and not their absolute size, the b values (ie, SD) of these psychometric functions will be analyzed as a proxy for the size of the TBW to avoid discrepancies in the literature that differ when defining the absolute size of the TBW [99-101]. Each task will be analyzed individually for each participant, with participant data fitted to both Gaussian and logistic functions.

RT Task

Data trimming procedures will not be applied [99,102]; however, responses faster than 100 ms and slower than 1500 ms will be set to infinity rather than excluded [99,103] where this method of data trimming was used. The mean RT for each modality (auditory, visual, or audiovisual) before and after the experimental and control conditions will be calculated individually for each participant, and appropriate analyses will be conducted to determine the impact of time and modality. Acute data (before and after exergaming or reading) will also be analyzed as described previously.

Physical Activity, Exercise Self-efficacy, and Mood

The responses to the structured surveys will be cleaned and analyzed using appropriate statistical methods. Data from web-based questionnaires and surveys will be classified and analyzed using Qualtrics software [65]. In addition, PASE scores will be calculated before and after experimental (exergaming) or before and after control (reading) conditions and analyzed using paired or independent 2-tailed t tests. Responses to the PAAS will be classified into one of the 4 affective subscales: positive affect, negative affect, physical exhaustion, and tranquility [77]. Scores within each subscale will be treated as independent outcomes to identify acute changes in affective states from before to after experimental and before to after control conditions. RPE, perceived enjoyment, exercise self-efficacy, and PAAS will be analyzed to determine potential changes over time (before vs after experimental or control conditions) and across conditions (eg, subscales and intensity).

Gameplay Metrics

Game metrics captured by the data logging system will be analyzed session by session, and specific metrics associated with game performance, errors, and RT will be extracted from the described variables. First, changes in SD units for each session will be determined for 3 main variables denoting game performance on each game activity: time to complete the tai chi condition, distance traveled during the rowing condition, and the number of fish caught in the fishing condition. The number of collisions will be identified as a potential variable to quantify errors during rowing. RT will be computed in the fishing condition, where the time taken by players to pull out the fishing rod after feeling the fish being hooked (controllers vibrating) will be extracted from the data files. Time will then be filtered, and values outside the 100 to 1000 ms range will be discarded [104]. All numerical data will be presented as means and SDs.

Exploratory Analysis

To better understand the relationship between lower-level perceptual processing and multisensory integration (assessed via the RT, SIFI, SJ, and TOJ tasks) and higher-order executive function (assessed via the modified flanker task, VF, and OTMT), exploratory correlational analyses will be conducted between the outcomes of each of the perceptual tasks (eg, TBW, point of subjective simultaneity, mean RT from the multisensory and unisensory conditions, and accuracy) and the outcomes of the modified flanker task (accuracy and mean RT), VF, and OTMT. Furthermore, exploratory analyses using correlations are planned using both game metrics and cognitive assessments (ie, modified flanker and RT tasks) for RT. Partial correlation analyses, including age, sex, and previous experience with video games as covariates, will be applied when appropriate. Correlational analyses will be conducted for outcome variables obtained before and after 6 weeks of the exergame intervention and before and after acute bouts of engagement with the exergame. The Bonferroni correction will be used to correct for multiple comparisons.

Handling of Missing Data

Any missing data will be reviewed and imputed based on the assessments that the participants complete on other days. If the missing data of a variable do not depend on the value of another variable, the analysis will be performed using both the complete data set and an analysis incorporating values from multiple imputations. If the missing data are not random, then the analysis will be completed using only the complete data set; however, differences between the 2 groups with missing and observed data will be reported.

Results

This study aims for an estimated adherence rate of ≥80%. To minimize potential attrition, all participants will be provided with a thorough remote one-on-one explanation of the anticipated participation burden (time commitment) at baseline. The participants will also be contacted regularly throughout the data collection process to maintain a good working relationship and answer any questions that they may have. The participants may choose to withdraw from the study at any time and for any reason. However, they will be asked if their collected data can be used by the research team for information and data analysis purposes.

We anticipate that most of the enrolled participants will adhere to the study and follow the protocol. However, potential challenges related to nausea and motion sickness when interacting with the VR technology may lead to some dropouts in the experimental group [105-108]. Challenges related to remote assessments as well as the length and complexity of the cognitive and multisensory integration tasks may also result in attrition [109-112].

In addition, we anticipate that most participants will learn how to navigate virtual environments and successfully perform the

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proposed physical activities within the different stages of our exergame [113,114]. This can potentially lead to high levels of perceived enjoyment and study adherence, as found in similar studies using immersive VR with the same duration and frequency [115]. However, it is also expected that some older adults might need more support than others to set up the VR system and adapt to the technology [113,114,116,117]. These supports might need to be individualized and tailored as the pilot progresses.

Both the experimental and control conditions have been reviewed and received ethics clearance through the University of Waterloo Research Ethics Committee (experimental condition ethics clearance in April 2021 and control condition ethics clearance in June 2021). The screening and recruitment process for the experimental group started in May 2021, and the data collection process will be completed by September 2021. As of August 16, 2021, 15 community-dwelling older adults have enrolled in the experimental group, of whom 2 (13%) have dropped out. The recruitment process and data collection for the control group will start in September 2021 and be completed by December 2021.

Discussion

Overview

The use of immersive VR for promoting exercise among older adults is an emerging field of research with special relevance because of the COVID-19 pandemic. Social distancing measures and the closure of exercise facilities have been creating a more demanding need for effective home-based programs to encourage physical activity participation and enhance older adults' well-being. This pilot study is a result of the need to move to remote research following pandemic restrictions and rapid technological advancements and adoption.

This study aims to assess the feasibility of exploring changes in perceived levels of physical activity, exercise self-efficacy, mood, executive function, and multisensory integration. Although some studies have been validated for at-home remote administration [47,52], this approach is still not commonly used and has not yet been used in conjunction with VR exergames. Challenges related to remote research, unstable internet connection, monotony with regard to multiple sessions, computer use, human errors, and eye strain are expected during remote testing [110,111,118-120]; part of this pilot is to hone ways to mitigate and solve these challenges remotely. This pilot will add insights into the feasibility of implementing a relatively complex, remotely administered assessment protocol for older adults living at home.

This protocol also addresses unexplored research questions regarding the use of state-of-the-art VR technologies and custom-made exergames tailored to older adults for home-based programs. First, this study will examine the feasibility of deploying exercise programs using immersive VR with *Seas The Day* during the COVID-19 pandemic. The study intervention has a longer duration than the average found in similar studies of the same nature [47,52]. Other studies using immersive VR in older adults have exposed participants to VR experiences ranging from 1 to 55 minutes, with 15 minutes being the most common exposure time [47,121,122]. Although many elements are included in this study to support community-dwelling older adults to easily set up and use the VR system at home, challenges associated with system calibration, the overall use of the tracking system, and potential motion sickness, among others, are to be expected during the study [105-108,113,114].

The deployment of VR systems at home also has the novel potential to capture data during gameplay, which may be able to capture changes not only in game performance but also in older adults' well-being. In this study, the VR system will capture a broad range of variables that will be used to recreate the microinteractions and behaviors of the participants during their interaction with *Seas The Day.* Although exploratory, previous work has shown how gameplay metrics have the potential to be powerful descriptors of elements related to physical and cognitive functioning, which are very important aspects when tracking the progress and benefits of exercise programs [121,122].

Strengths and Limitations

This study will establish the feasibility of deploying a VR system to older adults across Canada for health application purposes. This study will also assess the feasibility of a complex assessment protocol. Both may provide useful insights for the future of remote, virtual research and are specific not only to VR research but also more broadly applicable.

Reaching our target population may be challenging during the COVID-19 pandemic and will likely be restricted to older adults who are open to the use of technology and have the ability to do so (eg, have a computer or tablet and internet already). In addition, older adults may be hesitant to participate because of (1) technology apprehension, (2) availability of other physical activity options (as, at the time this paper was written, the restrictions had started to loosen up), and (3) time commitment (8 weeks total, with multiple tests and web-based meetings). We plan to minimize the impact of these limitations by carrying out introductory sessions to facilitate the usability of the technology at the beginning of the trial, using stand-alone VR systems that are portable and can be used without an internet connection, and building rapport with all the participants to facilitate a long-standing research relationship and reduce the burden of taking part in this research remotely.

Another important limitation associated with this pilot study protocol is a lack of control over the VR exergame and assessment environment. Although we will strongly suggest that the participants engage with the exergames in the mornings and preferably on the same days every week, we cannot ensure that these guidelines will be followed. Unlike tasks administered in a well-controlled laboratory environment, the cognitive and perceptual tasks will be administered to the participants in the comfort of their homes through a web-based platform, which reduces our control over the size, brightness, and intensity of the stimuli. Furthermore, variations in the size and positioning of the monitor and keyboard as well as the placement of the speakers further decrease experimental control. The participants will be encouraged to maintain their environment (eg, use the

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same monitor and stay in the same room) once they complete their first session of cognitive and perceptual tasks, establishing consistency within the participants. Although these challenges may make collecting data more difficult, they also represent data that are much closer to real-world everyday use than they would be in a laboratory environment.

Finally, the small sample size of this pilot study and the disadvantages associated with self-reported questionnaires (eg, inaccurate data and social desirability bias) limit the generalizability of the results and, thus, the statistical analyses must be interpreted with caution [123,124].

Dissemination

Dissemination of the results will be led by the authors in a collaborative effort and will include (1) presentations at international conferences and publications in scientific peer-reviewed journals on topics related to active aging, older adults' physical and mental well-being, VR exergaming, or other similar areas of interest; (2) reports to the study stakeholders (eg, the VR company); (3) webinars or similar for the general public (including older adults); and (4) information sessions with exercise professionals in long-term care facilities and retirement homes to explore potential applications of *Seas The Day* as a viable way to foster physical activity in their settings.

Conclusions

This pilot study will provide insights into the feasibility, acceptability, and usability of a custom-made VR exergaming intervention to promote at-home exercise in older adults, which may potentially benefit their physical and mental well-being. Integrating qualitative and quantitative methods will help identify potential barriers to and facilitators of home-based VR exergaming and explore older adults' perspectives and required accommodations to support their uptake. Findings from this feasibility study will also be useful to inform the methodology, design, study procedures, and assessment protocol for future large-scale trials of VR at home with older adults. It is anticipated that the results from this pilot can be used by others to support the design and deployment of other remote exergames and assessments.

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Authors' Contributions

All authors contributed to the study conception and development of the pilot protocol and procedures. SM, JEM, and AB prepared and submitted relevant materials for ethics approval. SM, JEM, and AB are implementing the protocol. SM drafted the manuscript with input from JEM and AB. All authors contributed to manuscript revision and read and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
COVID-19 virtual reality exergames standard operating procedures.
[PDF File (Adobe PDF File), 535 KB - resprot_v11i6e32955_app1.pdf]

Multimedia Appendix 2
Virtual reality exergame manual.
[PDF File (Adobe PDF File), 18330 KB - resprot_v11i6e32955_app2.pdf]

Multimedia Appendix 3
Interview and focus group guide (experimental and control groups).
[PDF File (Adobe PDF File), 402 KB - resprot_v11i6e32955_app3.pdf]

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Abbreviations

GAQ: Get Active Questionnaire
GDS-15: Geriatric Depression Scale-15
MoCA: Montreal Cognitive Assessment
OTMT: Oral Trail Making Test
PAAS: Physical Activity Affect Scale
PASE: Physical Activity Scale for the Elderly
RPE: rate of perceived exertion
RT: response time
SIFI: sound-induced flash illusion
SJ: simultaneity judgment
SOA: stimulus onset asynchrony
TBW: temporal binding window
TOJ: temporal-order judgment
VF: verbal fluency
VR: virtual reality

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Corrigenda and Addenda

Correction: Natural Language Processing to Identify Digital Learning Tools in Postgraduate Family Medicine: Protocol for a Scoping Review

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Related Article:

Correction of: https://www.researchprotocols.org/2022/5/e34575

(JMIR Res Protoc 2022;11(6):e40454) doi:10.2196/40454

In "Natural Language Processing to Identify Digital Learning Tools in Postgraduate Family Medicine: Protocol for a Scoping Review" (JMIR Res Protoc 2022;11(5):e34575) the authors noted two errors.

1. In the *Abstract* of the originally published article, the trial registration details did not appear correctly. These details have been corrected as follows:

> *OSF Registries osf.io/wju4k; https://osf.io/wju4k*

2. In the originally published *Ethics Approval* section under *Methods*, the statement regarding trial registration appeared as follows:

> *The study was registered with the Open Science Framework (0.17605/OSF.IO/WJU4K).*

It has been corrected as follows:

> *The study was registered with the OSF Registries (osf.io/wju4k).*

The correction will appear in the online version of the paper on the JMIR Publications website on June 24, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Aerobic Exercise in HIV-Associated Neurocognitive Disorders: Protocol for a Randomized Controlled Trial

Martins Nweke[1], MSc; Nombeko Mshunqane[2], PhD; Nalini Govender[3], PhD; Aderonke Akinpelu[4], PhD; Adesola Ogunniyi[5], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2022/1/e29230

(JMIR Res Protoc 2022;11(6):e40486) doi:10.2196/40486

In "Aerobic Exercise in HIV-Associated Neurocognitive Disorders: Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2022;11(1):e29230) the authors noted one error.

The name of the second author was incorrectly displayed as:

Mshunqane Nombeko

It has now been corrected to:

Nombeko Mshunqane

The correction will appear in the online version of the paper on the JMIR Publications website on June 28, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Neural Activity During Audiovisual Speech Processing: Protocol For a Functional Neuroimaging Study

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Related Article:

Correction of: https://www.researchprotocols.org/2022/6/e38407

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In "Neural Activity During Audiovisual Speech Processing: Protocol for a Functional Neuroimaging Study" (JMIR Res Protoc 2022;11(6):e38407), the authors noted one error.

The originally published article appeared with an incorrect Abstract. In the corrected version, the Abstract is updated as follows:

> ***Background:*** *Functional near-infrared spectroscopy (fNIRS) studies have demonstrated associations between hearing outcomes after cochlear implantation and plastic brain changes. However, inconsistent results make it difficult to draw conclusions. A major problem is that many variables need to be controlled. To gain further understanding, a careful preparation and planning of such a functional neuroimaging task is key.*
>
> ***Objective:*** *Using fNIRS, our main objective is to develop a well-controlled audiovisual speech comprehension task to study brain activation in individuals with normal hearing and hearing impairment (including cochlear implant users). The task should be deductible from clinically established tests, induce maximal cortical activation, use optimal coverage of relevant brain regions, and be reproducible by other research groups.*
>
> ***Methods:*** *The protocol will consist of a 5-minute resting state and 2 stimulation periods that are 12 minutes each. During the stimulation periods, 13-second video recordings of the clinically established Oldenburg Sentence Test (OLSA) will be presented. Stimuli will be presented in 4 different modalities: (1) speech in quiet, (2) speech in noise, (3) visual only (ie, lipreading), and (4) audiovisual speech. Each stimulus type will be repeated 10 times in a counterbalanced block design. Interactive question windows will monitor speech comprehension during the task. After the measurement, we will perform a 3D scan to digitize optode positions and verify the covered anatomical locations.*
>
> ***Results:*** *This paper reports the study protocol. Enrollment for the study started in August 2021. We expect to publish our first results by the end of 2022.*
>
> ***Conclusions:*** *The proposed audiovisual speech comprehension task will help elucidate neural correlates to speech understanding. The comprehensive study will have the potential to provide additional information beyond the conventional clinical standards about the underlying plastic brain changes of a hearing-impaired person. It will facilitate more precise indication criteria for cochlear implantation and better planning of rehabilitation.*

The correction will appear in the online version of the paper on the JMIR Publications website on June 28, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Passive Sensor Data for Characterizing States of Increased Risk for Eating Disorder Behaviors in the Digital Phenotyping Arm of the Binge Eating Genetics Initiative: Protocol for an Observational Study

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Abstract

Background: Data that can be easily, efficiently, and safely collected via cell phones and other digital devices have great potential for clinical application. Here, we focus on how these data could be used to refine and augment intervention strategies for binge eating disorder (BED) and bulimia nervosa (BN), conditions that lack highly efficacious, enduring, and accessible treatments. These data are easy to collect digitally but are highly complex and present unique methodological challenges that invite innovative solutions.

Objective: We describe the digital phenotyping component of the Binge Eating Genetics Initiative, which uses personal digital device data to capture dynamic patterns of risk for binge and purge episodes. Characteristic data signatures will ultimately be used to develop personalized models of eating disorder pathologies and just-in-time interventions to reduce risk for related behaviors. Here, we focus on the methods used to prepare the data for analysis and discuss how these approaches can be generalized beyond the current application.

Methods: The University of North Carolina Biomedical Institutional Review Board approved all study procedures. Participants who met diagnostic criteria for BED or BN provided real time assessments of eating behaviors and feelings through the Recovery Record app delivered on iPhones and the Apple Watches. Continuous passive measures of physiological activation (heart rate) and physical activity (step count) were collected from Apple Watches over 30 days. Data were cleaned to account for user and device recording errors, including duplicate entries and unreliable heart rate and step values. Across participants, the proportion of data points removed during cleaning ranged from <0.1% to 2.4%, depending on the data source. To prepare the data for multivariate time series analysis, we used a novel data handling approach to address variable measurement frequency across data sources and devices. This involved mapping heart rate, step count, feeling ratings, and eating disorder behaviors onto simultaneous minute-level time series that will enable the characterization of individual- and group-level regulatory dynamics preceding and following binge and purge episodes.

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Results: Data collection and cleaning are complete. Between August 2017 and May 2021, 1019 participants provided an average of 25 days of data yielding 3,419,937 heart rate values, 1,635,993 step counts, 8274 binge or purge events, and 85,200 feeling observations. Analysis will begin in spring 2022.

Conclusions: We provide a detailed description of the methods used to collect, clean, and prepare personal digital device data from one component of a large, longitudinal eating disorder study. The results will identify digital signatures of increased risk for binge and purge events, which may ultimately be used to create digital interventions for BED and BN. Our goal is to contribute to increased transparency in the handling and analysis of personal digital device data.

Trial Registration: ClinicalTrials.gov NCT04162574; https://clinicaltrials.gov/ct2/show/NCT04162574

International Registered Report Identifier (IRRID): DERR1-10.2196/38294

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KEYWORDS

digital phenotyping; eating disorders; personal digital devices; methodology

Introduction

Background

The widespread adoption of smartphones and consumer wearables (eg, the Fitbit and Apple Watch) by the public provides clinical researchers with exciting opportunities for studying and augmenting interventions for mental health disorders. However, this innovation also presents unique complications when using personal digital devices for research purposes. To maximize the potential of these opportunities, it is necessary for mental health researchers to be aware of both the capabilities and limitations of personal digital devices. We provide a general introduction to these methodological issues and describe the use of personal digital devices for characterizing binge and purge episodes in the Binge Eating Genetics Initiative (BEGIN) [1].

Over the past decade, advances in digital technology have led to a significant increase in the affordability and accessibility of personal digital devices, including smartphones and consumer wearables. Current estimates suggest that approximately 80% of the global population are active smartphone users, which is up from the 49% reported in 2016 [2]. Furthermore, although smartphone ownership is highest among individuals 18 to 49 years old in countries with advanced economies [3], growing research suggests that the digital divide is also narrowing among older adults [4], individuals affected by serious mental illness [5], and in countries with emerging economies [3]. Therefore, by capitalizing on the near ubiquity and the acceptability of personal digital devices, mental health researchers have the opportunity to reach larger and more representative populations than ever before.

In addition to the opportunities for increased scalability in mental health research, advances in the capabilities of personal digital devices also provide researchers with unprecedented access to real time behavioral and physiological data. Especially valuable is the ability to use personal digital devices to access data that are collected unobtrusively and continuously while individuals go about their daily lives. These types of data are commonly referred to as "passive" data and include sensor data (eg, GPS location, locomotion, and light level) and higher order features derived from the sensors (eg, type of activity and sleep), as well as information about device usage (eg, call and text logs or social media usage), proximity to other personal digital device users via Bluetooth, voice samples, lexical analysis, and metadata (eg, battery level and time to respond to a text or questionnaire).

In combination with self-reported (or "active") data collected from personal digital device users, researchers are able to use passive data to draw inferences about the individual and contextual factors preceding and following a particular behavior or event of interest. This process of using digital traces to draw inferences about individuals' psychological state is a methodology commonly referred to as digital phenotyping. Similar to other terms, such as personal sensing [6,7], reality mining [8], and personal informatics [9], digital phenotyping was defined by Torous and colleagues [10] as the "moment-by-moment quantification of the individual-level human phenotype in situ using data from smartphones and other personal digital devices." Digital phenotyping studies have gained increasing popularity in mental health research in the past 5 years and are being conducted on an ever-increasing range of psychological disorders (eg, social anxiety [11], depression and bipolar disorder [12], psychosis [13,14], and suicidal or nonsuicidal self-injury, the last for which Torous et al provide a review of the research [15]).

The seemingly limitless opportunities that personal digital devices offer mental health researchers are accompanied by several unique challenges, many of which stem from the fact that smartphones and consumer wearables are designed with user experience at the forefront. These devices must be aesthetically pleasing; easy to use, carry, or wear; have sufficient battery life and storage capacity; and provide their users with a high level of data privacy and security. However, achieving these goals comes at the expense of data that mental health researchers might desire. For example, to preserve battery power and optimize user experience, data collected from personal digital devices may be available at a less intensive sampling rate than what would be available from a comparable research grade device [16]. Similarly, to maximize user safety and privacy, data collected from personal digital devices are typically available in the form of summary values (eg, daily step count) created by proprietary algorithms. These design elements present challenges for researchers regarding what the data actually represent, and make it difficult to combine data collected from

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different devices or operating systems due to inconsistencies in the algorithms used. To address the issues of proprietary algorithms, multiple companies now exist (eg, Beiwe, the AWARE Framework, and The Effortless Assessment of Risk States [EARS] Tool) to provide researchers access to raw sensor data at the desired sampling rate as well as to higher order features (eg, activity and sleep) that can be collected consistently across devices and brands. These services, however, add a significant cost to researchers' budgets, thereby decreasing some of the benefits implied by relying on participants' existing personal digital devices. Finally, although the idiographic nature of personal digital device data presents several research opportunities, it also introduces many methodological challenges for handling missing data. Because each individual interacts with their personal digital device differently and because individual usage patterns change over time (eg, due to software updates or new applications and device features), it becomes increasingly challenging for researchers to make assumptions about the sources of missing data.

To illustrate these overarching issues in digital phenotyping research, we describe the challenges encountered and the methods used to address them in the BEGIN study—an ongoing study of BED and BN. The digital phenotyping arm of BEGIN is motivated by circumstances that are likely similar to many other studies using personal digital device data with a digital phenotyping approach. Though a number of interventions for BED and BN have at least some empirical support, between 20% and 65% of individuals who complete current best-available treatments demonstrate improvement; and, of those who do improve during treatment, only around half sustain those gains beyond 6 months after the end of treatment (this topic has been reviewed by Linardon et al [17], Peat et al [18], and Smink et al [19]). One particularly important treatment target in these interventions is the disordered eating behaviors that characterize BED and BN, which include binges (ie, episodes of uncontrollable eating), purges (ie, vomiting and misuse of laxatives or diuretics), and other compensatory behaviors (eg, excessive exercise and fasting). These behaviors have a clear beginning and end and happen repeatedly at varying time intervals both within and across individuals. An ideal intervention for disordered eating behaviors would therefore (1) help an individual recognize that they are at risk for engaging in one of these behaviors, (2) assist the individual in pre-empting the behavior, and (3) direct them toward coping strategies that are widely available and applicable to a large proportion of individuals with BED or BN (ie, cognitive, behavioral, or mindfulness interventions). The digital phenotyping arm of the BEGIN study is designed to accomplish the first step in the development of such an intervention by using sensor data from a consumer wearable to detect high-risk periods for a binge or purge episode.

Objectives

In this protocol paper, we describe the digital phenotyping component of BEGIN, a multipronged research study that is examining the etiology of BED and BN and developing indicators of risk, course of illness, and treatment response in individuals with BED and BN using genetic, gut microbiota, and digital phenotypic data. The focus of this paper is on how we addressed the methodological challenges associated with using "out of the box" passive sensor data (ie, heart rate and step count) and active data (ie, feelings and behaviors) collected via iPhone and Apple Watch devices. Our objective is to provide a thorough and transparent description of the steps we took and the decisions we made when preparing these data for analysis.

Methods

Ethics Approval and Funding

All BEGIN study procedures were approved by the University of North Carolina Biomedical Institutional Review Board (17-0242). Funding for this study from the National Institute of Mental Health (NIMH) commenced on November 20, 2019. The study was registered on ClinicalTrials.gov (NCT04162574) on November 14, 2019. Funding from other sources, including the National Eating Disorders Association, Foundation of Hope, and Brain and Behavior Research Foundation, allowed us to start a feasibility pilot prior to receiving NIMH funding. Therefore, trial registration is considered to be retrospective.

Study Design

Complete details about participant recruitment, study design, and procedures have previously been published [1]. In summary, participants were eligible if they were United States residents; existing iPhone users; between 18 and 45 years old; met the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition for lifetime BED or BN; reported experiencing current binge eating episodes; and had not received bariatric surgery, recent inpatient treatment, or hospitalization for eating disorders. All participants provided digital informed consent through the Recovery Record app to have specific types of their activity and self-reported data harvested for the purposes of this study. Once enrolled, participants used the Recovery Record app to record real time assessments of feelings and eating behaviors on their personal iPhone and then on a first-generation Apple Watch, which they received in the mail approximately 7 days after study enrollment. A version of the Recovery Record app adapted for the Apple Watch was loaded onto all the watches. Participants were instructed to wear the Apple Watch consistently throughout the 30-day study period to track heart rate and actigraphy data (only removing it for bathing, sleeping, and recharging the battery). Thirty days after enrollment, Recovery Record stopped sharing all active and passive data with the BEGIN study and participants were able to keep the Apple Watch for personal use.

Data Privacy and Confidentiality

To maximize data privacy and security, data from all sources were encoded and can only be matched using a key maintained in a password-protected file that can be accessed only by approved study personnel. Study data collected from the Recovery Record app and Apple Watches were maintained by Recovery Record and transferred with end-to-end encryption and authentication protocols. Further details have been described previously [1].

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Data Sources

Complete details for all BEGIN study data sources have been described previously [1]. A summary of the data sources relevant to the current protocol are presented below.

Participant Characteristics

Demographic data (age, sex, gender, ethnicity, and race) and lifetime eating disorder diagnostic history were collected from participants at the beginning of the study. The final sample included 96 participants from the feasibility pilot study. Pilot study participants were asked to report their biological sex (male or female), whereas participants in the main BEGIN study were asked to indicate which gender they most identified with (male, female, or other). Self-reported ethnic (Hispanic or non-Hispanic) and racial categories (African American or Black; Asian; American Indian or Alaska Native; Pacific Islander or Native Hawaiian; White; or other) provided to participants were consistent across the feasibility pilot and main study.

Active Data Collection

Daily Feelings and Meal Records

Participants were prompted 6 times per day, corresponding with 3 meals and 3 snack times, to complete meal records within the iPhone Recovery Record app. Meal records could not be logged on the Apple Watch. These meal records consisted of questions about meal characteristics (eg, what was eaten, how long ago, with whom, and where), current feelings (measured on a visual analogue scale from 0, depressed, to 100, overjoyed), and eating behaviors (eg, meal skipping). Participants also had the option to record additional information, including whether they engaged in or had the urge to engage in disordered eating behaviors (eg, binge eating or purging).

Disordered Eating Records

To capture event-contingent intensive measurements of disordered eating behaviors, participants were instructed to record all binge and purge episodes in the Apple Watch Recovery Record app. Within the app, participants indicated which behavior they engaged in and when it happened, with response options ranging from “right now” to “30 minutes ago” in 5-minute increments. Participants were additionally asked to record the strength of any urges to engage in disordered eating behaviors on a 5-point scale, ranging from “not at all” to “overbearing,” as well as to indicate their current feelings on an intensity scale of 0 to 100. Although participants were instructed to record binge or purge episodes, urges, and feeling ratings in the Apple Watch Recovery Record app, they also had the capability to do so in the iPhone version of the app. On the iPhone version of the app, participants could enter the exact time of a binge or purge event, meaning that on the iPhone, it was possible to record an event that happened more than 30 minutes previously.

Continuous Passive Data Collection: Heart Rate and Step Records

Heart rate data were collected passively from participants with the Apple Watch and harvested by the Recovery Record app using Apple’s native application programming interface. When the Apple Watch is charged and worn on the wrist, its sensor turns on approximately every 5 minutes to record heart rate at a frequency of 100 Hz using photo plethysmography. The number and timing of steps was also collected using the Apple Watch’s application programming interface and the Recovery Record app.

Data Analytic Plan

Data Cleaning

Figure 1 presents a schematic of all data cleaning and preparation steps. All percentages included in this figure were computed using the total number of precleaning observations available across all data sources. Prior to conducting analyses, all active and passive data were inspected for possible errors in recording or extraction. Details on the numbers and data sources of all raw data, as well as the observations removed from the final dataset prior to analysis, are presented in Table 1 and Table 2.

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Figure 1. Schematic of all data cleaning and preparation steps.

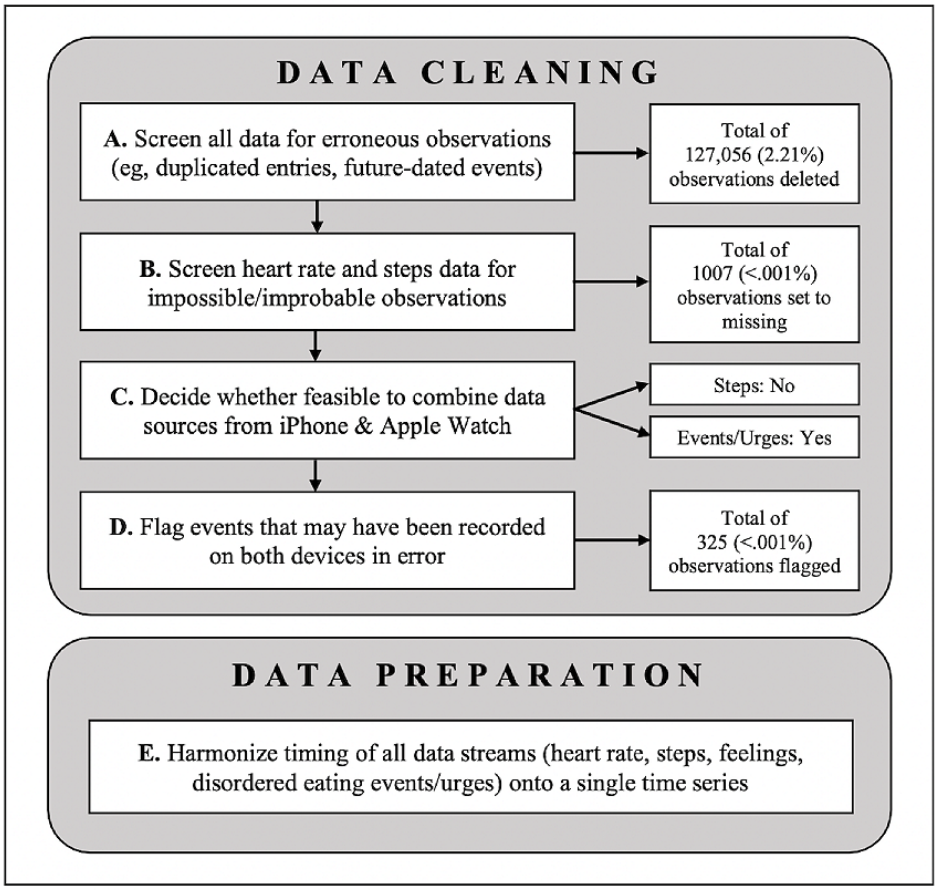

Table 1. Total number of observations across data sources available from iPhone and Apple Watch devices pre–data cleaning.

Data source	Number of observations
Heart rate[a]	3,502,315
Steps	2,118,410
Feelings	85,636
Binge events	7455
Purge events	883
Other eating disorder events[b]	21,431
Binge urges	7460
Purge urges	1219
Other eating disorder urges[c]	8001

[a]Heart rate data collected from Apple Watches only.

[b]Other eating disorder events included restricting, using laxatives, meal skipping, overeating, and compulsively exercising.

[c]Other eating disorder urges include the urge to restrict, urge to use laxatives, urge to meal skip, urge to overeat, and urge to exercise compulsively.

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Table 2. Summary of observations removed during data cleaning.

Reason for removing a data source[a]	Observations removed, n (%)[b]	Removal method
Duplicate		
Heart rate[c]	82,378 (2.4)	Deleted
Steps	43,994 (2.1)	Deleted
Feelings	320 (3.7)	Deleted
Binge events	40 (0.5)	Deleted
Purge events	0 (0)	N/A[d]
Other eating disorder events[e]	72 (0.4)	Deleted
Binge urges	22 (0.3)	Deleted
Purge urges	8 (0.7)	Deleted
Other eating disorder urges[f]	16 (0.2)	Deleted
Future-dated		
Feelings	116 (0.1)	Deleted
Binge events	23 (0.3)	Deleted
Purge events	1 (0.1)	Deleted
Other eating disorder events	28 (0.1)	Deleted
Binge urges	19 (0.3)	Deleted
Purge urges	3 (0.3)	Deleted
Other eating disorder urges	16 (0.2)	Deleted
Unreliable values		
Heart rate	250 (<0.001)	Set to missing
Steps	757 (<0.001)	Set to missing

[a]Including observations collected from iPhone and Apple Watch devices.

[b]Percentages based on total pre-cleaning number of observations for each data source.

[c]Heart rate data collected from Apple Watches only.

[d]N/A: not applicable.

[e]Other eating disorder events included restricting, using laxatives, meal skipping, overeating, and compulsively exercising.

[f]Other eating disorder urges included the urge to restrict, urge to use laxatives, urge to meal skip, urge to overeat, and urge to compulsively exercise.

Duplicate and Future-Dated Data

A total of 126,850 out of 5,752,810 data points, or 2.2% of the total raw data collected, were identified as duplicates and removed from the final data set. A data point was flagged as a duplicate when the timestamp and all associated data characteristics were identical to another observation from the same participant. These values were determined to be device recording errors and were deleted. Similarly, a small percentage of future-dated self-reported events, urges, and feelings were detected (comprising 427 out of 5,752,810 data points, or <0.1% of the total raw data collected). Since future-dating of events was not possible using the phone or watch versions of the Recovery Record app, these observations were attributed to temporary device malfunction and were deleted from the final data set.

Device Recording Errors and Unreliable Data

To check for potential recording errors in heart rate values from the Apple Watch (eg, due to the device shifting on the wrist or sweat interfering with the sensor), heart rate data were screened for values outside the typical range for healthy adults (50-150 bpm [20]). We decided that extreme heart rate values immediately preceded and followed by a sudden jump in heart rate (ie, a change greater than 50 bpm) were more likely indicative of device error than meaningful individual differences in cardiovascular fitness or activity and were set to missing. Although 256,590 heart rate observations were flagged as extreme, only 250 of these were classified as likely device recording errors (including 51 observations of 0 bpm) and consequently set to missing. A small number of unreliable or unusable step observations were also detected in the phone and watch data based on the number of steps recorded or the length of the associated recording interval. Step observations that were either impossible (eg, 384 steps recorded in less than one second) or associated with recording intervals that were too long to accurately capture activity dynamics at the desired sensitivity for the current study objectives (ie, greater than 15 minutes), were attributed to device error and set to missing in the final data set. In total, 757 out of 2,118,410 step

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observations, or less than 0.1% of all step observations recorded, were determined to be unreliable and set to missing.

Combining Data Across Devices

With the exception of heart rate, it was possible for participants to generate all forms of mobile data on both the iPhone and Apple Watch devices. Therefore, it was necessary to decide whether data collected from both sources could be combined prior to analysis. First, we inspected the quantity and characteristics of the data obtained from both devices. Table 3 shows descriptive statistics on device utilization across data sources.

Table 3. Participant device utilization across data sources.

Data source	Participants who provided the data (N=1019)	Participants who used both devices, n (%)	Participants who used iPhone only, n (%)	Participants who used Apple Watch only, n (%)
Steps	815	771 (94.6)	22 (2.7)	22 (2.7)
Feelings	1013	494 (48.8)	492 (48.6)	27 (2.6)
Binge events	861	283 (32.9)	569 (66.1)	9 (1)
Purge events	119	23 (19.3)	90 (75.6)	6 (5)
Other eating disorder events[a]	911	350 (38.4)	543 (59.6)	18 (2)
Binge urges	816	372 (45.6)	365 (44.7)	79 (9.7)
Purge urges	173	29 (16.8)	135 (78)	9 (5.2)
Other eating disorder urges[b]	722	279 (38.7)	276 (38.2)	167 (23.1)

[a]Other eating disorder events included restricting, using laxatives, meal skipping, overeating, and compulsively exercising.

[b]Other eating disorder urges included the urge to restrict, urge to use laxatives, urge to meal skip, urge to overeat, and urge to compulsively exercise.

Passive Data

For steps, 771 out of 815 participants (94.6%) provided data collected from both devices and only a small proportion (22/815, 2.7%) of participants recorded steps only on their iPhone or Apple Watch. Nevertheless, the quantity of step observations recorded on the Apple Watch was much greater than on the iPhone, which is most likely due to participants having the Apple Watch on their person more consistently than the iPhone. As originally planned, and to eliminate the risk of artificially inflating step counts due to simultaneous recording on both devices, we decided to use only step data obtained from the Apple Watch. Because participants did not receive the watch until around 7 days after study enrollment, fewer than 30 days of step data are available for analysis. We opted not to use steps recorded on the iPhone prior to when the Apple Watch was received by participants to limit potential sources of bias from differences in algorithms and sensors between the 2 devices. Step data for the 22 participants who only provided iPhone-generated step counts were therefore excluded, which resulted in a final sample of 793 participants with usable step data for analysis.

Active Data

Inspection of active data recorded on the 2 devices revealed that although many participants recorded momentary observations of feelings, disordered eating behaviors, and urges on both the iPhone and Apple Watch versions of the Recovery Record app, most observations came from iPhone entries (Table 3). This was somewhat unexpected, as participants were instructed to use the Apple Watch for these data, and the Apple Watch version of the Recovery Record app was specifically designed to increase ease of active data collection for participants. Since response options for recording eating disorder events, urges, and feelings were consistent across the iPhone and Apple Watch versions of the Recovery Record app, we decided to combine active data collected from both devices prior to analysis. To determine whether participants may have recorded some binge or purge events on both devices by mistake, we flagged any identical events with timestamps that were within 60 minutes of each other. This time interval was chosen based on existing research [21,22] and the clinical expertise of our team, who suggested that it would be unlikely for multiple binge or purge episodes to occur less than 60 minutes apart. A total of 301 out of the 7392 binge events available post–data cleaning (4%) and 24 out of the 882 post–data cleaning purge events (2.7%) were flagged as potential duplicate events to be investigated further using sensitivity analyses.

Data Preparation

For the analyses proposed for this study (discussed in the Planned Analysis section) it was necessary for us to create corresponding measurements of heart rate and step data that maximized data coverage over time. Although passive heart rate and actigraphy measurements can be assumed to come from continuous data sources, the iPhone and Apple Watch use sampling rates designed to preserve battery power and optimize user experience of other device applications. Furthermore, to maximize user privacy, Apple devices collect location and movement data over irregular time intervals using proprietary sampling algorithms. As a result of these constraints, heart rate and actigraphy data harvested via native application programming interfaces are available as discrete repeated measurements that are unequally and variably spaced across time.

The accuracy of the multivariate analytic approach chosen to address the objectives of the current protocol (also discussed in the Planned Analysis section) depends on observations from data sources being measured simultaneously and at repeated

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time intervals that capture the underlying continuous dynamics of interest—in this case, the coordination or discoordination between heart rate and steps preceding and following an episode of disordered eating. Therefore, to meet these assumptions, we created a time series for each participant that stretched from their earliest heart rate or step time stamp to their latest heart rate or step time stamp in increments of 1 minute. Time stamps for heart rate and step observations were then truncated to the minute level and heart rate and total step count values were assigned to the time series as follows: Heart rate values were assigned to a 1-minute epoch in the time series corresponding with their time stamps. If, due to truncation of time stamps, multiple heart rate observations were associated with the same minute in the time series, an average of the heart rate observations was computed and assigned to the corresponding minute. For steps, raw step count values were first divided and distributed equally across the number of minutes in their associated time interval. For example, if an observation of 500 steps was associated with a 10-minute time interval, 50 steps would be assigned to each minute within the interval. Step values were then assigned to each corresponding minute in the time series. As with heart rate, whenever multiple step observations were associated with the same minute due to truncation of the raw data to the minute level, an average step value was computed and assigned to the corresponding minute.

Planned Analysis

Our primary analyses will focus on identifying markers of risk for binge and purge events using a combination of multilevel modeling and mixture modeling techniques. We plan to accomplish this by modeling a person's current state as a function of their previous state and change in their state over time using values and derivatives of heart rate and step counts. We will run these models both as multilevel models, in which time until the next binge or purge event and time from the previous binge or purge event are included as moderators of these associations, and as mixture models, which take an exploratory approach to identifying different temporal patterns based on distributional properties of the data.

Results

Data collection, cleaning, and preparation are complete. A total of 1019 participants—including 96 participants from the feasibility pilot—completed the study between August 2017 and May 2021. Summary statistics of participant demographic variables are presented in Table 4. Of the full sample, 859 participants (84.3%) identified their biological sex or gender as female, 148 (14.5%) as male, and 12 participants (1.2%) identified with neither female nor male gender. None of the sample endorsed their race as Pacific Islander or Native Hawaiian, and 61 out of the 1019 participants (6%) identified with multiple racial groups. Of the 1019 participants included in our final sample, 790 (77.5%) provided usable heart rate data, 793 (77.8%) provided usable step observations from the Apple Watch, and 1013 (99.4%) provided usable real time assessments of feelings, disordered eating events, or disordered eating urges on the iPhone or Apple Watch versions of Recovery Record. Summary statistics for the number of days and total number of observations available from each data source after cleaning are presented in Table 5 and Table 6. Analyses for the primary aim will begin in the spring of 2022 and are expected to conclude by the end of 2022.

Table 4. Participant demographic data.

Variable	Full sample (N=1019)	Males only (n=148)	Females only (n=859)
Age (years), mean (SD)	29.6 (7.4)	31.7 (7.0)	29.3 (7.4)
Ethnicity, n (%)			
Hispanic	111 (10.9)	15 (10.1)	95 (11.1)
Non-Hispanic	908 (89.1)	133 (89.9)	764 (88.9)
Race, n (%)			
African American/Black	42 (4.1)	13 (8.8)	28 (3.3)
American Indian/Alaska Native	6 (<1)	1 (0.7)	5 (0.6)
Asian	39 (3.8)	11 (7.4)	28 (3.3)
White	845 (82.9)	114 (77)	723 (84.2)
More than one race	61 (6)	5 (3.4)	54 (6.3)
Not reported	26 (2.6)	4 (2.7)	21 (2.5)
Lifetime diagnosis,[a] n (%)			
Binge eating disorder	787 (77.2)	111 (75)	665 (77.4)
Bulimia nervosa	759 (74.5)	97 (65.5)	653 (76)
Binge eating disorder and bulimia nervosa	639 (62.7)	81 (54.7)	549 (63.9)

[a]Indicates that a subject met the diagnostic criteria at some point in their life.

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Table 5. Summary statistics of the number of days of data available across data sources.

Data source	Mean (SD)	Minimum	Maximum
Heart rate	18 (7)	0	29
Step count	20 (7)	0	30
Feelings, eating disorder events,[a] or eating disorder urges[b]	23 (8)	0	29
Any	25 (8)	0	30

[a]Eating disorder events included binge eating, purging, restricting, using laxatives, meal skipping, overeating, and compulsively exercising.

[b]Eating disorder urges included the urge to binge, urge to purge, urge to restrict, urge to use laxatives, urge to meal skip, urge to overeat, and urge to compulsively exercise.

Table 6. Total number of observations across data sources available from iPhone and Apple Watch devices post–data cleaning.

Data source	Number of observations
Heart rate[a]	3,419,937
Step count[a]	1,635,993
Feelings	85,200
Binge events	7392
Purge events	882
Other eating disorder events[b]	21,332
Binge urges	7419
Purge urges	1208
Other eating disorder urges[c]	7968

[a]Heart rate and step data from Apple Watches only.

[b]Other eating disorder events included restricting, using laxatives, meal skipping, overeating, and compulsively exercising.

[c]Other eating disorder urges included the urge to restrict, urge to use laxatives, urge to meal skip, urge to overeat, and urge to compulsively exercise.

Discussion

Contributions

To our knowledge, the digital phenotyping arm of the BEGIN project represents the first study using passive sensor data from personal digital devices to characterize states of increased risk for binge or purge episodes in individuals with BED and BN. By incorporating passive sensor data into mobile health apps, this work has the potential to improve the accessibility, potency, and durability of existing evidence-based treatments for eating disorders. Furthermore, this study lays the foundation for future just-in-time interventions that could utilize real time personal digital device data to alert individuals to impending high-risk states for engaging in eating disorder behaviors and direct them to specific therapeutic intervention strategies when they need them most. This work has the potential to improve therapeutic outcomes in the treatment of BED and BN and can also provide a blueprint for interventions with other health or mental health conditions characterized by discrete events (eg, addictive behaviors such as substance use, smoking, and gambling, and self-injurious or suicidal behaviors).

Limitations

The current study included only existing iPhone users and relied on the Apple Watch's native application programming interface for extracting raw passive sensor data. As a result, the data collected may be influenced by patterns of device usage and interaction specific to Apple customers and Apple operating systems. Also, some of our data handling decisions (eg, the definition of unreliable heart rate values) were influenced by the features of our sample and the Apple Watch application programming interface. Therefore, some of these decisions may not be appropriate for studies using more specific samples (eg, athletes) or personal digital devices that provide data at a higher resolution. This study only focused on 2 forms of sensor data (ie, heart rate and step count); however, it is possible to access many other passive data sources from personal digital devices (eg, screen time and call or text logs). This demonstrates that this is an area of research ripe for expansion in the future. Finally, the accuracy and reliability of the participants' self-reported binge or purge events will influence our ability to capture states of increased risk for these events using sensor data.

Conclusions

Our study highlights some of the methodological challenges associated with using "out-of-the-box" data from individuals' existing personal digital devices, and describes a novel approach for addressing these challenges when preparing data for multivariate time series analyses. Given the number of decisions to be made when cleaning and handling personal digital device data, we hope that this protocol will help serve as a guide to other researchers using personal digital devices for digital

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phenotyping work, while also contributing to greater transparency and reproducibility in this field.

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Conflicts of Interest

Author CMB is a grant recipient and Scientific Advisory Board member of Shire Pharmaceuticals (now Takeda); a grant recipient from the Lundbeck Foundation; an author and royalty recipient from Pearson; and a member of the Clinical Advisory Board of Equip Health Inc. Authors JT and SA are owners, shareholders, and employees of Recovery Record, Inc. The authors have no other conflicts of interest to declare.

Multimedia Appendix 1
Peer-reviewer report from the Psychosocial Risk and Disease Prevention (PRDP) Study Section - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 172 KB - resprot_v11i6e38294_app1.pdf]

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Abbreviations

BED: binge eating disorder
BEGIN: binge eating genetics initiative
BN: bulimia nervosa
PI: Principal Investigator

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Proposal

Optimizing an mHealth Intervention to Change Food Purchasing Behaviors for Cancer Prevention: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Dietary intake is a powerful modifiable factor that influences cancer risk; however, most US adults do not adhere to dietary guidelines for cancer prevention. One promising pathway for improving dietary adherence is targeting grocery shopping habits. Interventions might facilitate healthy grocery choices, with a combination of mHealth and traditional methods, by promoting the salience of dietary goals while shopping, enhancing motivation to make dietary changes, and increasing household support for healthy food purchasing.

Objective: This pilot study will assess feasibility and acceptability of intervention components designed to improve adherence to dietary guidelines for cancer prevention (preliminary aim). The primary aim of the study is to quantify the effect of each intervention component, individually and in combination, on dietary intake (primary aim) and grocery store food purchases (exploratory aim). Mediation analyses will be conducted to understand the mechanisms of action (goal salience, motivation, and household support—secondary aims). The overarching goal is to optimize an mHealth intervention to be tested in a future fully powered clinical trial.

Methods: The study enrolled adults (N=62) with low adherence to dietary recommendations for cancer prevention. In a 20-week program, all participants attend a nutrition education workshop and receive weekly educational messages through an app. A factorial design is used to test 4 intervention components: (1) location-triggered messages: educational messages are delivered when arriving at grocery stores; (2) reflections on the benefits of change: content is added to messages to encourage reflection on anticipated benefits of healthy eating, and participants attend an additional workshop session and 3 coach calls on this topic; (3) coach monitoring: food purchases are monitored digitally by a coach who sends personalized weekly app messages and conducts 3 coaching calls that focus on feedback about purchases; and (4) household support: another adult in the household receives messages designed to elicit support for healthy food purchasing, and support is addressed in 3 coach calls and an extra workshop session attended by the index participant and household member. Assessments are completed at weeks 0, 10, and 20 using self-report measures, as well as objective capture of grocery data from the point of purchase using store loyalty accounts.

Results: The National Cancer Institute funded this study (R21CA252933) on July 7, 2020. Participant recruitment began in the spring of 2021 and concluded with the successful enrollment of 62 participants. Data collection is expected to be completed in the summer of 2022, and results are expected to be disseminated in the summer of 2023.

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Conclusions: The results of this study will inform the development of scalable interventions to lower cancer risk via changes in dietary intake.

Trial Registration: ClinicalTrials.gov NCT04947150; https://clinicaltrials.gov/ct2/show/NCT04947150

International Registered Report Identifier (IRRID): DERR1-10.2196/39669

(JMIR Res Protoc 2022;11(6):e39669) doi:10.2196/39669

KEYWORDS

mHealth; cancer prevention; grocery shopping; diet; eating; mobile phone

Introduction

Background

In the United States, 1 out of 2 men and 1 out of 3 women will develop cancer during their lifetime [1]. Guidelines from leading organizations, including the American Cancer Society and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), highlight diet as a key factor influencing cancer risk [2,3]. Adherence to dietary guidelines is associated with reduced risk of cancer incidence and cancer-related mortality [4-8]. Certain foods have properties that are protective against cancer (eg, fruits and vegetables [9,10]), whereas others have carcinogenic properties (eg, processed meat [11-13]). Diet is also the primary driver of obesity risk, which increases cancer risk [14,15]. At the population level, the effect of dietary intake on cancer risk is significant. For example, 20% to 60% of digestive tract cancers can be attributed to the low consumption of fruits and vegetables; pancreatic cancer risk increases by 22% for each additional 25 g/day of added sugar intake, and a 10% increase in the intake of ultraprocessed foods prospectively predicts a 12% increase in cancer risk [16-18]. Most Americans do not meet the WCRF/AICR dietary guidelines [19,20], with 60% of adults having inadequate fruit and vegetable intake [21], and nearly 90% consuming too much processed meat [22].

An efficient and scalable way to improve dietary adherence may be to focus intervention efforts on the decisions made while purchasing food for consumption at home. Across socioeconomic and racial groups, approximately 60% to 70% of calories consumed by US adults come from foods purchased in supermarkets and grocery stores [23-25], which are visited 1 to 2 times per week on average [26-28], including in urban areas [29,30]. Purchasing decisions that occur while grocery shopping each week have an outsized effect on dietary intake. Food cues in one's environment strongly influence eating behavior [31-33]. Humans are biologically driven to have a hedonic response to foods that are high in salt, sugar, and fat; thus, if these foods are readily available in one's home, self-regulation of dietary intake in the home will be challenging [23,34]. The types and amounts of foods available in individuals' homes are strongly related to their dietary patterns, with the presence of unhealthy foods predicting greater calorie and fat intake and lower fruit and vegetable availability predicting lower consumption of these foods [35-40]. When healthy foods are purchased and brought into the home and unhealthy foods are not, minimal self-control is needed to make healthy eating choices at home, which should improve the overall dietary quality.

Making healthy decisions at the point of purchase is very challenging for several reasons: food decisions are often habitual, quick, and prioritize short-term perceived reward [41-43]; exposure to tempting food increases feelings of hunger and craving (likely driven by the dopamine system) [44]; and industry marketing fosters impulsive purchases of processed, palatable foods [45]. Previous interventions designed to change grocery shopping habits have primarily focused on providing dietary education but have produced only modest changes in food purchasing [46-48]. Other types of interventions in this area target the financial aspects of grocery shopping (eg, discounts and vouchers) and aspects of the grocery store environment (eg, item placement and advertising) to improve purchasing behavior [46]. These interventions show some initial efficacy, but widespread implementation of these approaches may not be feasible.

A review of the theory and literature in this area suggests that, to improve grocery shopping by enhancing self-regulation at the point of purchase, it may be necessary to target 3 key aspects involved in decision-making. First, goal salience is an underappreciated driver of eating behavior [49-52]. When individuals do not have nutrition-related goals in mind, food purchases are more likely to be influenced by factors such as familiarity, whereas reminding individuals of goals results in significantly healthier food purchases [50]. For example, adults in a grocery store who were primed with a healthy eating goal chose more minimally or nonprocessed foods and fewer ultraprocessed foods than those who did not receive a health goal reminder [53].

Second, the level of motivation to make healthy food choices is a key determinant of food purchasing decisions [54,55]. Reflecting on the anticipated benefits of healthy eating might facilitate dietary adherence by increasing motivation [56-63]. Supportive accountability is another factor that can enhance motivation and facilitate behavior change [64,65]. The presence of an observing other enhances accountability [66] by prompting self-evaluation and self-regulation [67-70], and positive feedback from an observer further enhances motivation [71,72].

Finally, social factors within one's household, including support for healthy eating and the perceived food preferences of family members, exert a strong influence on food purchases [73-77]. Experimental studies have demonstrated that modifying social factors can improve food choice [77,78]. In summary, interventions may be more successful in improving healthy grocery store purchases to change the home food environment if they (1) promote goal salience at key moments of food purchase decision-making, (2) enhance motivation to make and

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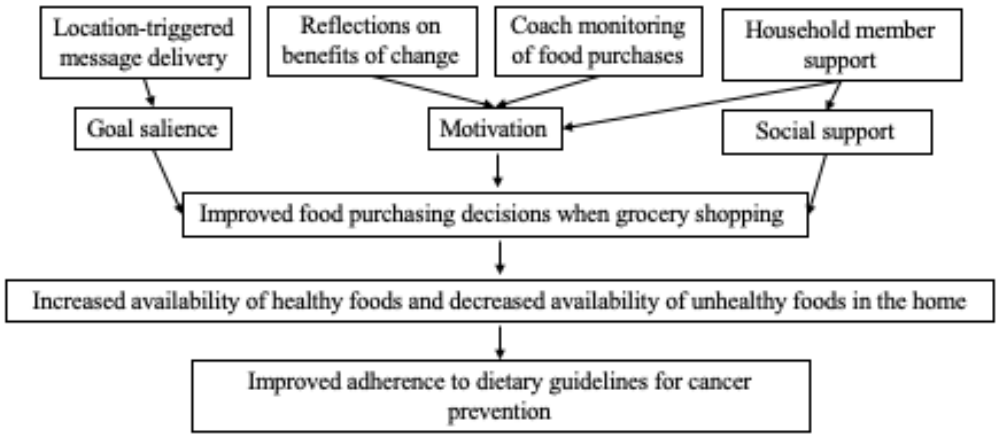
sustain changes to the diet, and (3) increase household support and accountability for healthy food purchasing.

To maximize the potential for dissemination of this type of intervention, it is sensible for it to be delivered remotely (eg, via individual phone calls or group workshop sessions held via videoconferencing) and to incorporate mobile health (mHealth) technology, such as a smartphone app. mHealth allows for scalable interventions to be delivered in real-world contexts, in real time, including to low-income, rural, and older adult populations [79-84].

This study tests 4 intervention components that target goal salience, motivation, and social support to facilitate food purchases that are consistent with cancer prevention dietary guidelines (Figure 1). The four intervention components are as follows:

1. Location-triggered messages: Educational messages are delivered via app just-in-time, that is, when individuals arrive at grocery shopping locations, to enhance goal salience. The mindfulness of program goals at the moment of decision-making is expected to facilitate program-consistent food purchasing behaviors.
2. Reflections on benefits of change: To enhance motivation, participants attend a 60-minute workshop and 3 coach calls to identify and reflect on the personal benefits of dietary change, and the content is added to educational app messages that prompt reflection on the anticipated rewards of healthy eating.
3. Coach monitoring: Food purchases are digitally monitored by a coach through a system that passively collects participants' item-level data from stores, and the coach sends weekly app messages designed to enhance supportive accountability and thus motivation. Participants also attend 3 video calls to discuss their recent purchases with their coach.
4. Household support: Another adult in the household attends a 60-minute workshop and 3 coach calls with the index participant and receives weekly text messages designed to elicit support for healthy food purchasing and provide another source of supportive accountability for the index participant.

Figure 1. Project EatWell conceptual model.



Objectives of This Study

This pilot study uses a factorial design to test the effect of these 4 intervention components on grocery store purchases and adherence to the WCRF/AICR dietary recommendations for cancer prevention. The preliminary aim will assess feasibility and acceptability of the intervention components. The study also will quantify the effect of each intervention component individually and in combination on dietary intake (primary aim) and grocery store food purchases (exploratory aim). The secondary aim will use mediation analyses to explore whether changes in goal salience, motivation, and household social processes mediate differences in outcomes between conditions. Overall, the goal of the study is to inform future development and testing of interventions designed to change dietary intake.

Methods

Study Design

This study is a National Cancer Institute (NCI)-funded pilot, randomized controlled trial (R21CA252933) using a factorial design to test the effect of 4 different intervention components on dietary intake and grocery store purchases (Multimedia Appendix 1). The 4 factors yield 16 different combinations of intervention components (Table 1). An equal number of participants were randomized to receive versus not receive each of the 4 experimental intervention components. For example, half of the participants (31/62, 50%) have their food purchasing data monitored by a coach and half (31/62, 50%) do not have this feature as part of their intervention. As another example, half of the participants (31/62, 50%) were randomly assigned to have household member involvement included in their intervention package, but this randomization was done independently of that for coach monitoring (ie, the 4 experimental intervention components were not bundled together). The baseline covariates used for randomization included biological sex, BMI, age, household size, and dietary adherence score.

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Table 1. Intervention components by condition.

Condition #	Condition	Workshops	Calls (all 20 minutes)	Messages per week
1	Control	Three 90-minute sessions	0	1 message (not location triggered)
2	LOC[a]	Three 90-minute sessions	0	1 message (location triggered)
3	BOC[b]	Three 90-minute sessions +one 60-minute BOC	3 BOC	1 message with BOC content (not location triggered)
4	HH[c]	Three 90-minute sessions +one 60-minute HH	3 HH	1 message (not location triggered) +1 HH text
5	CM[d]	Three 90-minute sessions	3 CM	1 message (not location triggered) +1 CM message
6	LOC+BOC	Three 90-minute sessions +one 60-minute BOC	3 BOC	1 message with BOC content (location triggered)
7	LOC+CM	Three 90-minute sessions	3 CM	1 message (location triggered) +1 CM message
8	LOC+HH	Three 90-minute sessions +one 60-minute HH	3 HH	1 message (location triggered) +1 HH text
9	BOC+HH	Three 90-minute sessions +one 60-minute BOC+one 60-minute HH	3BOC+3HH	1 message with BOC content (not location triggered) +1 HH text
10	BOC+CM	Three 90-minute sessions +one 60-minute BOC	3BOC+3CM	1 message with BOC content (not location triggered) +1 CM message
11	HH+CM	Three 90-minute sessions +one 60-minute HH	3 HH+ 3 CM	1 message (not location triggered) +1 CM message+1HH text message
12	LOC+HH+CM	Three 90-minute sessions +one 60-minute HH	3 HH+3 CM	1 message (location triggered) +1 CM message+1HH text
13	LOC+BOC+HH	Three 90-minute sessions +one 60-minute BOC+one 60-minute HH	3BOC+3HH	1 message with BOC content (location triggered) +1 HH text
14	LOC+BOC+CM	Three 90-minute sessions +one 60-minute BOC	3BOC+3CM	1 message with BOC content (location triggered) +1 CM message
15	BOC+HH+CM	Three 90-minute sessions +one 60-minute BOC +one 60-minute HH	3BOC+3HH+3CM	1 message with BOC content (not location triggered) +1 CM message+1HH text
16	LOC+BOC+HH+CM	Three 90-minute sessions +one 60-minute BOC+one 60-minute HH	3BOC+3 HH+3 CM	1 message with BOC content (location triggered) +1 CM message+1HH text message

[a]LOC: location-triggered messages.

[b]BOC: reflections on benefits of change.

[c]HH: household support.

[d]CM: coach monitoring.

Ethics Approval

This study was approved by the Drexel University Institutional Review Board (study ID 2003007695) on March 13, 2021.

Participants, Eligibility, and Recruitment

The study enrolled 62 index participants and 31 household members who served a support role. Participants were recruited from the Philadelphia area in 2 cohorts via targeted mailings, social media outreach, and Craigslist listings, and recruitment was supported in part by community recruitment resources from Thomas Jefferson University Sidney Kimmel Cancer Center. In particular, the Jefferson Regional Liaison Office used their honest broker system which aided in identifying and contacting potential participants using internal communication resources, community contacts, and other available resources (eg, participants within the Jefferson community who matched eligibility criteria were emailed about their interest in participating). Interested individuals completed a screening survey, and if deemed preliminarily eligible, attended an information session via videoconferencing. After the session, those interested in participating attended a baseline assessment to determine their final eligibility.

Index participants were required to be aged ≥18 years and fluent in English. In addition, participants were required to be the primary grocery shopper in their household and report shopping at stores that could passively stream item-level data from a store loyalty card to the study portal (Walmart, Target, ShopRite, or Wegmans). Inclusion criteria also included having a smartphone with an iOS or Android operating system that was compatible with the program app and living in a household with another

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adult who indicated willingness to participate in a support role. The exclusion criteria were as follows: medical condition or psychiatric condition (eg, active substance abuse or eating disorder) that would be a poor match with program content or limit ability to comply with program dietary recommendations, plans to enroll in another lifestyle modification program within 6 months of program start, bariatric surgery history, pregnancy or breastfeeding or plans to become pregnant in the next 6 months. All index participants provided written informed consent for participation, as did the 31 household members of the index participants randomized to receive the household support component.

Intervention

Uniform Components

All index participants attend a nutrition education workshop (3 sessions of 90 minutes each, all delivered via videoconferencing) focused on eating a diet consistent with the WCRF/AICR guidelines. Content is organized around the key WCRF/AICR dietary recommendations: (1) eat a diet rich in whole grains, vegetables, and fruit; (2) limit consumption of highly processed foods; (3) limit consumption of red and processed meat; and (4) eliminate consumption of sugar-sweetened beverages. Sessions consist of psychoeducation about these nutrition recommendations, group discussions on health behavior change (eg, common triggers for eating behavior), didactics on behavioral skills (eg, stimulus control, functional analysis, and problem solving), and hands-on practice (eg, reading a nutrition label). Each workshop concludes with goal setting and meal planning, where participants identify concrete guideline-related goals for the coming week, create a weekly meal plan, and begin constructing a grocery list for relevant items. They are encouraged to complete their meal plan and grocery list independently after each session. The workshop sessions consist of 10 to 15 participants each. Coaches are experienced in delivering lifestyle modification and have a master's degree or PhD in psychology, nutrition, or a related field. Each participant has continuity working with the same coach for all workshop sessions and, if applicable, any additional condition-specific contacts (ie, extra workshop sessions, coaching calls, and coach messages).

All index participants also download an app created for this program. A key feature of the app is the display of graphs that reflect how well the participant's grocery shopping purchases align with each of the program recommendations across the previous 4 weeks. Participants are encouraged to use these graphs to track their progress and improvement toward recommendations over time. The grocery shopping data displayed in the graphs are passively collected from participant's store loyalty accounts, as described in the *Grocery Store Purchases* section. During the 20-week intervention period, all participants also receive once-weekly educational messages in the app that remind them of program dietary recommendations and behavioral strategies that can promote adherence (eg, planning, self-monitoring, and goal setting). Message content includes tips for meeting program guidelines such as swapping out processed snacks for healthier alternatives or recipe ideas to incorporate fruits and vegetables (eg, "Replacing high-calorie, processed foods with fruits, vegetables, whole grains, beans, and legumes can help you feel fuller longer, have more energy, and better manage cravings and appetite, all of which can help you manage your weight. Identify one thing you could do this week to continue to make progress on the goal of replacing processed foods with healthier items"). These messages are standardized such that the content in any given week's message is the same for all participants.

Experimental Intervention Components and Contact Time

Overview

As described next, the 4 experimental intervention components are each provided to 50% (31/62) of the participants, in addition to the 3 workshop sessions and standard weekly messages that all participants receive. The study was designed such that the program contact time varies by condition to evaluate the benefit of added contact time. The total number of workshop sessions ranges from 3 to 5, with 26% (16/62) of the participants assigned to 3 sessions (ie, no extra workshop sessions), 48% (30/62) assigned to 4 sessions (ie, an extra workshop session), and 26% (16/62) assigned to 5 sessions (ie, 2 extra workshop sessions). The total number of coach calls ranges from 0 to 9, with 18% (11/62) of the participants assigned to 0 calls, 29% (18/62) assigned to 3 calls, 39% (24/32) assigned to 6 calls, and 14% (9/62) assigned to 9 calls.

As described in detail in the next 4 component-specific sections, all participants receive a message from the app each week, which includes standardized educational content, and half of the participants (31/62, 50%) have benefits of change content appended to the message. For half of the participants (31/62, 50%), the delivery of the educational app message is location triggered. Half of the participants (31/62, 50%; ie, those who receive coach monitoring) also receive a second message in the app each week, written by their coach. Half of the participants (31/62, 50%) have a message sent to their household member each week.

Location-Triggered Messages

Participants randomized to receive this component receive their weekly educational message in the program app when their smartphone is within a 50-meter geofence around designated grocery stores. At baseline, participants provided information about the venues where they regularly grocery shop, for geofence programming. If the system does not detect the designated location in a given week (eg, the participant does not visit the grocery store), the app message is delivered at the end of the week. The message is delivered only once per week, even if the participant is at a grocery shopping location more than once.

Participants who are not assigned to location-triggered message delivery receive their weekly educational messages at a fixed time (ie, Sundays, at 10 AM), regardless of location. The content of the messages does not differ according to whether location-triggered messaging is provided.

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Reflections on Benefits of Change

Participants randomized to receive the benefits of change component receive an extra 60-minute workshop session to reflect on the anticipated benefits of purchasing healthy food. They also attend 3 brief, individual coaching calls (20 minutes each) to further discuss personally meaningful benefits of change (at weeks 9, 13, and 17). Personalized content on their anticipated benefits is also added to each educational app message delivered after week 5. During the benefits of change workshop session, participants individually complete an exercise identifying short- and long-term benefits of healthy eating that are important to them, and message content is programmed according to the responses they record (eg, "Making healthy choices today will pay off in the long run because [I will be modeling these choices for my children, and they will benefit from healthier eating as well]," where bracketed input was generated by the participant).

Participants who do not receive the benefits of change component do not attend the additional workshop or these 3 coach calls focused on benefits of change and do not receive additional message content.

Coach Monitoring

For participants assigned to receive coach monitoring, the coach accesses a web-based portal where they view the participant's food purchasing data, which are passively collected from the point of purchase using store loyalty accounts. The coach sends the participant a personalized message each week in the app, sharing feedback and observations from the food purchasing data. The participant also completes 3 calls with the coach (20 minutes each, held at weeks 4, 10, and 15) designed to further enhance supportive accountability for program goals. The coach messages and calls provide reinforcement for purchases consistent with program goals (particularly those that represent a change from baseline) and express concern for areas in which adherence is low.

If a participant is not assigned to receive coach monitoring, the coach has no objective information about food purchasing, and the participant does not receive any personalized coach messages in the app or phone calls focused on coach monitoring.

Household Support

Participants assigned to receive household support as part of the intervention select an adult in their household to serve in the support role. This household member receives weekly text messages (eg, "Your household member is likely trying to keep up new healthy habits for meal planning and grocery shopping. Identify one thing you can do to support their efforts with these changes this week. For instance, communicating in advance about meal and snack preferences, showing appreciation, or offering to look for healthy recipes to try"). In addition, the index participant and household member jointly participate in an extra 60-minute workshop session and three 20-minute coaching calls focused on household support (held at weeks 7, 11, and 16; the household member does not attend any other workshop sessions or coaching calls). The content of the workshops and calls is designed to elicit support for changing the home food environment and enhance supportive accountability by making household members aware of the index participant's commitment to improving dietary intake.

For index participants who are not assigned to receive this intervention component, the household members have no program involvement.

Measures

Feasibility and Acceptability

Feasibility and acceptability data are being collected and will be compared with preestablished benchmarks. Recruitment feasibility will be operationalized with a benchmark of >5 participants enrolled per month of recruitment and <30% of those otherwise interested and eligible refusing participation. Retention feasibility will be operationalized with a benchmark of >70% of the participants completing each follow-up assessment. Feasibility and acceptability of food purchasing data will be operationalized with a benchmark of >90% of the participants having their food purchase digital data captured successfully. Feasibility of message delivery will be assessed by location-triggered messaging delivery, with successful receipt of messages measured by <5% of deliveries encountering technological problems. User-rated acceptability will be measured using the benchmark of a mean rating >28 on the Treatment Acceptability Questionnaire (adapted, 8-items, 7-point Likert scale; given at 10 and 20 weeks) [85]. Qualitative information on acceptability will be collected via postintervention focus groups. Focus groups will be audio recorded; transcribed, with responses coded for themes and patterns; and used to further refine the intervention for future testing.

Dietary Intake

All participants complete dietary intake questionnaires at weeks 0 and 20. Cohort 1 participants completed 3 days of food recall at each time point, administered by the Automated Self-Administered 24-hour Dietary Recall (ASA24), an NCI-designed software tool [86]. ASA24 is based on the well-validated automated multiple pass method, which has been shown to be as or more accurate than nutritionist-administered 24-hour food recall when using doubly labeled water as the criterion [87,88].

After baseline administration of the ASA24, many cohort 1 participants reported that they perceived this measure to be excessively burdensome. Given its low acceptability, we replaced the ASA24 with the Diet History Questionnaire (DHQ-III) [89] for cohort 2 participants, chosen for its streamlined format and reduced completion time. The DHQ-III is a food frequency questionnaire developed by the NCI. The nutrient and food group database for the DHQ-III is based on a compilation of national 24-hour dietary recall data from the National Health and Nutrition Examination Surveys. Cohort 2 participants completed the DHQ-III at baseline and will complete it again at 20 weeks. Given the different measures of dietary intake, differences in dietary intake variables across waves will be assessed and analyses of dietary intake will be conducted separately for each wave.

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Both the ASA24 and DHQ-III provide item-level nutritional information for all food and drinks consumed as well as daily totals of various nutrient variables [86,89]. For the NCI recommendation specific to highly processed food, food items will be flagged and included in this category based on those defined as highly processed according to the widely used NOVA classification system [90]. Items in the processed food category include salty snacks, frozen and prepared meals, baked goods, dessert, fried potatoes, candy, packaged bread and buns, refined grains, breakfast cereal, and processed cheese. Relevant items that fall into this category are pulled from the ASA24 item-level output based on their Food and Nutrient Database for Dietary Studies (FNDDS) food code [91] and from the DHQ-III item-level output based on their coding in the NCI's associated nutrient database [92] and included in nutrient total calculations for processed foods. Similarly, sugar-sweetened drinks are identified in the ASA24 (based on their FNDDS food code) and DHQ-III (based on nutrient database) and used to calculate adherence to relevant guidelines. Sugar-sweetened drinks include nondiet sodas, nondiet fruit drinks, energy drinks, and sugary coffee drinks.

The average daily intake of the following items relevant to the NCI dietary recommendations will be calculated from the ASA24 and DHQ-III:

1. Fiber: grams of fiber
2. Fruit and vegetables: cups of all fruit (intact whole or cut fruit not including fruit juices) and vegetables (all vegetables excluding starches)
3. Added sugar from processed food: grams of added sugar consumed from items flagged as highly processed (as described earlier)
4. Saturated fat from processed food: grams of saturated fat consumed from items flagged as highly processed (as described earlier)
5. Sodium from processed food: milligrams of sodium consumed from items flagged as highly processed (as described earlier)
6. Red meat: ounces of beef, veal, pork, lamb, and game meat
7. Processed meat: grams of frankfurters, sausages, corned beef, and luncheon meat made from beef, pork, or poultry
8. Sugar-sweetened drinks: ounces of sugar-sweetened beverages (as defined earlier)

Given that NCI dietary recommendations for red and processed meat are at the weekly (vs daily) level, the average daily intake of red and processed meat is prorated to reflect intake over 7 days.

Scores for adherence in each domain of the NCI dietary recommendations are calculated based on the 0, 0.5, and 1 cutoff values established previously [93], where 1 reflects fully meeting the recommended level of intake, 0.5 indicates partially meeting recommended levels, and 0 reflects failure to meet the recommendation. When guidelines include multiple subcategories (eg, fiber and fruit or vegetables), the guideline score was calculated as the average of adherence to subcategories. Two overall adherence scores were calculated: (1) the sum of adherence to the 4 guidelines (range 0-4) and (2) average adherence to the 4 guidelines (range 0-1). The subscores are (1) average of adherence scores for fiber and fruit and vegetables; (2) average of adherence scores for added sugar, saturated fat, and sodium in processed foods; (3) average of adherence scores for red and processed meats; and (4) adherence score for sugar-sweetened drinks.

As a secondary outcome for dietary intake, an adapted, 13-item food frequency questionnaire [94-96] is administered at baseline and 20 weeks. Each item pertains to 1 of the 4 dietary guidelines (eg, "Whole grain products or high fiber starches," "Red meats such as beef, pork, or lamb," or "Nondiet sweet drinks"), and participants are instructed to report the frequency with which they ate the foods in the past month with a 6-point Likert-type scale (ranging from 0—"Never" to 5—"Twice or more per day"). Total guideline scores will be calculated as the average of responses to all items pertaining to that guideline (eg, guideline 1 as the average of 0-5 response for fiber and 0-5 response for fruit or vegetables).

Mediators

Consistent with the conceptual model of the study, we measured 3 potential mediators. An adapted Goal Salience Questionnaire is administered at each time point (baseline and 10 and 20 weeks) to measure dietary goal salience; that is, the extent to which participants think about dietary recommendations when grocery shopping [97]. Motivation for dietary adherence is measured at each time point using items adapted from the Treatment Self-Regulation Questionnaire [98]. A total of 2 measures of household social factors are administered at baseline, 10 weeks, and 20 weeks, where items were adapted to apply to one's household rather than social network more broadly: the Supportive Accountability Questionnaire [71] and Sallis Social Support for Diet [99-101].

Moderators

Several potential moderators were measured at baseline. Participants completed a self-reported demographics questionnaire that gathered information about sex, race, ethnicity, age, education level, household size, and grocery shopping frequency. An adapted version of the Relationship Assessment Scale [102] was used to measure the quality of the relationship between the index participant and their household member. Weight, height, and weight history were measured using an investigator-developed weight-history questionnaire. Uncontrolled eating, cognitive restraint, and emotional eating were measured using a 21-item version of the Three Factor Eating Questionnaire-R21 [103] at baseline. The Three Factor Eating Questionnaire will also be completed after 10 and 20 weeks.

Household Member Information

Participating household members are administered the following questionnaires, which will be examined in exploratory analyses: an investigator-developed household demographics and goals questionnaire (at baseline only), the adapted food frequency questionnaire (same instrument administered to index participants, at baseline and 20 weeks), and the Treatment Acceptability Questionnaire (same instrument administered to index participants, at 20 weeks).

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Grocery Store Purchases

Beginning 4 weeks before the intervention start date and continuing until 4 weeks after the intervention end date, study software, using an application programming interface (API), will continuously collect each participant's item-level food purchases to objectively measure how grocery shopping changes over time. Participants provided store account credentials for loyalty programs at one or more of the four designated stores (Wegmans, Shop Rite, Target, and Walmart) to the study team at baseline. The API links item-level food purchases with nutrition databases (eg, FNDDS) to create summary nutrition variables, including added sugar, sodium, and saturated fat from processed foods for each item in a grocery trip. Change in purchase amounts in each nutrition category of interest related to the NCI guidelines (eg, ounces of sugar-sweetened beverages purchased per week) will be calculated. This will be an exploratory outcome because this method of data capture and categorization of grocery purchases is novel, and its feasibility has not yet been tested.

Data Analysis

As a preliminary trial, analyses will focus on estimates of effect size. This study was not designed to be powered by statistical significance. The study is designed to provide information about feasibility, acceptability, and effect estimates (as well as CIs and estimates of variability) that will inform decisions about which components should be retained in the intervention package, with the goal of crafting a package that will produce an improvement in dietary intake of at least 10%, which is a criterion that corresponds to clinically meaningful changes in cancer risk [17,104]. The population-level impact of such a change would be meaningful.

For each of the 4 experimental intervention components, estimates of main effects will be calculated by comparing participants assigned to receive that component (n=31) to those that did not (n=31); thus, confidence in effect sizes is equivalent to that which would be achieved with a 2-arm trial with 62 participants. Analyses of covariance will be used to examine the effect of each experimental condition on the outcomes of interest, while controlling for the outcome variable at baseline. To test potential moderators of these relationships (eg, gender and race), analyses of covariance will examine the influence of experimental conditions, hypothesized moderators, and their interaction on the outcomes of interest, while controlling for the respective outcome variable baseline. To better understand the underlying mechanisms of these relationships, we will conduct mediation analysis using the Hayes PROCESS macro in SPSS (model 4, SPSS Inc). Models will examine whether temporally precedent changes in the proposed mediators (eg, goal salience, motivation, and household social processes) mediate differences in the primary outcomes between experimental conditions, while controlling for the outcome variable at baseline.

Results

Overview

The NCI funded this study (R21CA252933) on July 7, 2020, to be funded from July 1, 2020, to June 30, 2022. Participant recruitment was conducted in 2 distinct cohorts, beginning in spring 2021 and ending in fall 2021. In total, we screened 556 participants, 494 (88.8%) of which were excluded for (1) not meeting the inclusion criteria (184/556, 37.3%), (2) not completing subsequent enrollment steps (300/556, 60.7%), or (3) declining to participate (10/556, 2%). Following recruitment, 62 participants were enrolled, and each additional intervention component was randomly assigned to 50% (31/62) of the participants (Figure 2). As of April 2022, cohort 1 had completed their intervention period and 20-week assessments. Data collection for cohort 2 is expected to be completed in the summer of 2022, and results are expected to be disseminated in the summer of 2023.

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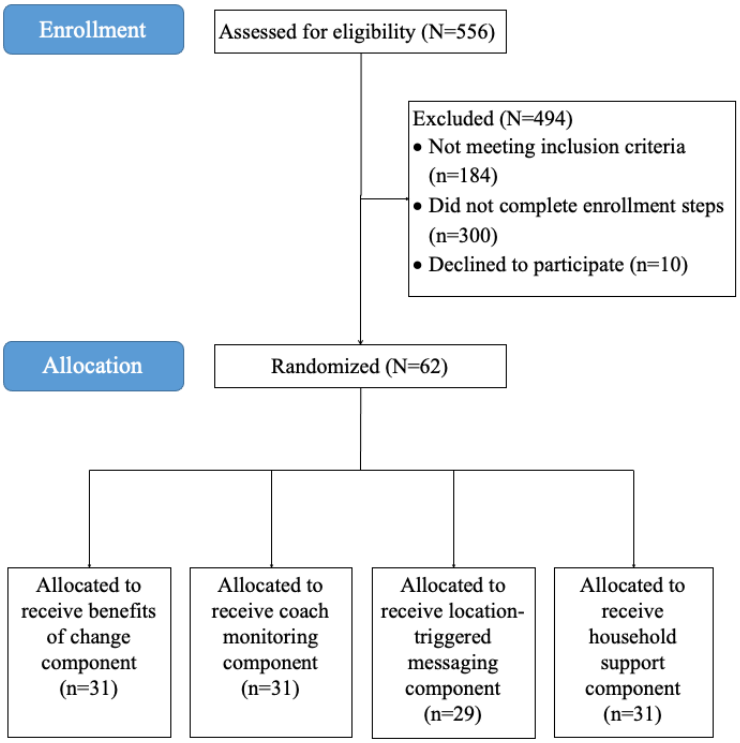
Figure 2. Project EatWell consort diagram.



Baseline Characteristics

Participant demographic information was collected at baseline (Tables 2 and 3). The majority (57/62, 92%) of participants were female, and the mean age at baseline was 47.2 years (SD 13.5). Approximately half of the participants in the sample (32/62, 52%) are non-Hispanic White and 34% (21/62) are Black or African American. Most participants (47/62, 76%) have a college, graduate, or professional degree. Self-reported BMI at baseline was in the overweight or obese range for 80% (49/62) of the participants.

Descriptive statistics for dietary intake at baseline are presented in Table 4. These were calculated using data from the ASA24 in cohort 1 and DHQ-III in cohort 2. Average adherence scores were also calculated, where 1 reflects fully meeting the recommended level of intake, 0.5 indicates partially meeting the recommended levels, and 0 reflects failure to meet the recommendation. Mean adherence score for the 4 dietary guidelines targeted in this program was 0.39 in cohort 1 and 0.46 in cohort 2.

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Table 2. Baseline demographic information (N=62).

Characteristics	Participants, n (%)
Sex	
Female	57 (92)
Male	5 (8)
Ethnicity	
Hispanic or Latino	6 (10)
Non-Hispanic or Latino	56 (90)
Race	
American Indian or Alaska Native	1 (2)
Asian	4 (7)
Native Hawaiian or Other Pacific Islander	0 (0)
Black or African American	21 (34)
White	33 (53)
More than one race	3 (5)
Education level	
Completed senior high	3 (5)
Completed some college	12 (19)
Graduated from college	29 (47)
Completed postgraduate or professional degree	18 (29)
Household size (including index participant)	
2	24 (39)
3	15 (24)
4	16 (26)
≥5	7 (11)
Grocery shopping frequency	
Less than once per week	6 (10)
Once per week	29 (47)
Twice per week	18 (29)
More than twice per week	9 (15)
BMI range, kg/m^2	
Underweight BMI (<18.5)	1 (2)
Normal BMI (18.6-24.9)	12 (19)
Overweight BMI (25-29.9)	17 (27)
Obese BMI (>30)	32 (53)

Table 3. Baseline age and average body composition measurement.

	Mean (SD)	Range	
		Minimum	Maximum
Age (years)	47.2 (13.5)	23	69
Weight (kg)	85.6 (21.7)	42.6	135.6
BMI (kg/m^2)	32.1 (8.0)	16.1	51.3

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Table 4. Baseline dietary intake.

Category	Cohort 1, mean (SD)	Cohort 2, mean (SD)
Daily averages		
Fiber (grams)	17.86 (7.06)	16.54 (8.63)
Fruit and vegetables (cups)	2.02 (1.23)	2.67 (1.55)
Added sugar in processed foods (grams)	38.43 (29.71)	26.22 (18.05)
Saturated fat in processed foods (grams)	14.83 (8.54)	8.56 (4.51)
Sodium in processed foods (milligrams)	1699.39 (842.84)	649.16 (315.19)
Sugar-sweetened beverages (oz)	10.96 (10.57)	20.82 (29.88)
Weekly averages		
Red meat (oz)	10.66 (15.48)	4.10 (3.12)
Processed meat (grams)	228.28 (335.15)	149.30 (214.15)
Adherence scores (range 0-1)		
Fiber, fruit, and vegetable guideline	0.39 (0.25)	0.43 (0.28)
Processed foods guideline	0.38 (0.26)	0.61 (0.23)
Red and processed meat guideline	0.50 (0.30)	0.56 (0.27)
Sugar-sweetened beverages guideline	0.30 (0.34)	0.22 (0.31)
Overall adherence (average)	0.39 (0.15)	0.46 (0.14)
Overall adherence (sum)	1.57 (0.62)	1.85 (0.55)

Discussion

Principal Findings

Dietary intake is a critical modifiable risk factor of cancer. Grocery shopping is a potentially efficient and powerful intervention target; if individuals can make healthy purchases in stores, this will create optimal defaults in the home food environment that will make healthy eating more likely. However, in our modern obesogenic food environment, there is frequent exposure to tempting food cues, which makes healthy grocery store decisions difficult and demanding on self-regulatory capacity. Therefore, interventions to improve grocery shopping habits could focus on bolstering self-regulation at the key point of purchase.

The conceptual model proposed in this protocol attempts to improve grocery store purchases by targeting three key aspects of decision-making (goal salience, motivation, and social support) through four intervention components (location-triggered messages, benefits of change, coach monitoring, and household support) delivered via remotely delivered coaching and mHealth tools. The intervention moves beyond basic applications of stimulus control with appreciation for how challenging it is to change food purchasing habits. The tools used to promote behavior change are innovative, including geofence-triggered in-app messages to increase the salience of dietary goals and benefits of change at the moment of food purchasing, passive streaming of food purchase data to enable supportive accountability from a third party, and messaging and coaching to increase support and accountability at the household level.

Given the early stage of research on this type of intervention, methodical testing of the intervention components is needed. This study uses a factorial design to test the 4 intervention components and examine their feasibility, acceptability, and effect on food purchases and dietary intake, both individually and in combination. If the intervention components were tested at this stage in a 2-arm study (full package vs comparison condition) and found to be effective, it would be unknown which components contributed to the effect, how components influenced each other, or how to best make the intervention scalable and efficient [105].

Strengths and Limitations

The tools used for the assessment and classification of food purchasing in this study are novel. The process of passively streaming item-level purchase data from the point of purchase to a database that can be used for both research (ie, outcome assessment) and clinical purposes (ie, coach monitoring) is a high-risk, high-reward element of the study. Successful demonstration of the use of this assessment tool would be a major contribution to the field's efforts to create low-burden, high-validity options for collecting dietary data. Of course, although the objective nature of these food purchasing data is a strength, purchasing behavior does not align perfectly with dietary consumption. For example, individuals may purchase items at the grocery store that they do not eat themselves (eg, buying a snack item for their child) or that they only eat a small portion of (ie, share with others in their household). Food purchasing data also provide an incomplete picture of dietary intake, in that individuals may shop at food retailers outside of those accessible by our API system (eg, other grocery stores, farmers' markets, or corner stores), and eat food items from other sources (eg, restaurants or social gatherings).

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The use of geofencing to send location-triggered messages is also novel, as this technology has had only limited use in intervention studies. Using this new technology comes with the risk that the system may deliver messages at unintended times (ie, not when arriving at the grocery store) or fail to send them when expected, which would decrease the potency of the location-triggered text component of the intervention.

The protocol was launched during the COVID-19 pandemic and has had an impact on grocery shopping habits. When the pandemic began, studies show that the frequency of grocery shopping decreased to minimize exposure, and the types of foods purchased changed, driven more by what was available than by preference [106]. There were increases in the number of foods purchased during single grocery shopping trips, with people *stockpiling* out of fear of supply shortages [107]. Use of grocery delivery and pickup services has increased sharply since the pandemic began [108], showing increases of 158% and 255%, respectively [107]. However, at the same time, during the pandemic, individuals were also consuming less food outside the home [108], so in some ways grocery shopping may be an even better indicator of food intake than it previously was. Taken together, it may be more difficult to detect the effects of the intervention components, as change in purchases across the 20-week program could be influenced by pandemic-related confounds.

The self-reported assessment of dietary intake used in this study differs for cohort 1 and cohort 2 participants. Although the ASA24 (used in cohort 1) is a well-validated, frequently used measure with strong psychometric properties [109], participants reported that it had high burden and low acceptability. Therefore, the DHQ-III was used for cohort 2 participants. The DHQ-III is a traditional food frequency questionnaire, which has been cited in some studies as having less validity relative to the ASA24 [110], but it is a single-use, briefer questionnaire with lower burden, which may be necessary to maintain retention and engagement. Another weakness of the study's assessment of dietary intake is that both the ASA24 and DHQ-III have limitations in their ability to capture all relevant food and drink items to quantify adherence to the WCRF/AICR guidelines. For example, in these types of dietary recalls, it can be difficult to differentiate between a processed can of soup that may contain high amounts of added sodium versus a homemade soup lower in sodium; however, these items have different implications in terms of adherence to guidelines for cancer risk.

Conclusions

Despite these limitations, this study has the potential to advance the science of diet-related cancer prevention. This study is expected to lead to a large trial that will test an optimized package of intervention components. This trial will have the resources to test intervention effects for a longer period with a larger sample. A larger trial may also have the resources to incorporate additional assessment methods, such as objective measurement of the home food environment through home visits, use of ecological momentary assessment to illuminate decision-making while grocery shopping, and comprehensive assessment of household members' dietary intake to measure the ripple effect of the intervention. If effective, these intervention efforts have the potential to meaningfully lower cancer risk at the population level. Importantly, although specific nutrition guidelines for cancer control may change in the future, this study's contributions to the science of eating behavior change may be applied to various nutritional targets.

Acknowledgments

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Data Availability

The data generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

MLB conceived and designed the study. OZH, NTC, and MLB wrote the initial draft of the manuscript. OZH, NTC, EMF, BJM, NLS, FZ, and MLB made substantial contributions to the planning and design of the study and contributed to the revision of the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Original peer-review report from the National Institutes of Health for the grant proposal for this study.
[PDF File (Adobe PDF File), 161 KB - resprot_v11i6e39669_app1.pdf]

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Abbreviations

AICR: American Institute for Cancer Research
API: application programming interface
ASA24: Automated Self-Administered 24-hour Dietary Recall
DHQ-III: Diet History Questionnaire-III
mHealth: mobile health
FNDDS: Food and Nutrient Database for Dietary Studies
NCI: National Cancer Institute
WCRF: World Cancer Research Fund

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Protocol

The Brain and Early Experience Study: Protocol for a Prospective Observational Study

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Abstract

Background: Children raised in conditions of poverty (or near poverty) are at risk for nonoptimal mental health, educational, and occupational outcomes, many of which may be precipitated by individual differences in executive function (EF) skills that first emerge in early childhood.

Objective: The Brain and Early Experience study considers prenatal and postnatal experiences that may mediate the association between poverty and EF skills, including neural substrates. This paper described the study rationale and aims; research design issues, including sample size determination, the recruitment strategy, and participant characteristics; and a summary of developmental assessment points, procedures, and measures used to test the study hypotheses.

Methods: This is a prospective longitudinal study examining multiple pathways by which poverty influences normative variations in EF skills in early childhood. It is funded by the National Institute of Child Health and Human Development and approved by the institutional review board.

Results: Recruitment is complete with a sample of 203 participants, and data collection is expected to continue from September 2018 to February 2024. Of those recruited as *low socioeconomic status* (SES), 71% (55/78) reported income-to-needs (ITN) ratios of <2.0, and 35% (27/78) reported ITN ratios of <1.0. Among participants recruited into the *not-low SES* stratum, only 8.8% (11/125) reported ITN ratios of <2.0, and no participant reported ITN ratios of <1.0. The average ITN ratio for participants recruited into the low-income stratum was significantly lower than the average for the high-income recruitment cell (P<.001). Comparable recruitment outcomes were observed for both Black and non-Black families. Overall, the sample has adequate diversity for testing proposed hypotheses, with 13.3% (27/203) of participants reporting ITN ratios of <1 and >32.5% (66/203) reporting ratios of <2.0.

Conclusions: Preliminary results indicate that the recruitment strategy for maximizing variation in family SES was successful, including variation within race. The findings of this study will help elucidate the complex interplay between prenatal and postnatal risk factors affecting critical neurocognitive developmental outcomes in early childhood.

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KEYWORDS

poverty; executive functioning; parenting; language; sleep; neurological development

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Introduction

Background

On average, children raised in poverty perform more poorly on cognitive assessments and achieve lower academic outcomes than children from higher-income families [1], possibly owing to the effects of nonoptimal environmental experiences compromising early brain maturation and executive function (EF) skills [2]. Despite its significance, limited information exists on the neural and cognitive precursors and the social determinants of EF skills, especially during the first 3 years of life [3]. To address this scientific gap, the Brain and Early Experience (BEE) study examines specific prenatal and postnatal pathways from economic disparity to EF skills mediated by environmental experience and early structural and functional brain development.

Study Design Considerations

Beginning in utero, poverty imposes numerous risk factors [4] that contribute to an achievement gap persistent throughout formal schooling for poor and nonpoor children [5]. This leads to less educational attainment, increased likelihood of single parenthood, lower occupational status, poorer physical and mental health, and increased risk for all causes of mortality [6]. The limited development of neural substrates supporting neurocognitive development and the disrupted or delayed emergence of EF skills and other cognitive and language abilities may serve as mechanisms by which poverty gets *under the skin* and alters developmental trajectories across the life span [7].

A variety of cognitive processes that support goal-directed behavior are subsumed under the construct of EF. In early childhood, the 3 most widely studied subdomains of EF include *working memory*, defined as the holding in mind and updating of information while performing some operation on it; *inhibitory control*, defined as the inhibition of prepotent or automatized responding when engaged in task completion; and *mental flexibility*, defined as the ability to shift attentional or cognitive set among distinct but related dimensions or aspects of a given task [8]. Identifying the specific experiential and neurocognitive mechanisms through which poverty leads to poor EF is essential for optimizing early intervention programs.

Neuroscientists investigating how poverty influences children's neural development have identified systematic differences in structural brain development that mediate associations between poverty and impaired academic outcomes [9-12]. Specific examples include developmental differences in the maturation of frontal and temporal lobe gray matter that explained up to 20% of the variance in low-income children's cognitive deficits [13] and different surface-based morphometry indexes (ie, cortical thickness, surface area, cortical folding, and combinations of these) between poor and not-poor children [3]. These brain regions (and associated neural networks) may be highly vulnerable to the early environmental risks associated with poverty. Therefore, the BEE study applies a developmental science approach to the study of prenatal [14] and postnatal [15] determinants of neurocognitive development and later EF.

As the earliest experience in development, the prenatal period is a highly sensitive time for neurocognitive development. Although there are numerous studies on women's physical health during pregnancy and offspring neurodevelopment [16-18], there is less research on how mental health and psychological experiences during pregnancy may be associated with subsequent neurodevelopmental outcomes. Factors such as elevated prenatal stress may influence early neurocognitive skills through their influence on the proliferation, differentiation, migration, and aggregation of fetal neurons [19,20]. For example, Buss et al [21] report that pregnancy-specific anxiety predicts reduced gray matter density in the cortex, the left middle temporal lobe, the entorhinal cortex, and the parahippocampal gyrus at 6 to 9 years of age. The BEE study examines both subjective measures of prenatal stress (via self-report) and objective measures (via biological stress markers) as potential mediators of associations between poverty and prenatal brain development.

Following birth, poverty adversely influences children's development through early proximal experiences [22], with negative associations reported between family socioeconomic status (SES) and caregiving behaviors [23,24], child sleep quality [25], and child language exposure [26,27]. In contrast, multiple studies indicate that the quality of early caregiver–child interactions predict childhood EF and changes in EF throughout time [28-30]. These effects may be owing to the support and stimulation provided by a responsive parent or the favorable environment in which children can practice these developing skills as active agents in their own learning and skill acquisition. Similarly, sleep hygiene in early childhood predicts emerging EF in children [31]. Bernier et al [32] report that sleep in the first year of life predicts improved EF at 26 months; however, it was not related to other cognitive outcomes such as verbal ability or broader cognitive functioning, suggesting that sleep may be particularly important for EF. Activities that engage executive control are effortful and may be supported through energy restoration that occurs during sleep [33,34]. Finally, early language exposure contributes to children's emerging language and EF skills [35,36]. Children's expressive language contributes to problem solving and self-directed speech to regulate thoughts, emotions, and behavior [37,38] and emerging EF skills [39-44].

Considering these findings, the BEE study examines caregiver–child interaction quality, child sleep hygiene, and language exposure as environmental experiences potentially mediating the associations between poverty, brain development, and emerging EF. These constructs were also selected because they (1) are among the most salient for all children and account for a large percentage of the child's daily lived experiences, (2) have reliable, valid, and developmentally appropriate methods of measurement across time, and (3) are moderately stable throughout time, providing confidence that our assessments will represent the overarching experience of the first 3 years of life. It is also important to note that extreme levels of poverty are not necessary for observing the associations between family income and child outcomes. Several studies report that children living above but near the poverty level—or even up to 2 times the poverty level—experience significant neurocognitive risk

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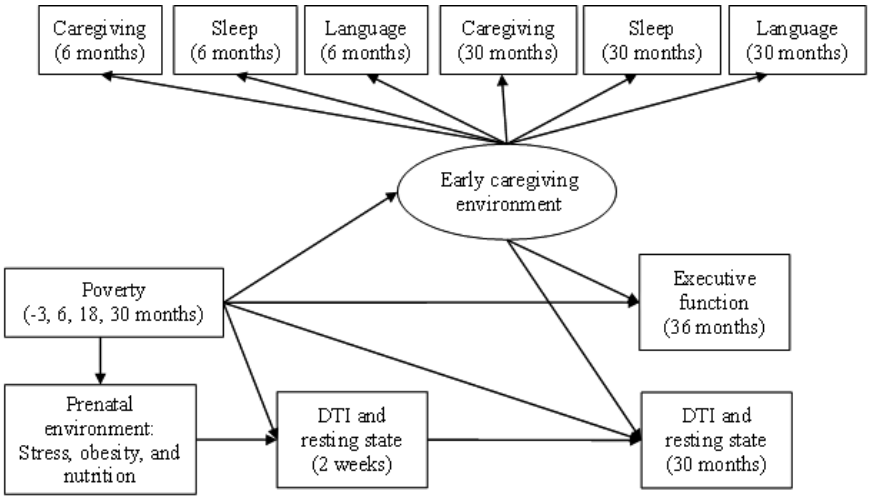
[9,12]. As described further, the BEE study purposefully sampled families along a range of socioeconomic risks (with oversampling for those in poverty) to capture the variability in poverty and poverty-related risk predictive of neurological and EF development.

The BEE study also uses state-of-the-art functional magnetic resonance imaging (fMRI) measurements to observe neurological development soon after birth and before the third year of life. Most studies examining associations between poverty and the brain used global metrics of brain development (eg, total gray matter and total surface area) and relied on cross-sectional data and mixed age samples. However, the development of EF skills involves efficient information processing between brain regions relying on the integrity of specific white matter tracts and the underlying neural networks connecting them [45]. Moreover, it may be that the developmental pattern during this earliest period of life is most informative, given that the most prolific changes in brain development that inform early EF occur from birth to 3 years [46]. The BEE study addresses these limitations by examining associations between poverty and early structural (ie, white matter integrity via diffusion tensor imaging [DTI]) and functional (ie, resting state [rs] networks via fMRI) aspects of brain development at 2 weeks and 30 months of age. In this study, we will interpret brain development at 2 weeks of age as a product of prenatal experiences and brain development at 30 months of age as a combination of prenatal and postnatal experiences.

Aims and Hypotheses of the BEE Study

The BEE study addresses 3 specific aims. Aim 1 involves the examination of associations between poverty and neonatal structural and functional brain development at 2 weeks of age. Two sets of hypotheses are proposed for aim 1. The first is that poverty will predict individual differences in neonatal structural brain development (specifically for white matter tracts that support cognitive processes of emerging EF) and functional brain development (including rs networks related to attention, salience, executive control, and default mode); the second is that these associations will be partially mediated by prenatal experiences, including stress, nutrition, obesity, and toxic environmental exposures. Aim 2 involves the examination of associations between poverty and toddler structural and functional brain development at 30 months of age and potential mediators of these associations. Three sets of hypotheses are proposed for aim 2. The first is that poverty will predict individual differences in changes in toddler structural and functional brain development. The second hypothesis is that prenatal experiences will partially mediate these associations. The third hypothesis is that postnatal experiences (ie, caregiving, sleep hygiene, and language exposure) will partially mediate the association between poverty and toddler brain development. Finally, aim 3 involves the examination of pathways from poverty to EF at 36 months of age. Three sets of hypotheses are proposed for aim 3. The first hypothesis is that poverty will be negatively associated with EF, the second is that prenatal experiences will partially mediate the association between poverty and EF, and the third is that postnatal experiences will also partially mediate these associations. The path model in Figure 1 illustrates these aims and hypotheses.

Figure 1. Conceptual model depicting research aims. DTI: diffusion tensor imaging.



Methods

Sample

Power Analyses to Determine Sample Size

Two Monte Carlo studies were conducted to determine the statistical power to evaluate study aims given the proposed sample size and design. Both studies, which adopted the approach of Thoemmes et al [47], included a population generating model of 200 participants, assumed a type I error rate of 0.05, and involved 5000 replications. With these parameters, for tests of main effects (encompassing associations between poverty child outcomes, including brain development at 2 weeks and 30 months and child EF, general cognitive ability, and language development at 30-36 months), the sample has the power (≥0.98) to detect small to medium (R^2=0.075) sized main effects but has limited power (0.51) to detect small (R^2=0.02) main effects. For tests of mediation (encompassing

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the main effects as mediated by prenatal and postnatal experiences), the sample has power (>0.99) to detect single mediated effects when both the *a* and *b* paths are of medium size (R^2=0.13). The study has power (>0.89) to detect a mediated effect when both *a* and *b* paths are of small to medium size (R^2=0.075). However, the power to detect a mediated effect drops to 0.45 when either *a* or *b* paths are of small size (R^2=0.02), even if the other path is of medium size. As a point of reference for those readers who are unfamiliar with Monte Carlo methods, 200 results in a power of 0.80 to detect bivariate correlations $|r| \geq 0.20$, which also corresponds to a small to medium–sized effect per the Cohen conventions [48]. The study will rely on high-quality measurement and repeated measures to improve the magnitude of the effects.

Recruitment Strategy

From August 1, 2018, through October 31, 2020 (26 months), we used multiple methods to reach the population of interest (pregnant women in their second trimester). These include targeted advertisements on social media, online community message boards, hospital records in the local university-based medical center, listserv emails to local university staff and students, paper fliers posted in obstetrician–gynecologist offices in the local geographic area, and personally staffing information tables at the Women, Infant, and Children centers before, during, and after local pregnancy and birthing classes. Individuals interested in participating in the study were directed to a brief web-based survey that asked questions targeting inclusion criteria, including being currently pregnant with a single fetus and speaking primarily English at home. If both criteria were met, subsequent questions regarding due date, contact information, and permission to be contacted for participation were asked. Next, a study personnel used this information to schedule a phone call with each participant. During this phone call, the researcher confirmed the inclusion and exclusion criteria and obtained the person's address to confirm that they lived within a 45-minute radius of the study location and that there was no intent to move out of the geographic area in the next 3 years.

The research staff then asked demographic questions to assign potential participants to 1 of 4 recruitment cells based on a 2×2 (SES×race) design. This categorization as part of the recruitment process was important because, as a study focusing on the role of poverty in early development, we sought to limit confounding between income and race by oversampling (relative to local family demography) for combinations of (1) lower SES and non-Black racial identity and (2) not-low SES and Black racial identity. Three demographic questions were asked for all potential participants who met inclusion criteria. The first question was about the person's race and ethnicity. The second question was about the individual's highest level of education. The third question asked about the use of a range of federal social services that are eligible to families at or below 185% of the federal poverty level, including Women, Infant, and Children program, Temporary Assistance for Needy Families, Supplemental Nutrition Assistance Program, or Medicaid. Following the precedent established by other large-scale developmental studies of families living in poverty [49], we used these questions to assign potential participants into a *low-SES* group if they had no education beyond a high-school diploma or general education degree or if they currently used a social service. Otherwise, they were classified as *not-low SES*. We designated a participant as *Black* if they self-identified as Black, African American, or multiracial Black; otherwise, they were designated as non-Black. These 2 dimensions were cross-tabulated to create 4 target recruitment cells with the goal of recruiting comparable numbers of low-SES and high-SES families within each racial group to reduce potential confounding between race and family income. The assignment of families into cells was intended solely to guide recruitment efforts and should not be used for hypothesis testing regarding family income and race. Families were considered formally enrolled if they completed 2 of the first 3 data collection visits (including the prenatal visit, the 2-week postnatal visit, and the 6-month postnatal visit). If a family did not meet these inclusion criteria, they were dropped from the study and replaced by a newly recruited family with comparable SES and racial identities. See Multimedia Appendix 1 for a flowchart documenting recruiting and sampling numbers that resulted in the final sample size of 203 participants.

Sample

On average, biological mothers of BEE participants were aged 30.53 (SD 5.35, range 18-46) years and had completed 15.36 (SD 2.66) years of education at the prenatal visit. Approximately 33% (67/203) of the sample identified as Black or African American, and approximately 8.9% (18/203) identified as Hispanic or Latina. At the prenatal visit, 90.1% (183/203) of mothers were currently in a romantic relationship, 66.9% (136/203) were married to their partner, and 84.06% (170/20,223) were living with their partner, defined as spending a minimum of 3 nights together at the same residence).

Design and Procedures

Overview

The COVID-19 pandemic had 3 impacts on the design and execution of the BEE study. First, the pandemic interrupted and prolonged study recruitment procedures resulting in a recruitment window of 26 months. Second, some of the in-person planned visits were adapted to be conducted on the web and involve family-led data collection activities. This was most disruptive during the prenatal, 2-week, and 6-month visits that had already begun as *in-person* protocols and were shifted to web-based protocols because of the COVID-19 pandemic. Third, the timings of some visits were delayed. Although the original plan included 15- and 24-month visits, the final data collection timeline shifted these visits to 18 and 30 months. Each of these issues is discussed in the context of a brief synopsis of the overall study timeline.

Following recruitment, pregnant women are seen at a prenatal laboratory-based visit. Research staff follow up with participants around the expected due dates to speak with the participant as soon as possible following the child's birth. During this conversation, staff determines if any new exclusion criteria for participation in the study are present—this includes being born with low birth weight (<2500 grams) or a gestational age below

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36 weeks and 4 days, being in the neonatal intensive care unit for >24 hours after birth, being on a ventilator at birth, having had surgery or a chronic illness that would prevent participation, or demonstrating a medical reason that would prevent them from entering the fMRI scanner (eg, cochlear implants or other metal in the body). Exclusion criteria are consistent with our emphasis on the influence of poverty on individual differences in typically developing children. Those retained in the study are scheduled for a laboratory visit at 2 weeks postpartum. Participants are next seen during a home visit at 6 months of age (some were seen only via video-based visits on the web because of the COVID-19 pandemic) and then on a video-based visit on the web at 18 months of age (because of the COVID-19 pandemic). Next, participants are seen for a video-based visit on the web at 30 months of age, followed immediately by a laboratory visit also at 30 months of age (for the second fMRI scan). Finally, participants are seen at the laboratory for their last data collection visit at 36 months of age.

Prenatal Laboratory Visit (and Web-Based Visit During the COVID-19 Pandemic)

Pregnant women were invited to participate in their first data collection visit for the BEE study at the Biobehavioral Laboratory at the University of North Carolina (UNC) at Chapel Hill School of Nursing. Following a description of the overall study and the prenatal data collection protocol, informed consent for participation was obtained. Next, participants were interviewed by research staff, completed a series of questionnaires, a series of computer-based cognitive assessment tasks, and engaged in a qualitative interview about their experiences during pregnancy and expectations about motherhood. Finally, the research staff collected hair, blood, saliva, and urine samples that were immediately processed and placed in cold storage at −80 °C. Participants were compensated for their travel costs and provided US $50 for their time. For this visit protocol, some visits were conducted in person in the laboratory, and others were done via Zoom call because of the human participants contact restrictions related to the COVID-19 protocols. The same tasks and instructions are used in each visit, but the computer-based cognitive assessment tasks and the blood collections were no longer possible in the web-based protocol. For participants who needed internet or computing devices for the Zoom call, we provide tablets and wireless hot spots to facilitate the web-based visit. For those receiving the web-based protocol, biospecimen collection materials were mailed to the home, and participants returned the materials to the study via mail.

The 2-Week Laboratory Visit (and Web-Based Visit During the COVID-19 Pandemic)

Participant mothers and children visited the UNC Biomedical Research Imaging Center for the 2-week laboratory visit. After providing informed consent for the visit, mothers complete a short series of questionnaires, and infants are fed, swaddled, and rocked or held comfortably by the mother until they fall asleep. Parents apply ear protection when they determine it will be most tolerable for their child. The brain scanning occurs during natural sleep using a Food and Drug Administration–approved 3 Tesla fMRI scanner and under continuous monitoring by study personnel. A pulse oximeter is placed on the child's toe to monitor oxygen levels and heart rate. Parents who complete an fMRI safety form are also allowed into the scanner suite with their child. Participants were compensated for their travel costs and provided US $100 for their time. For this visit protocol, some visits were conducted in person in the laboratory, and others were done via Zoom call because of the human participants contact restrictions related to the COVID-19 protocols. For web-based protocol participants, no fMRI scan was completed; only questionnaire data were collected.

The 6-Month Home Visit (and Web-Based Visit During the COVID-19 Pandemic)

Research staff visit participants in their homes for the 6-month home visit. After providing informed consent for the visit, mothers answered interview items and completed a series of questionnaires, and then the mother and child participated in 2 parent–child interaction tasks. The first involves playing together with a standardized set of toys for 10 minutes; the second involves the mother going through a wordless picture book with her child for 5 minutes. Both tasks are video and audio recorded for later behavioral coding. After these tasks, the research staff explain the extended data collection protocols for child sleep hygiene (7 days) and language exposure (2 days) after the visit. To collect sleep hygiene data, mothers are provided with a wearable actigraphy device (Actiwatch-2) for the child and instructed on how to attach it to the infant's ankle. Mothers are asked to leave the device on the child's ankle for 7 full days, remove it only during bath times, and then reattach it once the child is dry. Mothers are also provided a sleep diary to complete every morning for the next 7 days. To collect language exposure data, mothers were provided with a Language Environment Analysis (LENA) recording device, 2 vests, and 2 daily diaries. Mothers are asked to identify 2 typical days (out of the next 7) in which they will be spending most of their time with their child. On those days, mothers are asked to dress their child as they normally would first thing in the morning, then turn on the LENA recorder and place it in the pocket of the vest before putting the vest on the child. Mothers are asked to leave the device on all day. These steps are repeated for another day during the 7-day period. Mothers are also asked to complete daily diaries about the contexts and people in the child's environment during those days. Both the actigraphy and the LENA devices are retrieved from the participant's home on the seventh day following the 6-month home visit. Participants were compensated for their travel costs and provided US $50 for their time.

For this visit protocol, some visits were conducted in person in the participant's home, and others were done via Zoom call because of the human participants contact restrictions related to the COVID-19 protocols. The same tasks and instructions are used in each visit, but the parent–child interaction tasks were recorded using Zoom instead of in-person cameras. For participants who needed internet or computing devices for the Zoom call, we provide tablets and wireless hot spots to facilitate the web-based visit. For those receiving the web-based protocol, wearable devices and biospecimen collection materials were

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mailed to the home, and participants returned the materials to the study via mail.

The 18-Month Remote Visit

The research staff invited participants to join a video call for the 18-month Zoom visit. After providing informed consent (electronically) for the visit, mothers answer interview items and complete a series of web-based questionnaires. Wearable devices and biospecimen collection materials were mailed to the home, and participants returned the materials to the study via mail. Participants were compensated US $50 for their time.

The 30-Month Remote Visit

The research staff invited participants to join a video call for the 30-month Zoom visit. After providing informed consent (electronically) for the visit, mothers complete a series of questionnaires, and then mother and child participate in a parent–child interaction task. This task involves presenting the child with a series of 3 peg puzzles of increasing difficulty and instructing the mother that she can provide any assistance that she chooses. The task is video and audio recorded for later behavioral coding. The research staff explain the extended data collection protocols for child sleep hygiene (7 days) and language exposure (2 days) that continue after the visit. Additional components of this study visit are identical to those protocols used in the 6-month home visit described earlier (eg, actigraphy, LENA, and biomarkers). Wearable devices and biospecimen collection materials were mailed to the home, and participants returned the materials to the study via mail. Participants were provided US $50 for their time.

The 30-Month Laboratory Visit

Participant mothers and children came to the UNC Biomedical Research Imaging Center for the 30-month laboratory visit for their second fMRI scan. As at the 2-week visit, this scan occurs while children are naturally sleeping. To facilitate this, the 30-month visits are scheduled during the evening at the child's usual bedtime. After providing informed consent for the visit, mothers complete a short series of questionnaires, and children's natural bedtime routine is replicated to facilitate child sleep. Next, the research staff administer the Receptive Vocabulary, Information, Block Design, and Object Assembly subscales of the Wechsler Preschool and Primary Scale of Intelligence (the former 2 subscales index vocabulary acquisition and the latter 2 index visual-spatial abilities) [50]. Mothers apply ear protection when they determine it will be most tolerable for their child. At this point, the research staff follow the same fMRI protocol as used during the 2-week laboratory visit. Participants were compensated for their travel costs and provided US $125 for their time.

The 36-Month Laboratory Visit

Participant mothers and children came to the Biobehavioral Laboratory at the Frank Porter Graham Child Development Center at UNC Chapel Hill for the 36-month laboratory visit. After providing informed consent for the visit, mothers answer interview items and complete a series of questionnaires. During this time, research staff assess children's EF using the EF Touch battery [51] and assess children's language using the Peabody Picture Vocabulary Test [52]. Participants were compensated for their travel costs and provided US $50 for their time.

Measures

A list of all interviews and questionnaires administered at each data collection visit is provided in Multimedia Appendix 2. In the further sections, we describe the measurement of each key construct used to address the specific aims 1, 2, and 3 in greater detail.

Household Income

At each data collection visit, mothers reported (1) their annual income, (2) the annual income of their partner (if co-residing in the home), (3) the annualized contributions to the household of all others in the household, and (4) the annualized contributions from *other* sources of income (eg, unemployment insurance, worker's compensation, and social security retirement). Using this information, an annual household total income variable is created by summing all sources of income. Next, we divide this total amount by the federal poverty threshold for a family of that particular size and composition to create the income-to-needs (ITN) ratio—a standard measure of a family's economic situation where a value of 1.0 indicates living right at the poverty line. This approach to quantifying household income has been used extensively in population-based studies of poverty and child development [49].

Prenatal Stress

Self-report of Subjective Stress Experience

In all, 3 self-report questionnaires on experiences of stress are completed at the prenatal visit. The Cohen Perceived Stress Scale is a 10-item questionnaire measuring *general perceived stress* during the past month [53]. The items are rated on a 5-point Likert scale ranging from *never* (0) to *very often* (4) and have demonstrated high reliability; the reliability of Perceived Stress Scale in this study is 0.88. The Pregnancy-Related Anxiety Questionnaire–Revised-2 is a 10-item measure assessing *pregnancy-related stress* [54]. The items are rated on a 5-point Likert scale ranging from 0=*definitely not a concern at all* to 4=*definitely a very big concern*. The reliability of this scale in this study is 0.85. A modified 6-item version of the Economic Strain Questionnaire measures *financial stress*, including concerns about the inability of families to *make ends meet* and not having enough money for a home, clothing, food, and medical care [55]. Items are rated on a 5-point Likert scale (0=great deal of difficulty to 4=no difficulty at all) and on a 4-point Likert scale (0=strongly disagree to 3=strongly agree). Previous studies report adequate reliability of this scale and suggested that all 6 items could be standardized and summed or averaged to create a global measure of economic strain [55,56]. The reliability of this scale in this study is 0.88.

Biological Indexes of Prenatal Stress

A total of 2 classes of biological measures of stress were collected during the prenatal visit. The first includes hair cortisol concentration measured from hair strands close to the scalp from the posterior vertex area of the participant's head (this area has shown the lowest coefficient of variation [CV]). The 3 cm of hair closest to the hair roots are analyzed [57], reflecting

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exposure during the last 3 months (based on the hair growth rate of approximately 1 centimeter per month) [58]. Cortisol is measured in methanol extracts of hair using a competitive radioimmunoassay following standard assay procedures. The intra-assay CV is 1.17%, and the interassay CV is 5.12% in this sample—both values indicate reliable assaying results.

The second class of biological stress indexes includes multiple inflammatory markers observed during the prenatal visit. A total of 2 EDTA tubes are used to conduct antecubital venipuncture to collect nonfasting plasma samples from participants. Plasma samples are assayed for cytokines using a Meso Scale Discovery multiplex kit; this panel includes interleukin-6, interleukin-10, tumor necrosis factor, interleukin-1RA, interleukin-2, and interleukin-8, each measured in pg/mL. C-reactive protein is assayed using Meso Scale Discovery single-plex kit and is measured in mg/L.

Early Postnatal Experience

Caregiving

Video recordings of parent–child interactions will be coded by trained and certified coders to rate caregiving behaviors on the following dimensions: sensitivity, intrusiveness, detachment, stimulation of cognitive development, positive regard, negative regard, and animation. *Sensitivity* indexes the degree to which the caregiver is attuned and responsive to the physical and emotional needs of the child. *Intrusiveness* indexes the degree to which the caregiver is controlling and imposes their own agenda on the activity of the child. *Detachment* indexes the degree to which the caregiver is emotionally and physically detached and uninvolved with the feelings and activities of the child. *Stimulation of cognitive development* indexes the degree to which the caregiver provides linguistic stimulation in a developmentally appropriate way and scaffolds the activity to maximize the child's cognitive experiences of the task. *Positive regard* indexes the degree to which the caregiver directs feelings of warmth, love, and enjoyment toward the child. *Negative regard* indexes the degree to which the caregiver directly displays harshness and hostility toward the child. *Animation* indexes the level of energy and enthusiasm that the caregiver displays while interacting with the child. Each dimension is rated on a 7-point scale ranging from *not at all characteristic of this caregiver* to *extremely characteristic of the caregiver*. After being certified as reliable, each coder will continue to code a minimum of 20% of cases with a master coder for each coding assignment to prevent coder drift. Previous use of this parent–child interaction task and coding protocol have repeatedly identified 2 parenting composites guided by factor analyses [24,59], and we anticipate observing comparable factors. The first is referred to as *sensitivity* and is the mean of sensitivity, detachment (reversed), stimulation of cognitive development, positive regard, and animation. The second is *harsh intrusiveness* and is the mean of intrusiveness and negative regard.

Sleep Hygiene

A multi-method approach will be applied to assess sleep hygiene [60,61]. The actigraphy monitor worn on the child's ankle contains an accelerometer that measures limb movement in 15-second epochs. At the end of the sleep assessment week, actigraphy data are downloaded to a computer and edited using Phillips Actiware software (version 6.0). The Actogram algorithm settings are as follows: immobile minutes for sleep onset were set to 5 minutes; minimum rest interval size was set to 20 minutes; multiple rest intervals per day were allowed; automatically set minor rest intervals were allowed. The activity threshold for scoring the child as awake is set to the automatic setting (0.888×average activity count)—both the algorithm and threshold for scoring sleep or wake state have been previously validated [62].

The output from the Actiware program includes a listing of all sleep and wake intervals. Infant sleep onset time is determined as the start time of the sleep interval closest to the caregiver-reported bedtime (see sleep diary description below). Similarly, the child's rise time is determined as the end time of the sleep interval closest to the caregiver-reported rise time. Using sleep onset time and rise time, we subsequently calculate the duration of the child's sleep period. Child sleep time in minutes is determined by summing infant sleep time in each sleep interval between sleep onset time and rise time. Child wake time in minutes is determined by summing infant wake time in each sleep interval during the sleep period. Child night wakings are determined by subtracting 1 from the number of sleep intervals during the nighttime sleep period (ie, if the child sleeps in 3 sleep intervals, there are 2 night wakings). Finally, the longest sleep period equals the duration of the longest sleep interval during the nighttime sleep period.

In addition to actigraphy measures, the parent completes daily sleep diaries for the child. Every day during the sleep assessment week, research staff call mothers to obtain information about the previous day's naps and nighttime sleep, including number, location, and duration of naps, child bedtime, number of night wakings, types of interventions used during night wakings, and infant rise time [63]. Mothers also report any unusual occurrences that may have influenced the previous night's sleep, such as child illness.

Language Exposure

The LENA digital recorder and software automatically processes the audio-based language environment the child experiences during the 2 days of data collection. As a wearable device, the LENA recorder collects recordings of the language environment for the entire day (16 hours; for the purposes of this study, wake time to bedtime). After 2 full days of data collection, the LENA recorder connects to a computer, and its software automatically uploads and analyzes the language data using a series of iterative modeling algorithms developed by the LENA Research Foundation. This process segments the recordings based on acoustic energy and generates 3 language measures mapping onto the Hart and Risley language exposure dimensions—adult word, conversational turn, and child vocalization counts [64]. Adult word count is the total number of adult words spoken near the child. Conversational turn count is the total number of conversational interactions the child engages in with an adult (this involves one person speaking and the other responding within 5 seconds). Child vocalization count is the total number of speech-like utterances produced by a child. LENA software

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also generates other language indexes, such as overlapping speech, television and media, and background noise. This study focuses on adult word count and conversation turns as key indicators of child language exposure in the first 3 years of life.

Brain Development

DTI and rs fMRI scans are acquired at 2 weeks and 30 months of age. Scanning sequences are fully compatible with the Human Connectome Project (Multimedia Appendix 3). We use previously established image processing pipelines, quality control measures, and analysis protocols, which have proven successful for repeat scanning with infants and young children [65-68].

DTI Analysis

Diffusion images are screened using an automatic program for quantifying motion artifacts and corrupted sections using the diffusion-weighted imaging or DTI analysis quality control tool DTIPrep [69]. This program includes the correction of motion, eddy of current artifacts, and removal of outliers. Diffusivity property maps, such as fractional anisotropies, are estimated using standard weighted least square fitting [70]. The Brain Extraction Tool [71] is used for the skull stripping of all images. Unbiased atlas building [70] with large deformation diffeomorphic metric mapping registration [72] is used after a linear registration [73]. All data to be analyzed in this study are used to build the atlas. Transformations obtained from the atlas building are applied to warp the original tensor images to the atlas space, and the final DTI atlas is obtained by averaging the warped images. DTI tractography in atlas space yields all fiber bundles of interest [74].

Our established tractography pipelines generate quantitative DTI data for cohesive analysis of imaging data collected at 2 weeks and 30 months of age. Diffusion properties (fractional anisotropy, axial diffusivity, and radial diffusivity) are generated for white matter tracts hypothesized to support emerging EFs and language, including arcuate, uncinate, and anterior cingulum. Tractography algorithms with Runge-Kutta integration are performed in the atlas tensor image constructed from the unbiased DTI registration. The improved signal-to-noise ratio of participant-specific atlases (integrating data from 2 weeks to 30 months), deformed to a group atlas, allows reliable extraction of fiber bundles that would be hard to extract consistently from individual data (ie, arcuate). Fiber tracts are parameterized by length to represent diffusion properties as a function of location along the selected tracts [73,74].

Resting State

We will primarily use a seed-based approach to characterize the dynamic developmental changes of functional networks related to attention, salience, executive control, and default mode. Specifically, network-specific seeds will be defined according to our previous studies and used to generate functional connectivity maps of each network for the scans collected at 2 weeks and 30 months. Two measures of network integrity will be derived: mean functional connectivity and network maturation score. For the former, after defining the functional connectivity map of each network, individual clusters of significance will be extracted, and a cross-correlation matrix among all clusters within the same network will be calculated for each participant. The mean functional connectivity will be defined as the average of all pair-wise correlations within the network. This measure quantifies the individual functional network integrity in an age-adaptive fashion based on age-specific functional connectivity maps. For our measure of network maturation score, we will calculate a network maturation score using adult functional network topology as a reference to quantify the degree of maturation toward adult-like network topology [75]. On the basis of the same adult reference, this measure facilitates statistical comparisons across age groups and has been shown to be sensitive to SES during infancy [76]. Specifically, using the adult group-level significant functional networks as references, a binary mask was derived for each network. Subsequently, the within-network connectivity was defined as the mean functional connectivity strength within the mask, indicating the degree of within-network synchronization, whereas outside-network connectivity was the mean functional connectivity of areas outside the network mask, indicating the degree of outside-network specialization. Finally, based on a previously established network matching concept [77], the subtraction of the outside-network connectivity from within-network connectivity yields a network matching score, indicating the degree of similarity between the network in question and the adult reference network in terms of functional connectivity strength distribution of the whole brain. This network matching score will be used as an overall measure to quantify the maturation of individual networks.

To test the robustness of our results, a data-driven independent component analysis approach [78], which has been used extensively in previous studies, will be applied to extract the corresponding networks and subsequent network-level functional connectivity measures [79]. Identical analysis as listed above will be carried out based on independent component analysis–based measures to replicate our findings using a seed-based approach. Finally, given the controversy of the preprocessing step of global signal regression [80,81], our results will also be tested with or without this step to identify converging findings.

EF Skills

Children's EF is measured at 36 months using the EF Touch, a computerized battery of EF tasks that have been iteratively developed over the last 10 years [82-84]. Each EF task takes 3 to 7 minutes to complete. A total of 2 *warm-up* tasks are typically administered first to acclimate children to using the touch screen. The reliability and validity of the EF Touch battery have been extensively documented, including with children aged as young as 3 years [85]. Mean accuracy across items within each task will index task performance.

Three tasks assess children's *inhibitory control*: *Spatial Conflict Arrows*, *Silly Sounds Stroop*, and *Animal Go/No-Go*. Two tasks will assess children's *working memory* at 36 months of age: *Working Memory Span* and *Pick a Picture*. One task will assess children's *attention shifting* at 36 months of age: *Something's the Same*. In addition to performance-based measures, assessors will complete the Preschool Self-Regulation Assessment

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following the administration of tasks. The Preschool Self-Regulation Assessment consists of 28 items that are combined to form attentional control and positivity scales that reflect behavior during EF task completion [86].

Analysis Plan for Key Aims

Before conducting statistical analyses, the psychometric properties (ie, item to total correlations and α coefficients) of all questionnaires will be evaluated, and the interrater reliability (ie, intraclass correlations and α or κ coefficients) of measures that were based on observational coding will be documented. Descriptive statistics will be computed for all measures with an emphasis on distributions and outliers. Data transformations will be considered for variables appreciably skewed. When multiple measures are correlated within an assessment period (eg, caregiver-reported stressors during the prenatal visit), principal components and factor analyses will be used to create composite scores.

A structural equation modeling approach will be used to test all study aims. All structural equation modeling models will be estimated using a robust full information maximum likelihood estimator. The robust full information maximum likelihood estimator accommodates nonnormally distributed outcome variables and represents a statistical best practice for accommodating missing or unbalanced data [87,88]. To maximize power and avoid distributional assumptions, bootstrapped tests of indirect effects will be used to test questions of mediation related to aims 2 and 3 [89,90]. An exemplar path diagram corresponding to aims 1 to 3 is depicted in Figure 1 (residual variances or covariances are omitted to simplify the presentation).

Examination of direct and indirect effects will provide formal tests of aim 1. This will include testing a direct effect of prenatal poverty on brain development at 2 weeks of age and testing this path as an indirect effect mediated by subjective measures of prenatal stress (from self-report) and biological indexes of stress (indexed by hair cortisol and inflammatory markers).

Examination of direct and indirect effects will provide formal tests of aim 2. Direct effects from postnatal poverty (aggregated across 6, 18, and 30 months of age) on brain development at 30 months (controlling for comparable neurological indexes at 2 weeks of age) will test the association between poverty and brain development in the first 30 months of life. We will evaluate a measurement model for a latent caregiving environment variable based on observed caregiving, sleep hygiene, and language exposure at 6 and 30 months of age. This latent variable will be examined as a partial mediator in the indirect path from postnatal poverty to brain development at 30 months of age. If the measurement model fails to establish an adequate fit, we will use each individual's indicators of early life experience as predictors or mediators in the model.

Each of the models described for testing hypotheses in aims 1 and 2 will be extended to include an EF composite, measured at 36 months, as a distal outcome. The EF composite will be regressed onto the 2-week and 30-month parameters for each DTI and rs metric, caregiving environment latent variable, prenatal stress measure, and prenatal and postnatal indicators of poverty (if prenatal and postnatal indicators of poverty are collinear, a single combined index will be used). The tests of direct and indirect effects of prenatal and postnatal poverty will provide a formal test of aim 3.

The previous analyses will provide definitive tests of all study aims. However, as described in the *Measures* section, we will also collect multiple indicators of general cognitive development (eg, Wechsler Preschool and Primary Scale of Intelligence and expressive language) at earlier assessments, and these interim measures will be used as outcomes in analyses that begin to test the guiding questions of this study before the completion of final data collection. These analyses will consist of simplified variations of the models described above. Interim measures will also be used for sample description.

Ethical Considerations

The study has institutional review board approval from the University of North Carolina at Chapel Hill (study number 17-1914).

Results

Recruitment is complete with a sample of 203 participants. Data collection began in September of 2018 and is expected to conclude by February 2024. This is a prospective longitudinal study; thus, analyses addressing the project's specific aims are not yet available. However, analyses addressing the validity of the project's recruitment strategy are provided by examination of the distribution of ITN ratios (a ratio of annual household income relative to a federal poverty threshold for a given household size, as described in the *Measures* section), the amount of money immediately available in savings or checking accounts, and homeownership data (all reported at the prenatal visit). We identified a participant as an outlier with an ITN ratio of 37.88; to limit the effects of this extreme value, we winsorized it to the next highest value of 15.79. The ITN distribution remained positively skewed with a minimum value of 0.00 and a maximum value of 15.79 (see Multimedia Appendix 4 for descriptive ITN information for the entire sample and separately by recruitment cell). For the total sample, 32.5% (66/203) of the participants reported an ITN ratio of <2.0 (interpreted as *near poor* or *working poor*), and 13.3% (27/203) of the participants reported an ITN ratio of <1 (interpreted as *poor* per the US federal definition of poverty). Next, we examined ITN distributions by recruitment SES designation. Of those recruited as *low SES*, 71% (55/78) reported ITN ratios of <2.0, and 35% (27/78) reported ITN ratios of <1.0. Among participants recruited into the *not-low SES* stratum, only 8.8% (11/125) reported ITN ratios of <2.0, and no participant reported ITN ratios of <1.0. The average ITN ratio for participants recruited into the low-income stratum was significantly lower than the average for the high-income recruitment cell (t_{188}=−9.643; P<.001; Figure 2).

Comparable percentages of income levels across SES designations at recruitment were observed for Black and non-Black participants. As seen in Figure 2, within racial categories, (1) non-Black low-income participants reported lower ITN ratios than non-Black high-income participants

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(P<.001), and (2) Black low-income participants reported lower ITN ratios than Black high-income participants (P=.002). Within SES categories, (1) non-Black low-income participants were not statistically different from Black low-income participants, and (2) non-Black high-income participants were not statistically different from Black high-income participants.

Although ITN is a broad indicator of a family's financial standing, another indicator of economic insecurity is the availability of liquid funds, such as money in bank savings or checking accounts. According to the US Federal Reserve, in 2018, only 61% of Americans had immediate access to funds to cover a US $400 emergency expense [91]. In the study sample participating in this study, there are similar distributions and mean differences for participant reports of money immediately accessible in bank savings and checking accounts (Multimedia Appendix 5) compared with household ITN ratios. The average bank savings for the low-income recruitment cell was significantly lower than the average for the high-income recruitment cell (t_{181}=−5.44; P<.001; Figure 3).

Although ITN and immediately accessible funds are important indicators of economic security, individual differences among families in overall wealth may also differentially buffer families from stress and negative life events (and racial disparities in wealth have been studied less than income despite being potentially larger in magnitude). An indicator of family wealth is homeownership. Among those recruited as high-SES, 76.8% (96/125) owned their homes compared with 20.8% (26/125) that rented their homes (note that these percentages do not sum to 100% because some participants lived with family and thus neither owned nor rented their homes). Conversely, among participants recruited as low-SES, only 8% (6/78) owned their homes, whereas 82% (64/78) rented their homes. Rates of homeownership for non-Black participants were similar to the overall sample. However, for Black participants, homeownership rates were lower. For high-SES Black families, only 35% (6/17) owned their own homes; for low-SES Black families, only 6% (3/48) owned their homes.

In summary, across these 3 indicators (ITN ratio, bank savings, and homeownership), there is convergent evidence validating the recruitment strategy's goal of establishing a sample that is (1) economically diverse with adequate representation of low and very low-income participants and (2) economically diverse within Black and non-Black subsamples to reduce potential confounding between race and income.

Figure 2. Means and SEs (−2 to 2) for income-to-needs ratios across recruitment cells. (A) Socioeconomic status (SES)-only cells and (B) level and SES×race cells.

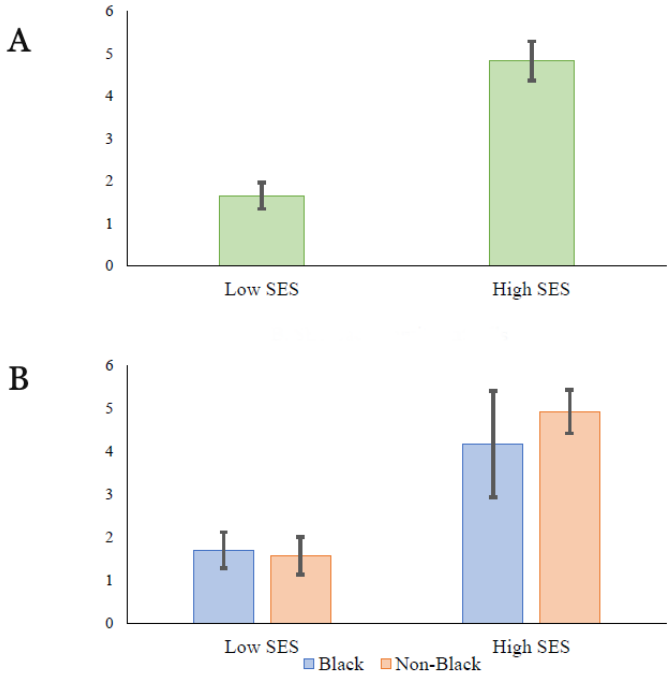

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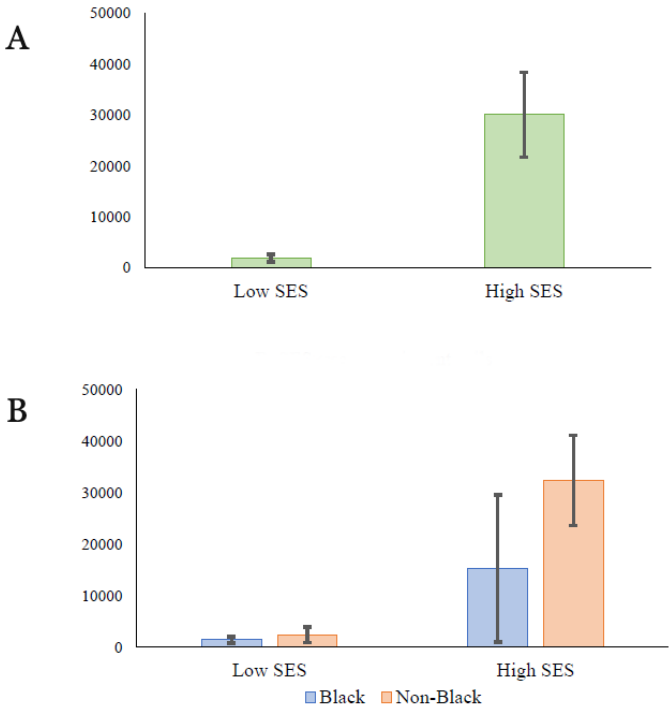
Figure 3. Means and SEs (−2 to 2) for bank savings across recruitment cells. (A) Socioeconomic status (SES)-only cells and (B) level and SES×race cells.



Discussion

The BEE study is one of the first prospective longitudinal studies of the prenatal and postnatal environmental influences on emerging EF in the first 3 years of life with specific foci on the potential effects of poverty, poverty-related stressors, and neurological substrates underlying cognitive abilities. Three primary aims examine (1) the associations between objective poverty and subjective prenatal experience on prenatal structural and functional brain development, (2) the associations between objective poverty and subjective postnatal experience on structural and functional brain development during the first 2.5 years of life, and (3) the associations between objective poverty and subjective postnatal experience on EF at 3 years of life. As described in this paper, several accommodations to this study were made in response to the COVID-19 pandemic, including prolonged participant recruitment, shifts to web-based data collection for some measurements, and alternation in the timing of visits and assessments. These accommodations have minimized the potential threats posed by the COVID-19 pandemic to the internal validity of the study. Despite the prolonged recruitment period, the results support the validity of the overall recruitment strategy, which was designed to establish a socioeconomically diverse sample with adequate variability in family incomes within both Black and non-Black families to reduce the potential confound of race and income. The web-based data collection of questionnaire data and observational protocols and the remote-based data collection of language exposure and child sleep hygiene have resulted in data comparable (qualitatively and quantitatively) with in-person data collection protocols. Finally, the changes in the timing of data collection visits maximized the number of participants that could participate in fMRI data collection while remaining within the targeted developmental window for examining neurological development pertinent to emerging EF within the first 3 years of life. We believe that the data being collected and subsequent analyses addressing the specific aims of this study will not be compromised by the COVID-19 pandemic.

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Authors' Contributions

CBP and SJS are principal investigators for this project, and WRMK and MTW are co–principal investigators; they equally contributed to the overall protocol design. WRMK wrote the complete first draft of the paper with the assistance of MTW, SJS, and CBP. All the authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Recruitment flowchart leading to the sample of 203 participants.
[DOCX File , 22 KB - resprot_v11i6e34854_app1.docx]

Multimedia Appendix 2
Questionnaires administered across data collection visits.
[DOCX File , 16 KB - resprot_v11i6e34854_app2.docx]

Multimedia Appendix 3
Magnetic resonance imaging acquisition and preprocessing methods.
[DOCX File , 14 KB - resprot_v11i6e34854_app3.docx]

Multimedia Appendix 4
Descriptive statistics for income-to-needs ratios for the total sample and stratified by recruitment cell.
[DOCX File , 14 KB - resprot_v11i6e34854_app4.docx]

Multimedia Appendix 5
Descriptive statistics for bank savings for the total sample and stratified by recruitment cell.
[DOCX File , 14 KB - resprot_v11i6e34854_app5.docx]

Multimedia Appendix 6
Peer-review report from the National Institute of Child Health and Human Development - Psychosocial Development, Risk and Prevention (PDRP) Study Section - Risk, Prevention and Health Behavior Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 154 KB - resprot_v11i6e34854_app6.pdf]

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Abbreviations

BEE: Brain and Early Experience
CV: coefficient of variation
DTI: diffusion tensor imaging
EF: executive function
fMRI: functional magnetic resonance imaging
ITN: income-to-needs
LENA: Language Environment Analysis
rs: resting state
SES: socioeconomic status
UNC: University of North Carolina

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Protocol

Dynamic Regulatory Processes in the Transition From Suicidal Ideation to Action in Adults Leaving Inpatient Psychiatric Care: Protocol for an Intensive Longitudinal Study

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Abstract

Background: US suicide rates have risen steadily in the past decade, and suicide risk is especially high in the months after discharge from inpatient psychiatric treatment. However, suicide research has lagged in examining *dynamic within-person processes* that contribute to risk over time among individuals known to be at high risk of suicide. Almost no research has examined how affective, cognitive, and physiological processes change over minutes, hours, or days to confer risk of suicidal behavior in daily life.

Objective: This protocol describes a longitudinal study designed to examine real-world changes in risk of suicide across multiple assessment domains. Specifically, the study involves following adults known to be at high risk of suicide after discharge from inpatient psychiatric care using self-report, interview, actigraphy, and behavioral methods to identify proximal contributors to suicidal thoughts and behaviors. First, we hypothesize that negative affective experiences, which are featured in most major suicide theories, will comprise a latent factor indicative of psychache (emotional pain), which will predict increases in suicidal thinking over time. Second, we hypothesize that poor inhibitory control in the context of negative affective stimuli, as well as emotion-related impulsivity, will predict the transition from suicidal thinking to suicidal behavior over time. Third, we hypothesize that short sleep duration will precede within-person increases in suicidal ideation as well as increased odds of suicidal behavior among those reporting suicidal thoughts.

Methods: The desired sample size is 130 adults with past-week suicidal thoughts or behaviors who are receiving inpatient psychiatric treatment. Participants will complete a battery of measures while on the inpatient unit to assess negative affective experiences, emotion-related impulsivity, inhibitory control, typical sleep patterns, and relevant covariates. After discharge from inpatient care, participants will complete 4 weeks of signal-contingent ecological momentary assessment surveys, as well as mobile behavioral measures of inhibitory control, while wearing an actigraphy device that will gather objective data on sleep. Participants will complete interviews regarding suicidal thoughts and behaviors at 4 and 8 weeks after discharge.

Results: The study was funded by the National Institutes of Health in November 2020. Recruitment began in April 2021. Data analysis will begin after completion of data collection.

Conclusions: This study will elucidate how affective, cognitive, and physiological risk factors contribute (or do not contribute) to within-person fluctuations in suicide risk in daily life, with important implications for extant theories of suicide. Of import, the examined risk factors are all modifiable; thus, the results will inform identification of key targets for just-in-time, flexible, personalized, digital interventions that can be used to decrease emotional distress and prevent suicide among those at highest risk.

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KEYWORDS

ecological momentary assessment; suicidal ideation; suicidal behavior; actigraphy; sleep; cognitive control; longitudinal; affect; impulsivity

Introduction

Background

US suicide rates have risen steadily in the past decade [1], particularly in rural areas [2,3]. Risk of death by suicide is especially high in the months after discharge from inpatient psychiatric treatment [4,5], particularly for people hospitalized because of suicidal thoughts and behaviors (STB) [6]. Despite this well-documented risk, research has made little progress in improving suicide prediction over the past 50 years [7]. Suicide research has been stymied by a focus on between-person factors that differentiate those who have and have not attempted (or died by) suicide, but many of these risk factors are relatively static, such as gender and race; research has lagged in examining dynamic, within-person processes that contribute to shifting risk over time among individuals who are already known to be at highest risk [8].

Leading *ideation to action* theories have enumerated negative affective experiences thought to contribute to suicidal ideation (SI), such as low connection [9], pain [9,10], hopelessness [9,11], thwarted belongingness [12], burdensomeness [12], defeat [13], and entrapment [13]. Negative affective experiences have been associated with between-person differences in current and past SI [9,12,13], and there is some evidence that within-person fluctuations in negative affective experiences may proximally predict SI [14-16]. Risk factors that are associated with the transition from SI to suicide attempts (SA) have been far less well studied [17]. More broadly, almost no work has examined our hypothesized cognitive, behavioral, and physiological risk factors of SA in daily life. We describe our protocol for a novel, transtheoretical, comprehensive examination of near-term risk factors for SI and SA among adults leaving psychiatric inpatient care, using multimodal ambulatory assessment of affective, cognitive, and physiological processes in an intensive longitudinal design.

Negative Affective Experiences

Shneidman [10] argued that suicide is fundamentally rooted in unbearable psychache, “hurt, anguish, soreness, aching, psychological pain.” Psychological pain is robustly associated with suicide, whether because of psychiatric disorders [18], stressful life events [19], or physical pain or illness [20,21]. Nonetheless, modern suicide theories differ in the relative importance of negative affective experiences as they relate to suicide. For example, the Interpersonal-Psychological Theory [12,22] focuses on interpersonal facets of pain, namely perceived burdensomeness and thwarted belongingness [23]. The Three-Step Theory formulated by Klonsky [9] takes a broader view of pain as a prerequisite for SI, positing connectedness as a protective factor against severe SI in the context of pain. Both the Three-Step Theory and the hopelessness model described by Beck [11] emphasize hopelessness regarding the likelihood of negative affective experiences improving over time as a key predictor of SI. The Integrated Motivational-Volitional model described by O’Connor [13] argues that SI is prompted by feelings of defeat (consistent with the view expressed by Baumeister [24] of suicide as escape from aversive self-awareness) and entrapment.

Although these models indicate multiple nuanced facets of negative affective experiences, it is unclear whether people experiencing suicidality differentiate these facets and whether they have differential predictive power. Recent network analyses suggest that many of these negative affective experiences cluster together among individuals [25]. However, to date, these studies have not conducted analyses of how these negative affective experiences covary over time within individuals or how they differentially predict outcomes. We aim to test the coherence of negative affective experiences to determine whether these are, in fact, differentially related to SI or whether they are more accurately conceptualized as indicators of the broader construct of emotional pain (eg, psychache).

Although a plethora of cross-sectional studies have shown associations between these negative affective experiences and SI [26-33], little work is available on negative affective experiences as prospective predictors of SI. Longitudinal work has primarily examined negative affective experiences as predictors of SI over months or years [34,35] rather than as predictors of within-person short-term changes in SI. Recent ecological momentary assessment (EMA) research has demonstrated that many negative affective experiences fluctuate markedly at the within-person level, as does SI [15,36-40]; however, these studies have been limited by small sample sizes [15,36], short durations [37,38], and use of analog (community) samples [39-41]. Furthermore, negative affective experiences tell us little about which people with suicidal thoughts will go on to attempt, or die by, suicide, a central issue across ideation-to-action models.

Emotion-Related Impulsivity

Research examining the broad domain of impulsivity in relation to STB has been mixed [41,42]. However, emotion-related impulsivity, the tendency to behave impulsively during high-arousal negative or positive affective states [43-46], shows clear associations with STB [47-55], nonsuicidal self-injury (NSSI) [56-60], and self-rated likelihood of future SA [51]. Furthermore, emotion-related impulsivity seems to amplify the association between other suicide risk factors, such as negative affective experiences, and SA [48]. Daily diary research further suggests that high emotion-related impulsivity is related to stronger within-person associations between negative affective experiences and NSSI urges [61], consistent with literature demonstrating that emotion-related impulsivity is characterized by problematic responses to negative affective experiences, rather than by greater affective intensity itself [44,45,62-66].

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Emotion-related impulsivity is genetically driven and highly stable over time [67] and may thus serve as a trait-like marker of SA risk among those who experience SI.

Cognitive Inhibition

Correlational research suggests that deficits in inhibitory control in the context of negative affective experiences are associated with SA and NSSI [47,60,62,68-70], especially among psychiatric populations [49]. Null effects for inhibitory control deficits related to SA have emerged when there was a lack of consideration of affective state [69-71]. That is, meta-analyses indicate that poor inhibitory control is tied to STB when people are tested while experiencing depressed mood or major depressive disorder or when negative stimuli are incorporated into the task [53,72]. This pattern of results highlights the need for integration of affective and cognitive domains jointly to consider STB risk [46,49,62,73].

Sleep Disturbances

Sleep disturbances are associated cross-sectionally with SI and SA [74-77], and sleep problems predict later SA in adolescents [78]. Most of this work has used self-report omnibus measures of sleep [75], with limited ability to identify specific sleep domains as they relate to STB or to disentangle effects of objective and subjective sleep disturbances. To our knowledge, only 2 studies have examined prospective associations between actigraphy-assessed sleep and subsequent SI: Littlewood et al [79] found that short sleep duration predicted within-person changes in SI across days, and Bernert et al [80] found that variability in sleep duration predicted later SI above and beyond depression. No published work has examined objective sleep indices as predictors of SA in daily life.

However, there is strong evidence from neuroimaging [81] and behavioral research using naturalistic [82] and experimental [83] paradigms that sleep disturbances diminish inhibitory control [84-87] and that sleep problems are associated with other self-harm behaviors that can occur impulsively, such as NSSI [88]. Furthermore, prior work has shown that sleep disturbances contribute to impulsivity among patients diagnosed with psychiatric disorders [88]. Thus, based on the limited literature, we predict that reduced total sleep time (compared with an individual's mean sleep duration) will affect likelihood of SA in the context of SI through decays in inhibitory control.

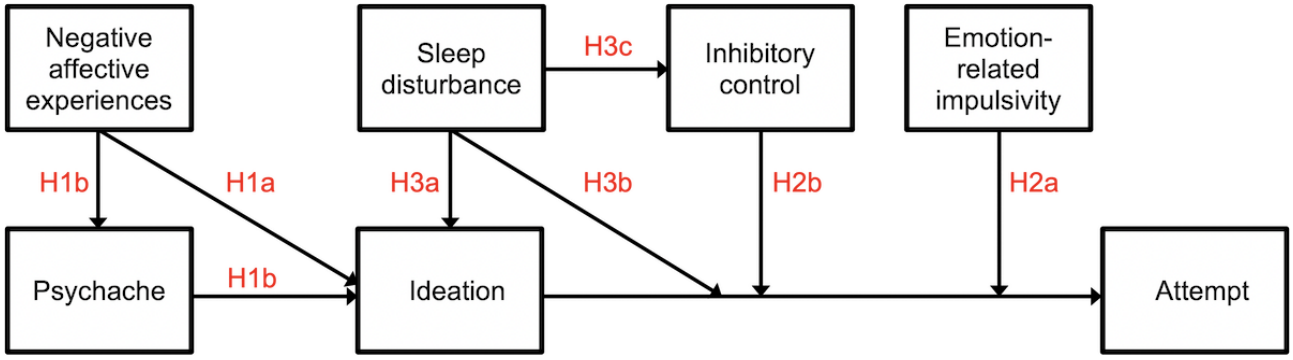
Hypotheses

The goal of this study is to integrate examination of affective, cognitive, and physiological risk factors for short-term changes in suicidal thinking and suicidal behaviors among adults known to be at high risk within an ideation-to-action framework. To that end, our hypotheses are as follows:

- Hypothesis 1a (H1a): within-person increases in affective suicide risk factors conceptually related to psychache (negative affective experiences) will individually precede within-person increases in SI.
- Hypothesis 1b (H1b): negative affective experiences will co-occur in daily life such that they are best conceptualized as indices of a single latent construct capturing emotional distress (psychache), which will itself predict short-term increases in SI.
- Hypothesis 2a (H2a): among those with SI, higher baseline self-reported emotion-related impulsivity will predict greater odds of SA over follow-up.
- Hypothesis 2b (H2b): among those with SI, poorer baseline behavioral indices of inhibitory control in the context of negative affective stimuli will predict greater odds of SA over follow-up. We also predict that, among those with current SI during EMA, lower EMA-assessed inhibitory control will prospectively predict subsequent SA.
- Hypothesis 3a (H3a): during the EMA protocol, short sleep duration will predict within-person increases in SI.
- Hypothesis 3b (H3b): during the EMA protocol, short sleep duration will predict greater risk of next-day SA among those with SI.
- Exploratory hypothesis 3c (H3c): the within-person effects of short sleep duration on SA will be mediated by within-person changes in inhibitory control assessed during EMA.

A visual depiction of these hypotheses is provided in Figure 1.

Figure 1. Visual depiction of study hypotheses.



Methods

Project Overview

This is a single-group, repeated-measures (within-persons) observational study following adults with recent STB receiving inpatient psychiatric treatment (N=130). An ethnically diverse sample of participants will be recruited during inpatient psychiatric treatment in Lubbock, Texas, United States, based on past week STB. Eligible and interested participants will then complete the informed consent process, self-report surveys, clinical interviews, a computer task assessing cognitive

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inhibition, and a debriefing procedure. After discharge from inpatient care, participants will engage in a 4-week (28-day) EMA protocol that involves receipt of 7 signal-contingent self-report survey prompts per day between participants' self-reported wake times and bedtimes. Participants will also be prompted to complete an abbreviated version of the cognitive inhibitory control task after each survey and asked to wear an actigraphy device for the 28-day follow-up period to assess objective indicators of sleep. Participants will be invited to complete a remote (phone or videoconference) follow-up interview assessing recent STB at 4 weeks and 8 weeks after discharge.

Ethics Approval

All study procedures have been approved by the Texas Tech University Institutional Review Board (IRB2020-713; October 27, 2020). The study procedures were further approved by the first recruitment site (Covenant Health) on March 15, 2021. The study procedures, hypotheses, and all relevant documents were preregistered on the Open Science Framework on August 25, 2021 [89].

Power Analyses and Sample Size Considerations

Given variability in EMA adherence, we conducted power analyses for 100 participants, while planning to recruit 130 participants to account for those with inadequate compliance. Most study aims will be tested using dynamic structural equation modeling, as described herein. In a recent Monte Carlo simulation study [90], adequate power (>0.80) for modeling of a single process (eg, SI) was demonstrated for moderate effects where n=100 with as few as 50 repeated measures (t=50). Thus, this study (t=196, 7 prompts per day for 28 days) is well powered even with a compliance rate as low as 57.1% (112/196; 4 prompts per day for 28 days) to examine within-person processes (H1a, H1b, and H2b). To provide more conservative estimates of power, a series of simulations with 100 replications were conducted for a random-effects (multilevel) logistic outcome using R software (The R Foundation for Statistical Computing) [91]. The assumptions for these simulations were as follows: (1) n=100, (2) within-person effects for all predictors, (3) standard normal distributions for all predictors, and (4) an intercept variance of 0.3. On the basis of these models, the study is well powered (>0.8) to detect standardized within-person effects as low as 0.1 with compliance as low as 64%.

For H2a, we used G*Power (Heinrich Heine University) [92] to conservatively determine the minimum detectable effect predicting any SA over follow-up with n=100, Cronbach α=.05, and β=.8, controlling for a moderate effect of SI on SA (0.3). We assumed an event proportion of 10% for the outcome based on recent literature [93]. On this basis, the study is powered to detect an odds ratio >2.63 for the effect of baseline emotion-related impulsivity or inhibitory control on follow-up SA risk. By way of comparison, recent research has demonstrated significant predictors of follow-up SA risk with odds ratios from 6 [94] to 13 [93].

For H3a and H3b, the models are identical to those for H1a, H1b, and H2B, except that analyses are conducted at the day level (t=28) to examine the effects of sleep. Previous studies have shown significant effects for the impact of sleep quality on next day SI (β=–.11) [79]. Although examination of within-day fluctuations in inhibitory control is exploratory (H3c), prior work showing large differences in inhibitory control between self-harm and control groups (Cohen d=0.84) [70] allowed us to conservatively estimate how day-level inhibitory control predicts SI and SA. Thus, we repeated our simulations outlined for H1a using t=28 and single predictors for sleep (H3a and H3b) and inhibitory control (H3c) in separate models. Models converged across repetitions, indicating that with n=100, the study is well powered (>0.8) to find standardized regression effects as low as 0.15 (representing small effects) for the within-person regressions of SI and SA on day-level inhibitory control or sleep disturbance.

Study Procedures

Recruitment and Informed Consent

Participants will be recruited from the inpatient behavioral health units located in Lubbock, Texas. The inclusion criteria are as follows: (1) current inpatient behavioral health treatment, (2) aged at least 18 years (no maximum age), and (3) SI or suicidal behavior in the week before admission. The exclusion criteria are as follows: inability to complete tasks because of (1) impaired mental status (orientation score <5 on the Montreal Cognitive Assessment), (2) acute psychotic or manic symptoms, or (3) low English fluency. Treatment team members (eg, attending physicians and nursing staff) will identify individuals who are potentially eligible for the study and ask these individuals for verbal consent to be approached by a team member regarding the study. Informational flyers describing the study will be provided to treatment team members to offer to interested patients; team members will also be provided scripts to describe the study orally. With approval, a study team member will then approach potential participants during times that do not conflict with treatment or unit activities to discuss the study. The study team member will meet with the potential participant in a private area on the unit to explain the study design, procedures, risks and benefits, compensation, confidentiality and its limits, and eligibility criteria. Oral and written consent will be obtained from participants before proceeding. Study consent forms, the prescreening form, and summary information sheets are available alongside the Open Science Framework preregistration [89]. A diagram showing the flow of potential participants through study procedures is presented in Figure 2.

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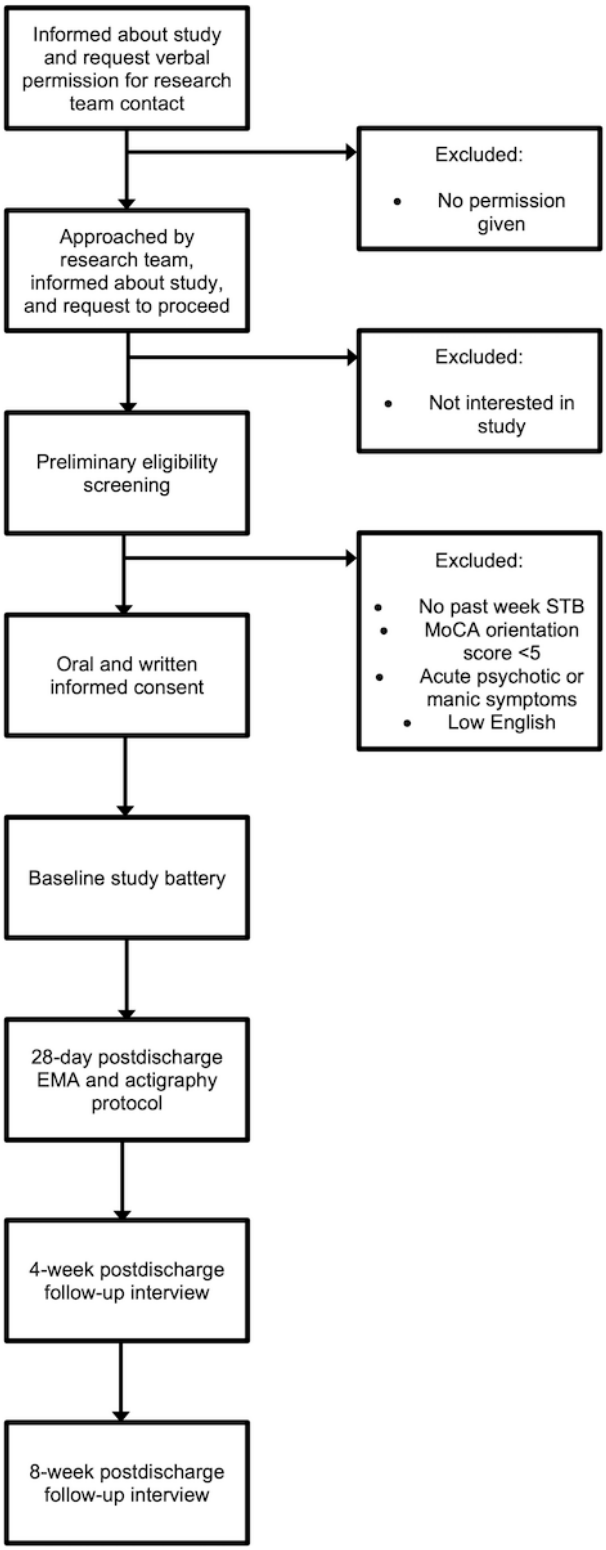
Figure 2. Study recruitment, enrollment, and procedures flow chart. EMA: ecological momentary assessment; MoCA: Montreal Cognitive Assessment; STB: suicidal thoughts and behaviors.



Baseline Session

The baseline session will take place on the inpatient behavioral health unit and last for 2 to 3 hours. Participants will complete self-report surveys, clinical interviews, a computer task (Emotional Stop-Signal Task), and a debriefing procedure. Participants will also be instructed on how to complete the follow-up EMA surveys and mobile computer tasks, as well as how to use the actigraphy device. A complete list of self-report measures and clinical interview assessments is provided in Table 1. A summary of study data collection procedures as well as all baseline measures are provided alongside the Open Science Framework preregistration [89].

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Table 1. Self-report and clinical interview measures for the baseline session.

Measure type and construct	Measure
Self-report	
Age, race, ethnicity, gender, and other demographics	Demographics
Positive and negative affect	Positive and Negative Affect Schedule
Emotion-related impulsivity	Three-Factor Impulsivity Scale
Thwarted belongingness	Interpersonal Needs Questionnaire
Perceived burdensomeness	Interpersonal Needs Questionnaire
Defeat	Defeat Scale
Entrapment	Entrapment Scale
Hopelessness	Beck Hopelessness Scale (4-item version)
Emotional pain	Psychache Scale
Physical pain interference	PROMIS[a] Pain Interference Scale
Sleep chronotype	Smith Morningness-Eveningness Scale
Severity of insomnia	Insomnia Severity Index
Symptoms of sleep disorders	Sleep Disorders Symptoms Checklist-25
Coping strategies for suicidality	Suicide-Related Coping Scale
Exposure to traumatic events	List of Threatening Experiences Questionnaire
Recent depression, anxiety, and stress symptoms	Depression Anxiety Stress Scales (21-item version)
Capability for suicide	ACSS[b] Fearlessness About Death Subscale
Access to lethal suicide means	PhenX[c] Access to Lethal Means protocol
Onset and typical patterns of menstrual cycle	Menstrual history (women only)
Interview	
Past week suicidal ideation or behavior	Past Week Suicide Assessment
Lifetime, past year, past month, and past week suicidal ideation and behavior	Columbia Suicide Severity Rating Scale
Lifetime, past year, past month, and past week nonsuicidal self-injury urges and behaviors	Self-Injurious Thoughts and Behaviors Interview (NSSI[d] items)
Lifetime and past year alcohol use disorder symptoms	Structured Clinical Interview for DSM-5[e] Disorders (Alcohol Use Disorder items)
Lifetime and past year substance use disorder symptoms	Structured Clinical Interview for DSM-5 Disorders (Substance Use Disorder items)
Borderline personality disorder symptoms	Structured Interview for DSM-IV[f] Personality Disorder (Borderline Personality Disorder items)
Current medications and dosages	Medication Interview

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]ACSS: Acquired Capability for Suicide Scale.

[c]PhenX: Phenotypes and Exposures.

[d]NSSI: nonsuicidal self-injury.

[e]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[f]DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

Participants will complete an adapted version of the Emotional Stop-Signal Task [95] to behaviorally assess impulsivity. To focus on emotion-relevant response inhibition, we use an adapted version in which participants are presented with either neutral or negatively valenced images. In *Go* trials (75%), participants press a key to indicate the valence of the image within 1500 milliseconds. *Stop* trials (25%) involve a sound played through headphones at a variable delay after stimulus presentation and indicate that participants should inhibit their response to the image. The delay begins at 250 milliseconds and then increases or decreases by 50 milliseconds in response to successful or failed inhibitory control, respectively. The scores, then, reflect the difference in commission error rates between negative and neutral stimuli, which is an indicator of

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deficits in cognitive inhibition specific to negative affective contexts. During the baseline session, participants will complete practice trials followed by 3 blocks of 64 trials (192 trials, 48 *stop* trials).

Intensive Longitudinal Protocol

During the baseline session, participants will be asked to provide their typical wake times and bedtimes, as well as any specific windows of time in which they will be unavailable to answer surveys (for instance, work shifts in which they are not allowed to access their phone), which are then used to schedule the EMA survey distribution. Participants who do not own a mobile phone capable of accessing the internet will be provided with a *loaner* phone to use for the EMA surveys; other participants will use their own mobile phone. All participants will be walked through practice EMA items to familiarize them with the structure of the EMA surveys and the mobile version of the Emotional Stop-Signal Task before discharge.

The EMA surveys will be distributed using a proprietary distribution system that integrates with Amazon Web Services' Simple Notification Service system to send SMS text messaging notifications of survey availability. These notifications will include a link to a Qualtrics survey that will be available for 30 minutes only after each notification.

Participants will receive 7 pseudorandom notifications between specified wake times and bedtimes, avoiding the blackout windows specified by the participant. We will add 15 minutes to the wake time to avoid missed surveys because of variability in wake times as well as to ensure that participants will be able to respond effectively to items regarding affect and related constructs after waking. Notifications will be randomized by *binning* the participants' available hours into 7 equal windows and then randomly choosing a survey time within each bin. Notifications cannot occur within 30 minutes of another notification. If participants do not click the survey link within 10 minutes of notification, they will receive a reminder message. At each EMA prompt, participants will be asked to complete self-report items assessed using Qualtrics and then to complete the Emotional Stop-Signal Task on their mobile phone using the Inquisit web platform (Millisecond Software, LLC; available for both iOS and Android platforms). This adapted version of the task also uses negative and neutral stimuli. At the first survey completed each day, the task will have 128 trials (64 negative and 64 neutral trials interspersed). At each subsequent pseudorandom prompt, participants will complete 64 trials (32 negative and 32 neutral trials interspersed) to reduce participant burden while allowing within-person dynamic modeling of changes in affective inhibitory control. The domains assessed using EMA self-report items are listed in Table 2, and specific items are provided alongside the Open Science Framework preregistration [89].

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Table 2. Domains assessed using self-report ecological momentary assessment items.

Survey and construct	Number of items
Morning survey only	
Sleep quality	1
Sleep characteristics (time to bed, time to wake up, awakenings, and nightmares)	8
Menstrual cycle (only for participants with regular menstrual cycle reported at baseline)	2
All surveys	
Current suicidal ideation	2
Current urges for nonsuicidal self-injury	2
Current negative affect	6
Current positive affect	2
Current hopelessness	1
Current agitation	2
Current emotional pain	2
Current defeat	2
Current entrapment	2
Current self-criticism	2
Current suicide capability	4
Current physical pain interference	1
Current belongingness	2
Current burdensomeness	2
Current perceived emotional support	2
Current perceived practical support	2
Since last survey: suicidal behavior	1
Since last survey: nonsuicidal self-injury	1
Since last survey: stressors	3
Since last survey: complimented or praised	1
Since last survey: alcohol use	2
Since last survey: drug use	4

At baseline, participants will also be provided with the actigraphy device (wActiSleep-BT; ActiGraph, LLC) and instructed on how to wear it during the follow-up period. Participants will be asked to wear the device as much as possible for 28 days after discharge. The device continuously records activity through accelerometer (approximately 30-hertz data sampling with timestamps) with a single charge typically exceeding 28 days [96]; however, participants will also be provided with a charger and asked to charge the device at least twice during follow-up at times when the watch would not otherwise be worn, such as when bathing. The device continuously records data to provide valid scores for a variety of indices, including sleep duration, sleep onset latency, total awakenings, length of awakenings, overall sleep efficiency, intensity of movement during sleep awakenings, and light exposure during sleep [97]. Participants will be provided with a self-addressed, postage-paid envelope to return the actigraphy device, charger, and loaner phone (if applicable) to the research team after study completion.

Follow-up Interviews

Participants will be asked to complete a brief remote (phone or videoconference) follow-up interview assessing STB at 4 weeks and 8 weeks after discharge, with the goal of ensuring that the follow-up data capture all experienced STBs even if not reported on the EMA surveys. Specific follow-up interview items are provided alongside the Open Science Framework preregistration [89].

Risk Assessment, Crisis Response Planning, and Strategies for Retention and Study Engagement

Participants who consent to participate in the EMA portion of the study will be contacted on a regular basis to identify concerns with the study, issues regarding receipt of the EMA notifications, and to assess ongoing suicide risk. All participants, regardless of their level of compliance with the EMA protocol and indicated suicide risk, will be contacted by the research team through SMS text messaging weekly (4 times over the 28-day period). Participants will also be contacted on day 5 of

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the EMA protocol if under half of the expected surveys are completed during the first 4 days of the protocol to remind them of the compensation rate per survey and to ascertain if any issues were inhibiting completion of the surveys. Participants will then be contacted if they demonstrate 1, 2, and 4 consecutive days of nonresponse to any surveys. After the first occurrence of extended periods of noncompletion, check-ins will only be conducted after 2 or 4 full days without completing any surveys to avoid excessive or intrusive follow-ups.

Participants will also be contacted within 24 hours of any EMA surveys in which they indicated engaging in suicidal behavior. These contacts will follow a specified risk assessment and crisis response plan dependent on participants' responses and indicated level of imminent risk. The procedures used during these follow-ups are available in documentation alongside the Open Science Framework preregistration [89].

Compensation

Participants' compensation will depend on the specific study components completed. Payments will be provided either through a digital Amazon gift card (by email) or a physical Walmart gift card (during face-to-face interactions or by mail). All participants who complete the informed consent process at baseline will receive a US $30 gift card, regardless of how many measures they complete.

All participants who consent to complete the EMA and actigraphy follow-up portion of the study will receive a US $50 gift card, regardless of the number of surveys completed or amount of time the actigraphy device is worn. Participants will receive an additional US $1 for each survey completed (up to an additional US $196). If participants complete at least 75% (147/196) of the surveys received, they will receive a bonus US $25 gift card. Participants will receive a US $20 gift card for completion of a follow-up interview, up to a maximum of US $40 for both the 4-week and 8-week follow-up assessments.

Data Analysis Plan

Before conducting analyses, we will clean and check data for errors, address outliers, ensure that statistical assumptions for analyses have been met, and examine potential confounders to include in subsequent analyses as warranted. Variables that may exhibit skewness (eg, number of lifetime episodes of NSSI) will be examined for skewness and kurtosis and, if necessary, either rank transformed or log transformed. We will include the effect of time (196 prompts over 28 days) to account for habituation and examine potential nonlinear effects of, for instance, age. Most analyses will use time-series (dynamic) structural equation modeling [98,99], which uses Bayesian estimation, conducted with MPlus statistical software (Muthén & Muthén) [99]. Dynamic structural equation modeling is robust with regard to high rates of missing data, zero-inflated categorical variables, and variable time intervals among observations, all of which are common in EMA with these types of data, and allows for latent decomposition of constructs into their constituent between- and within-person components [98]. Dynamic structural equation modeling also facilitates within-person lagged analyses to examine prospective relationships between time *t* predictors and time *t*+1 outcomes; by controlling for autoregressive effects over time, these methods can model within-person change in constructs over time.

For H1a, we will examine whether within-person changes in negative affective experiences precede proximal within-person changes in SI using 2-level random slope models. Each of 7 momentary negative affective experiences reported at time *t* will be regressed on itself at time *t*–1, producing a measure of residualized change in each negative affective experience. Momentary SI reported at time *t* will be regressed on itself at time *t*–1, as well as the 7 negative affective experience change indicators, yielding an estimate of the within-person effect of changes in all negative affective experiences on subsequent within-person changes in SI, controlling for autoregression. For H1b, we will examine the within- and between-person factor structures of the 7 negative affective experiences using multilevel exploratory factor analysis [100]. Using established best practices, we will identify the most appropriate structure and use these within-person factors to predict changes in SI over time, similar to the procedures used for H1a.

For H2a, we will estimate the effects of baseline emotion-related impulsivity and inhibitory control on odds of SA over follow-up, controlling for between-person differences in SI severity. To do this, person-mean estimates of SI and person-maximum estimates of SA (yes or no) will be calculated using EMA data. SA can then be predicted by baseline emotion-related impulsivity and inhibitory control scores using logistic regression analysis, controlling for participants' SI severity. For H2b, we will then test whether within-person changes in state inhibitory control precede subsequent SA among individuals reporting SI. Using a 2-level random slope model, we will model time *t* inhibitory control (controlling for inhibitory control measured at time *t*–1) as a predictor of time *t*+1 SA, controlling for time *t* SI.

For sleep-related hypotheses, we will use 2-level random slope models, as described previously, but in which survey-level data on SI and SA have been pooled to create day-level variables (because sleep varies at the daily, but not survey, level). For H3a, we will use person-mean–centered total sleep time on day *d*–1 to predict next-day (day *d*) SI, controlling for day *d*–1 SI. Models for H3b will parallel those used to test H2a, whereby total sleep time on day *d*-1 will be used to predict next-day SA (day *d*), controlling for day *d* SI. For H3c, we will test whether the sleep-SA association (H3b) is mediated by within-person changes in inhibitory control. Building on the H3b model, we will add in the effect of sleep on day *d*–1 predicting inhibitory control on day *d*. To ensure that we are capturing sleep-related changes in inhibitory control, inhibitory control on day *d* will also be regressed on inhibitory control measured on day *d*–1. Finally, day *d* inhibitory control will be used to predict day *d* SA, controlling for day *d* SI. Indirect and direct effects will be calculated and tested for significance using the MPlus *model indirect* command.

With respect to the criteria used for statistical inferences, these will vary by model and hypothesis. For logistic regression analyses (H2a), 2-tailed *P* values <.05 will be used as our criteria to make inferences. For dynamic structural equation models (H1a, H1b, H2b, H3a, H3b, and H3c), which use Bayesian

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estimation, 95% credibility intervals will be used; those intervals that do not include 0 will be evidence of a statistically significant effect. For multilevel exploratory factor analysis (H1b), we will examine unrestricted models with 1 to 7 factors at the within- and between-person levels, consistent with the components of the negative affective experiences construct. We will determine the most appropriate model fit based on an examination of model fit indices [101] as well as eigenvalues.

Results

This study was funded by the National Institute of Mental Health (R21 MH124794) in November 2020 with a start date of December 1, 2020, and an end date of October 31, 2022 (Multimedia Appendix 1). Recruitment and data collection began in April 2021, and 46 individuals were consented into the study through November 2021. Of note, the first study recruitment site (Covenant Health's adult behavioral health inpatient unit) was unexpectedly closed on November 15, 2021, which resulted in a pause in recruitment while an alternative site was identified. As of February 2022, a new recruitment site has provided preliminary approval to restart study data collection, which began in June 2022. Data collection is anticipated to be completed by winter 2023.

Discussion

Expected Implications and Conclusions

Although suicide research has proliferated in the past 50 years, this work has not moved the needle substantively on suicide prevention, primarily because of a focus on static, between-person risk factors (*who* is at risk) rather than modifiable, within-person risk factors (*when* or *why* is a particular person at risk). Major suicide theories have proposed key drivers of STB, but very little research has directly compared the relevance of constructs across theories or tested whether these risk factors are related to dynamic fluctuations in suicide risk. In addition, empirical research on hypothesized cognitive and physiological contributors to suicide risk has been limited by an inability to measure these phenomena as they occur and change in daily life.

This study aims to address limitations in the research on SI and behavior in several ways. First, by examining between- and within-person experiences of a multitude of conceptually derived negative affective experiences, the results will clarify whether these are, in fact, uniquely and differentially related to suicide outcomes or whether they are more appropriately construed as indicators of a single latent construct, such as psychache. The results will thus clarify the utility of existing theories in which fine-grained, nuanced distinctions among risk factors may (or may not) map onto experiences that people with STB themselves discriminate among in daily life. Second, by using baseline and ambulatory measures of sleep disturbance and impaired inhibitory control, the results will clarify whether these serve as more stable or trait-like indicators of risk or whether fluctuations in these experiences relate to changes in risk over time. The results will inform the development of interventions designed to modify these risk factors in their most relevant contexts to decrease the odds of suicide among those at high risk.

Methodological and Other Considerations

The primary methodological decisions in study design were with respect to the inclusion criteria, intensity of follow-up data collection methods, and level of monitoring and responsivity to indicators of suicide risk during follow-up.

First, we considered whether to limit the sample further (eg, individuals with recent SA) or whether to expand the inclusion criteria to include anyone receiving inpatient psychiatric care, regardless of recent STB. Individuals with a history of SA are at higher risk of later suicidal behavior than individuals with SI only [102], which would increase the odds of suicidal behavior during the follow-up period and plausibly increase statistical power. However, we felt that further restriction of the inclusion criteria would be likely to slow the speed of recruitment, a significant concern for a grant-funded study with a 2-year timeline. Recruiting a more heterogeneous sample will also allow us to examine the generalizability of predictors across a more diverse patient population. By contrast, expanding eligibility to all individuals receiving inpatient psychiatric care would likely reduce the odds of suicidal behavior over follow-up compared with individuals with recent STB [4].

Second, we considered the significant trade-offs between level of detail and frequency of follow-up assessments with the need to reduce participant burden (and, relatedly, the odds of attrition from the study). Prior research has shown that a greater number of surveys per day [103] and a greater number of items per survey [104] predict lower compliance with momentary assessment (EMA) research, which then affects the ability to adequately capture outcomes of interest (STB) during the EMA period. In addition, asking follow-up questions about the nuances of STB based upon *yes* responses during the EMA may increase the odds of participants choosing to deny these experiences that do occur to avoid additional follow-up questions, which take time and may be sensitive in nature. The duration and frequency of assessments chosen for this study were based on prior research suggesting that these parameters were feasible for the population of interest [105]. Finally, the 4- and 8-week follow-up interviews were added to the study protocol in response to grant reviewer feedback as a check against missed STB that were not captured during the EMA to increase statistical power for between-person models.

Finally, intensive longitudinal studies examining suicide risk and related constructs vary in the strategies used to monitor incoming data and to respond to indicators of elevated suicide risk [106]. These decisions often involve trade-offs of study investigator and staff time, guarantees of anonymity for participants, balancing participant safety with the risks involved in interventions by outside parties, avoidance of unintentional reinforcement of STB through study staff contact, and the goals of observational versus intervention-based research. Although we considered real-time monitoring of participants' full range of EMA responses concerning suicide risk factors and contacting participants on the basis of these responses, we ultimately determined that this was scientifically unjustified because we do not know precisely what level of SI or other risk factors are

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related to imminent (proximal) risk for suicide. Follow-up with participants during the EMA protocol was limited to disclosures of suicidal *behaviors* only, following the aforementioned procedures.

However, we did make several choices across the study to promote truthful responding on suicide risk indicators by participants to ensure that they had adequate access to safety planning and other crisis resources and to avoid development of an intervention study when the study aims were exclusively observational. First, participants will be informed repeatedly at baseline that the study involves many assessments of STB and that many of these experiences will not lead to violations of their confidentiality. Participants will be informed that the confidentiality of information provided during the study will only be broken if the participant indicates imminent (within 1-2 days) desire, intent, and plans to attempt suicide and the research team member is not able to develop a safety plan with the participant to address this risk. Second, crisis hotline information and local, national, and web-based resources related to self-harm and suicide will be provided to participants at the baseline session, at which time all participants will be offered the opportunity to complete a suicide safety plan with the research team; if a safety plan is created, it will be given to the participant to keep and a copy will be retained by the research team. Furthermore, at the start of each EMA survey, participants will be offered live links to call or text 24/7 crisis hotlines, alongside a reminder that responses will not be monitored in real time; the same message will be displayed on the final page of each EMA survey. Each intervening page of questions will have a link at the bottom of the page that opens a full list of resources in a separate web browser if needed. Thus, participation in the research study will involve greater-than-usual exposure to, and reminders of, available crisis supports but will not involve routine additional intervention by the research team based on SI or related experiences.

Strengths and Limitations

As with all empirical research, this study includes several important limitations to consider. Several of these factors relate to the nature of the specific sample being recruited for the project. First, because of the nature of recruitment from an inpatient psychiatric treatment setting, the study sample is geographically restricted to adults from Lubbock, Texas, and the surrounding areas, and the results may differ from those obtained in larger metropolitan areas and in other parts of the United States, as well as internationally. Second, patients with manic or psychotic symptoms as well as those with cognitive impairment may be underrepresented in the sample, given the exclusion criteria related to the ability to provide informed consent to participate in the study. Third, the decision to base eligibility on recent STB will necessarily limit our ability to make inferences about postdischarge suicide risk among patients with no, or more distal, history of STB, who are at lessened, but nonzero, risk of postdischarge STB [4,5]. Fourth, although adequately powered, the desired sample size (N=130) will limit the ability to examine potential moderators of the study results across demographic and clinical characteristics (eg, race and ethnicity, sexual orientation, and mental health diagnoses).

Limitations also exist with respect to study methodology. Owing to concerns regarding the length and intensity of our baseline session, many study constructs will be assessed using self-report survey instruments, which can be subject to response biases and whose associations with each other may be attributable to shared method variance. Although several strategies have been implemented to improve completion rates of self-report, behavioral, and physiological data collection during the EMA protocol, we expect participants to vary in level of adherence to study procedures, which will also influence data quality and statistical power for planned analyses.

Despite these limitations, the study has numerous strengths. Data will be collected from a population known to be at exceptionally high risk for STB and for whom prior research has been limited by practical challenges involved in collecting data from inpatient psychiatric settings. This particular sample will be drawn from a high-need region where mental health care access is limited, facilitating understanding of risk factors for suicide in an underserved community where mobile interventions may be particularly critical to ameliorate suicide risk. Using a transtheoretical approach to understanding the transition from suicidal thoughts to behaviors, this study will facilitate direct comparison of key hypothesized risk factors as potential real-world contributors to suicide, moving forward both theoretical and empirical understanding of these phenomena. Furthermore, data collection will span a number of methodological approaches, including self-reports, interviewer ratings, behavioral measures, and ambulatory physiological readings, facilitating multi-trait, multi-method examination of STB risk. Finally, and most importantly, the intensive longitudinal design provides a novel opportunity to understand within-person changes in STB risk over time in contrast to prior work that has focused on between-person characteristics that relate to historical experiences of STB.

Dissemination Plan and Future Directions

Numerous steps will be taken to ensure that data collected through this study are used in an effective manner to improve the scientific understanding of STB and the experiences of people with STB interacting with the mental health system. Upon beginning data collection, the study procedures and aims were registered on the Open Science Framework [89] to improve the transparency and reproducibility of the study analyses and findings. Raw (deidentified) data from this study will also be made available to other researchers through the National Institute of Mental Health Data Archive (refer to the *Data Availability* section). Research outputs generated from this project (eg, conference presentations and scientific manuscripts) will be shared broadly with other STB researchers as well as the general public through translational mechanisms (eg, posters and social media dissemination).

Data from this study will serve as the foundation of future projects to examine tested risk factors for STB in greater detail. First, our data on negative affective experiences as contributors to suicidal thinking will inform the design of future EMA tools tailored to those experiences most strongly predictive of within-person changes in SI. These data will also clarify which therapeutic interventions may be most effective for addressing

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SI; for instance, if thwarted interpersonal needs are identified as key proximal SI risk factors, interpersonally focused interventions for STB may be more effective than intrapersonally focused interventions. Second, should impaired cognitive control be identified as a key factor in the transition from SI to SA, future research could test whether cognitive interventions are effective in reducing STB risk in this population. Finally, future research may build upon our sleep physiology findings by developing and testing suicide-specific sleep treatments among groups known to be at high risk, such as adults leaving inpatient psychiatric care.

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Data Availability

Consistent with the requirements of National Institute of Mental Health grant funding, all study data will be deidentified and uploaded to the National Institute of Mental Health Data Archive at 6-month intervals.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviewer report from the National Institute of Mental Health (NIMH).
[PDF File (Adobe PDF File), 341 KB - resprot_v11i6e38582_app1.pdf]

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Abbreviations

EMA: ecological momentary assessment
NSSI: nonsuicidal self-injury
SA: suicide attempts
SI: suicidal ideation
STB: suicidal thoughts and behaviors

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Protocol

Development, Testing, and Implementation of the Belgian Patient Reported Experience Measure for Pancreatic Cancer Care (PREPARE) Project: Protocol for a Multi-Method Research Project

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Abstract

Background: Patients with pancreatic cancer do not feel involved in the development of their treatment and care plans. In Belgium, these plans are decided on during multidisciplinary team meetings. However, limited time is spent on the discussion of the preferences of the patient during these meetings. This research project aims to develop a patient-reported experience measure (PREM) for pancreatic cancer and assess if its use can support collaborative treatment decision-making.

Objective: This paper aims to outline the protocol for a multi-method research project to improve person-centered pancreatic cancer care in Belgium. Three subobjectives are pursued: (1) to develop a PREM to assess the experiences of care-related aspects in pancreatic cancer care, (2) to validate the PREM, and (3) to develop and evaluate an educational intervention to support the use of the PREM's results.

Methods: For the development of the PREM, an exploratory mixed methods study design will be used. The study will start with a survey followed by a telephone interview involving patients with pancreatic cancer and digestive oncology health care professionals. Study two is the testing of the content and construct validity of the PREM. Study three involves the implementation study according to the Medical Research Council framework of a complex intervention introducing the PREM in practice. The effectiveness of the intervention will be investigated using a pragmatic randomized controlled trial study design.

Results: The protocol presents the entire structure of the research project. Ethics approval to conduct the exploratory mixed methods study (objective 1) has been obtained, and recruitment has started since January 2022.

Conclusions: The poor prognosis of patients with pancreatic cancer should not be considered a hurdle to not study this patient population group. Involving patients in the research and decision-making processes early on is key. This project aims to realize a scientifically sound research process providing research outputs that can easily and timely be implemented in the care trajectory of patients with pancreatic cancer. This research project will also lead to recommendations on how to involve patients with pancreatic cancer and how the methodology of this research project can be translated to other patient groups.

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KEYWORDS

patient-centered care; quality of health care; interdisciplinary research; decision-making; pancreatic cancer; quality; outcome; assessment; cancer; pancreas; development; testing; implementation; patient-reported; experience; protocol; participatory medicine

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Introduction

Background

Consensus grows that patients' needs and experiences should be at the center of quality improvement initiatives. Person-centered care emerges internationally as a key indicator of the quality of (value-based) health care [1].

Person-centeredness is rooted in the definition of "patient-centeredness." The standard definition of Stewart et al [2] states that patient-centeredness encompasses six interconnecting dimensions: exploring both the disease and the illness experience, understanding the whole person, finding common ground between the physician and patient, incorporating prevention and health promotion, enhancing the doctor-patient relationship, and "being realistic" about personal limitations and issues such as the availability of time and resources [2]. High levels of positive patient experiences are associated with higher levels of adherence to recommended prevention or treatment processes, better clinical outcomes, a better patient safety culture within hospitals, and less unnecessary use of health care [3].

Psychometric solid patient-reported experience measures (PREMs) are used as tools to assess person-centered care [4]. PREMs measure the patient's experiences with health care services based on validated questionnaires. Greenalgh et al [5] frame the positive influence of well-implemented routinely collected patient-reported measures on patient health outcomes including their effects on doctor-patient communication, monitoring of the treatment response, detection of unrecognized problems, patients' health behavior, and clinician's management of the patient [5]. One other important benefit that PREMs bring along is their ability to enrich the practitioner-patient conversations in various ways; for example, the PREM's results can be used to help support the patients' reflection and expression during consultations [4].

PREMs in Oncology

A recent systematic review concludes that oncology PREMs with good psychometric characteristics are lacking; most identified PREMs scored low on reliability, effectiveness, content, and construct validity [6]. General PREMs for all types of cancer are not recommended. The review argues that the specificity of measures and responsiveness of a PREM can be realized by developing a PREM for a specific type of cancer [6]. In 2019, a British pancreatic cancer survey was developed to measure the needs and experiences of patients with pancreatic cancer and to assess the services provided by the charity Pancreatic Cancer UK [7]. This survey is used for cross-sectional measurements [7].

Besides methodological issues, the use and impact of PREMs in clinical practice remains relevant. Furthermore, more knowledge grounded in research on how and when to introduce PREMs data during consultations is needed [4]. Some evidence identified critical moderating mechanisms to implement patient-reported data such as providing multiple moments of feedback over a period of time [8-11]; addressing different stakeholders (physicians, nurses, allied health care professionals, as well as patients) with simple, clear, graphical, and longitudinal meaningful interpretation of the measurement results; providing training for both health care professionals and patients; and offering decision-making aids, clear management plans, and clinical pathways including referrals [12-14]. Hampering factors are classified as people-based barriers, questionnaire-based barriers, and barriers related to access and interpretation of PREMs data.

Rationale for a Pancreatic Cancer PREM

In 2018, a total of 2024 of the 70,468 (~3%) Belgian people diagnosed with cancer have pancreatic cancer [15]. It ranks as the 10th most common cancer type in Belgium [15]. Pancreatic cancer is often detected at a late stage frequently combined with metastases or growth in the surrounding tissue [16]. Only 12.4% of patients live for more than 5 years [15]. For the majority of patients, the tumor cannot be removed. Palliative treatment with chemotherapy, whether or not supplemented with radiation, is most often considered [17].

An assessment of the organization of pancreatic cancer treatment and care in Belgium mentioned the lack of concentration of expertise in hospitals to treat and care for patients with pancreatic cancer [17]. In July 2019, expertise centers were formally recognized for, for example, complex surgical interventions. At the same time, quality indicators to monitor care and treatment were identified: the time between confirmed diagnosis and the start of the treatment; 1-, 3-, and 5-year observed survival; and relative survival. It is essential to also assess patient experiences, but a pancreatic cancer PREM is not yet available in Belgium. A specific instrument measuring the experiences of the patient's entire care trajectory (from diagnosis to follow-up) will support the quality improvement process.

Overall, patients with pancreatic cancer are underrepresented in psychosocial research owing to the limited prognosis of the disease [7]. Patients with pancreatic cancer do not feel involved in the development of their treatment and care plans mainly because they are stressed by the life-threatening nature of their condition [7,18]. Nonetheless, this is a population with potentially severe needs [18]. Hence, the specific PREM—the results of which are immediately used to improve care and treatment delivery—could also be highly relevant, additionally for strengthening a team-based approach [18].

Pancreatic cancer treatment and care requires a multidisciplinary collaboration including professionals directly involved with the care of patients with pancreatic cancer such as digestive oncologists, nutritionists, psychologists, (digestive) oncology nurses, social assistants, physiotherapists, and occupational therapists [17]. Timely and appropriate care can only be delivered when these health care professionals work as a multidisciplinary team [17].

A multidisciplinary team is defined as two or more health care professionals interacting in a dynamic and flexible way working toward collectively agreed goals [19]. An often used tool to coordinate activities and decision-making processes are team meetings [20]. In Belgium, multidisciplinary team meetings in oncology take place in different formats; that is, formally regulated and financed multidisciplinary oncology consultations

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(MOCs), patient ward rounds, and ward meetings [20]. The benefits of multidisciplinary team meetings are well documented; for example, their ability to realize better team performance after case discussion being one of them [21]. However, one can question whether these MOCs are truly multidisciplinary, considering all types of patient needs [21]. Notwithstanding, a recent study found that in the context of MOCs, these in fact do not show a true multidisciplinary character [20]. This has mainly to do with physicians taking the upper hand during MOCs, mostly discussing biomedical information leaving nurses and psychologists with limited time to exchange information related to patient preferences and psychosocial aspects. This negatively impacts the implementation of treatment recommendations; for example, making nonholistic treatment recommendations [22,23]. Horlait et al [20] argue that the findings of their study can be used as a basis to design and implement interventions aiming to reinforce the inclusion of psychosocial information and patient preferences during MOCs [20]. This research project takes this recommendation on board, aiming to study if, for example, an intervention entailing the inclusion of PREM results during MOCs or other consultation settings can improve the delivery of person-centered pancreatic cancer care.

Study Purpose

Within this research project, three subobjectives are pursued:

1. To develop a PREM measuring the experiences of care-related aspects in pancreatic cancer care;
2. To validate the PREM; and
3. To develop and evaluate an (educational) intervention to support the use of the PREM results in clinical multidisciplinary practice.

Methods

Design

This study is based on a multi-method approach combining qualitative and quantitative research methodologies. Three sequential studies are planned where the results of a step feeds into the next substudy.

Objective 1: Development of the PREM

An exploratory mixed methods study design will be used to accomplish objective 1. The development of the PREM items starts with a systematic exploration of opinions on items to take into account by (a) patients with pancreatic cancer and their relatives and (b) health care professionals working in digestive oncology. The study will start with a (quantitative) survey followed by a (qualitative) telephone interview study. This latter strategy proved to be effective in other studies [4].

In the survey, respondents will be asked to assess the relevance of a list of items to include in the PREM using a Likert-based scale from 1=Very Important to 5=Very Unimportant. These items are extracted from the literature and the evidence with regard to needs and experiences of patients with pancreatic cancer. This survey will be piloted first to make sure that all items and the information in the supporting documents are well understood. Participants of the survey will be asked if they want to take part in a follow-up telephone interview, seeking more qualitative in-depth information about their vision on the importance of measuring patient experiences, which factors could influence this process, how and in which consultation setting these PREM results should be used, and on which time points PREM completions should be scheduled. The interviews will be semistructured, leaving sufficient leeway and flexibility to adapt to participants' contribution, but structured by means of an interview guide topic list. These topics are also extracted from the evidence regarding barriers and facilitators when implementing the PREM's results. The topic list will also be piloted first. The number of interviews will be defined by principles of saturation; that is, the moment on which no new data will be generated [24].

Respondents will be recruited via all Belgian digestive oncologists who treat patients with pancreatic cancer and who are in charge of multidisciplinary health care provision. These oncologists will receive an email asking to participate in the study and to help with the recruitment forwarding this call for participation to other digestive oncology health care professionals and patients with pancreatic cancer.

The data from the surveys will be descriptively analyzed, and an item will be included in the PREM if at least 75% of the respondents gave it an average rating of 2 or less on the Likert scale of importance. This 75% consensus determination is based on the recommendation of Keeney et al [25]. The list of domains that will eventually be consented on will then be reformulated to items for the PREM. These are then further evaluated in the validation study. The aim is to have at least 100 participants, which is a number suggested in the study by Boulkedid et al [26] to make sure a solid consent is realized [26].

The qualitative data generated via follow-up telephone interviews will be thematically analyzed using a grounded theory approach in which the principles of inductive reasoning will be applied, resulting in labels supported by quotes of the interviews [27]. This methodology allows us to analyze in a descriptive, explorative, and detailed way focusing on different research questions at the same time. The same analysis will be performed by two researchers; that is, investigator triangulation will be realized to reduce researcher's bias when looking at the same data and when defining the themes [28]. The results of this qualitative analysis will provide input for the implementation intervention that will be developed, piloted, and tested as part of objective 3. All these data will be anonymized, and possible respondent-identifying information will be deleted from the interview transcripts. The audio files will be stored on a password-protected server.

Objective 2: Validation of the PREM

Validation of the PREM will take place in several steps. The *content validity* of the PREM will be tested through focus groups (maximum of 7 persons per focus group) or individual interviews with patients with pancreatic cancer. They will be asked to assess the items in terms of the formulation or chosen terminology, the response scale, and the relevance of each item. After this, the stability of the items will be examined by means of a test-retest of the PREM. This involves a limited number of patients with pancreatic cancer, who will be asked to complete

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the survey presenting the PREM on two different time points. The construct validity will be tested on the PREM data set that will be generated via the PrCT (see objective 3) and by means of an exploratory factor analysis (EFA) that will be executed on the trial data. This will allow us to investigate how many dimensions can be determined in a construct and it will help to reduce items because items that have no contribution to the factors can be deleted [29]. Principal components analysis will be the statistical measure used. To be able to perform an EFA, a minimum of 100 patients is necessary [30].

The COSMIN (COnsensus-based Standards for the selection of health status Measurement INstruments) checklist will be used to assess the methodological quality of the PREM throughout its entire development and validation process [31]. This checklist specifies the standards related to the design of a PREM development study and the nine measurement-related property standards; that is, content validity, structural validity, internal consistency, cross-cultural validity or measurement invariance, reliability, measurement error, criterion validity, hypotheses testing for construct validity, and responsiveness.

Objective 3: Testing the Effectiveness of the PREM Implementation Intervention

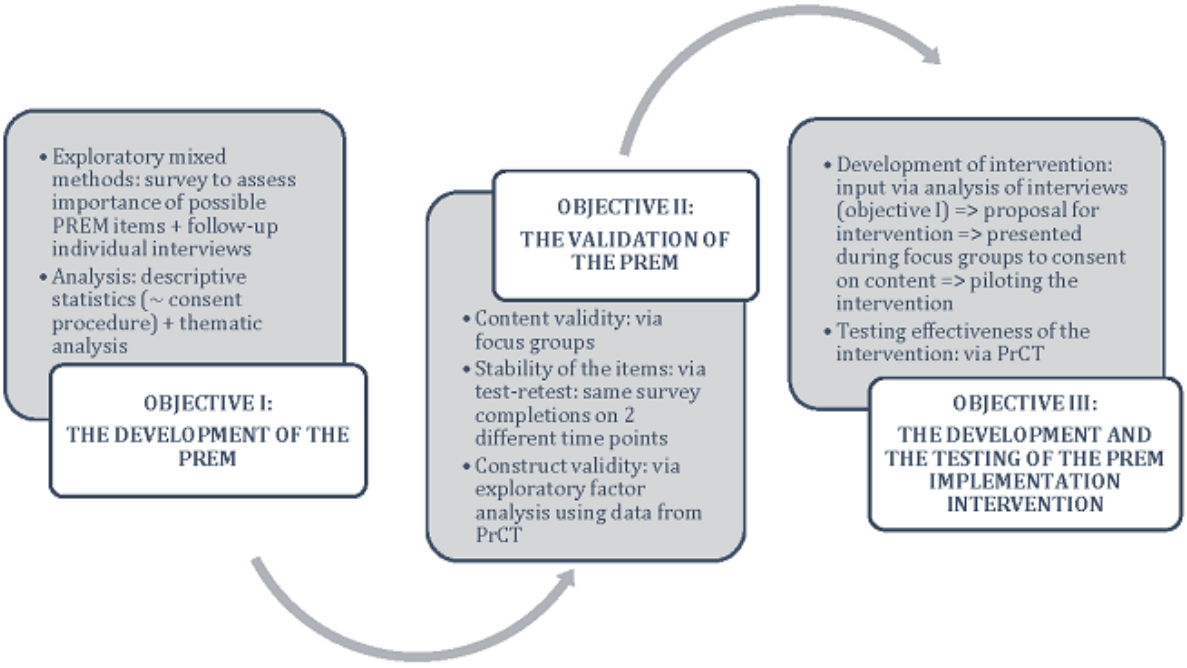
The results of the primary inductive analysis of the follow-up telephone interviews will be integrated in the framework of the development of a complex intervention according to the Medical Research Council (MRC) framework realizing a framework analysis. The results of this framework analysis will help identify the key elements for an intervention to implement the PREM. This proposed intervention will be presented to patients with pancreatic cancer and their health care professionals via focus groups aiming to explore its feasibility and to provide consent on the prefinal content of the intervention. Before testing the effectiveness of the PREM implementation intervention using a PrCT study design, a pilot study will be carried out. We chose a PrCT design because we will study the effectiveness of the intervention in a real-world setting or direct practice, and the results will be used to inform treatment effectiveness and health care decisions [32]. The intervention group will be the consultation setting using PREM results with, for example, facilitating (educational) interventions. The control group involves the standard consultation setting. We will use effectiveness criteria as proposed by Chen et al [7] (the effects it has on the treatment response; the changes to patient health behavior; the changes to clinicians' management of the patient; and the improvement of health outcomes) as well as the experience of the patients.

The PrCT will follow the steps as specified in the Consolidated Standards of Reporting Trials 2010 checklist. This checklist indicates the aspects such as trial objectives, trial design, interventions, outcomes, sample size, randomization, blinding, statistical methods, participant flow, recruitment, baseline data, and numbers analyzed, which will need to be reported when carrying out the trial.

The PREM's implementation intervention will need to be flexible enough to be used and adapted to each specific practice; hence, we can consider it a complex intervention [33]. In this perspective, we will use the MRC Framework for the development, evaluation, and implementation of complex interventions as our general guidance throughout the research project [33].

Figure 1 below visualizes the different steps within the research project.

Figure 1. Diagrammatic representation of the steps and methods within the Patient Reported Experience Measure for Pancreatic Cancer Care (PREPARE) research project. PrCT: pragmatic randomized controlled trial; PREM: patient-reported experience measure.



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Ethical Considerations

Ethics approval to conduct the exploratory mixed methods study (objective 1) has been obtained (B14320200000170) from the Medical Ethics Committee of the University Hospital Brussels that will be the central committee. If necessary additional ethical approval will be obtained from the participating hospitals.

Results

The protocol presents the entire structure of the research project entailing three different studies each feeding into each other. For now, a steering group has been composed with representatives of the Belgian federal government of Public Health and Social Affairs, the National Institute for Sickness and Disability Insurance, the Belgian College of Oncology, Sciensano, two digestive oncology specialists, and the director of the Belgian pancreatic cancer community. This steering group gives direction to the research project and has already met and reviewed the research protocol, the survey and the interview guides that will be used for the study of objective 1. The tools (ie, survey and interview guides) that will be used within study 1 have been piloted in a group of 3 patients with pancreatic cancer and the health care professionals of the steering group. During this pilot, we asked these patients and health care professionals to complete the survey and read through the interview guides. After this, we explored their experiences in reference to the understanding of the items, the length of the survey and guides, and if additions were needed. Recruitment for objective 1 via the recruitment leaflets that were sent via email to the digestive oncologists has started since January 2022.

Discussion

This paper presents a research protocol on the development and implementation of a PREM for patients with pancreatic cancer. Since person-centered care is one of the gold-standard practices, we wanted to understand how this can be strengthened. PREMs are measurement tools to assess the person-centeredness of care delivery. The project aims to study how a dedicated PREM for patients with pancreatic cancer can support collaborative treatment decision-making.

The choice of patients with pancreatic cancer is mainly grounded in the underrepresentation of patients with pancreatic cancer in psychosocial research [7]. Moreover, patients with pancreatic cancer do not feel involved in the development of their treatment and care plans [18]. The poor prognosis of patients with pancreatic cancer should not be considered a hurdle to study this patient population group. In particular, for this group, research outputs that can easily and timely be implemented in the care trajectory of patients with pancreatic cancer are needed.

This research project takes place in Belgium where decision-making processes on care and treatment plans take place in different types of multidisciplinary team meetings, but where treatment preferences of the patient are not very well taken up [20]. This observation calls for interventions that support and facilitate the patient's voice during consultations. Moreover, in Belgium, a PREM for pancreatic cancer is not available. Developing a PREM incorporating the experiences of patients with pancreatic cancer adapted to the local context increases the specificity of the measurement tool and consequently its ability to capture the true situation of this patient group. The study is research-oriented but uses iterative involvement cycles of all stakeholders to develop the PREM item list and the intervention. One of the strengths of this research project is the involvement of patients with pancreatic cancer as well as oncology and digestive health care professionals, taking into account and comparing their perspectives. If discrepancies occur, it will provide us insight on aspects that should be considered when developing the implementation plan of the PREM; that is, it will help us assess the feasibility. By involving health care professionals and patients together with their family in the development, validation, and implementation process of the PREM, a common ground for the necessity of patient experience measurements will be achieved. The bottom-up approach to develop an (educational) intervention to introduce PREM results in the collaborative treatment decision-making process also makes the research project vigorous.

To prevent methodological errors, some particular quality control mechanisms and tools are used. These will strengthen the robustness of the research design. Throughout the entire research project, special attention will be paid to pilot the data collection instruments, such as surveys and interview guides, before effectively using them. User-friendliness and unambiguous understanding are aspects that, for example, will be evaluated during the piloting. Impact assessment tools with regard to patient engagement will be used to critically evaluate the way we involved patients and if the predicted aim of their involvement is achieved. The steering group will meet on critical moments throughout the research project to guard if the focus of the research project is retained.

The project will end up with recommendations on how to involve patients with pancreatic cancer in shared decision-making processes, on the international relevance of the findings and on how the methodology used can be translated to other patient groups.

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Data Availability

The data sets that will be generated during the different studies will be available from the corresponding author on reasonable request.

Authors' Contributions

All authors have read and approved the final manuscript. KM, MH, and ML designed the research project. KM wrote the first draft of the manuscript, and MH, ML, MVdB, and MP contributed to the revisions.

Conflicts of Interest

None declared.

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Abbreviations

COSMIN: COnsensus-based Standards for the selection of health status Measurement INstruments
EFA: exploratory factor analysis
MOC: Multidisciplinary Oncology Consultation
MRC: Medical Research Council
PrCT: pragmatic randomized controlled trial
PREM: patient-reported experience measure

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Protocol

Developing a One-Stop Platform Transportation Planning Service to Help Older Adults Move Around in Their Community Where, When, and How They Wish: Protocol for a Living Lab Study

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Abstract

Background: Multiple mobility-related challenges frequently appear with aging. As a result, many older adults have difficulty getting around, to go, for example, to doctors' appointments or leisure activities. Although various means of transportation are currently available, older adults do not necessarily use them, partly because they do not know which ones are adapted to their needs and preferences. To foster older adults' autonomy and freedom in their decision-making about transportation, it is crucial to help them make informed decisions about the means that suit them best.

Objective: Our aim is to develop Mobilainés, a one-stop platform transportation planning service combining different transport modes and services to help older adults move around in their community where, when, and how they wish. More specifically, we aim to (1) define older adults' mobility needs and preferences in order to conceptualize a one-stop platform; (2) cocreate a prototype of the one-stop platform; and (3) test the prototype with users in a real-life context.

Methods: This ongoing study uses a "Living Lab" co-design approach. This approach differs from traditional research on aging by facilitating intersectoral knowledge sharing and innovative solutions by and with older adults themselves. A steering committee of 8 stakeholders from the public, scientific, and private sectors, as well as older citizens, will meet quarterly throughout the study. The design comprises three phases, each with several iterative subphases. Phase 1 is exploration: through co-design workshops and literature reviews, members of the intersectoral committee will define older adults' mobility needs and preferences to support the conceptualization of the one-stop platform. Phase 2 is experimentation: 4 personas will be produced that reflect the different needs and preferences of typical older adult end users of the platform; for development of a prototype, scenarios and mockups (static designs of the web application) will be created through co-design sessions with older adults (N=12) embodying these personas. Phase 3 is evaluation: we will test the usability of the prototype and document changes in mobility, such as the ability to move around satisfactorily and to participate in meaningful activities, by and with older adults (N=30) who use the

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prototype. The steering committee will identify ways to support the adoption, implementation, and scaling up of Mobilainés to ensure its sustainability. Qualitative and quantitative data will be triangulated according to each subphase objective.

Results: The first phase began in September 2019. The study is scheduled for completion by mid-2023.

Conclusions: This innovative transportation planning service will merge existing transportation options in one place. By meeting a wide variety of older adults' needs and preferences, Mobilainés will help them feel comfortable and safe when moving around, which should increase their participation in meaningful activities and reduce the risk of social isolation.

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KEYWORDS

aged; mobility limitation; transportation; community-based; participatory research; information system; mobility; older adults

Introduction

Background

According to the World Health Organization, the number of people aged 60 years or older will rise from 900 million in 2015 to 2 billion by 2050 [1]. Difficulties related to mobility frequently appear with aging. For example, a decline in physical abilities, such as balance [2], may increase risks when walking, such as falling on icy sidewalks or not having enough time to cross the road at traffic lights, or when using public transportation, such as when getting on and off the bus. A decline in cognitive abilities [3] and lack of digital literacy [4] can lead to difficulty planning outings and understanding public transportation options. Poor vision, slow reaction time, and reduced range of motion interfere with safe driving, an important symbol of autonomy in North America [2,5,6]. In addition, having few financial resources [7] and living in a rural area [8] make access to taxi and bus services more problematic. Many older adults have a small social network, which limits the number of people they can ask for help when they want to go out. These issues also increase the risk of being sedentary and isolated [9]. It is now well established that social participation is a significant determinant of older adults' health and quality of life. Social participation may be defined as a person's involvement in activities providing interactions with others [10] in community life and in important shared spaces; social participation evolves according to the available time and resources, with the societal context, and with what individuals want and what is meaningful to them [11]. Recent studies show that isolation is detrimental to older adults' physical and mental health and leads to similar or even greater mortality risks than smoking and obesity [12]. Older adults' ability to get to desired locations, such as the grocery store, hospital, or theater, is a vital aspect of their independence and an essential vector of their social participation [13].

Although options other than driving are available, such as taxis and buses, these means of transportation are not necessarily familiar to older adults, are sometimes not used by them, and are associated with various fears, such as getting lost, not being able to find a place to sit, or having unwanted social contacts [9]. Indeed, safety is one of the main concerns for older adults when using public transportation [14]. The recent COVID-19 pandemic revealed how the fear of public transportation could increase social isolation. Moreover, older adults often have different travel patterns from younger adults, because lifestyle transitions and age-related changes influence their needs, destinations, and travel time [15]. Shrestha and colleagues [14] reported that, ideally, transportation services for older adults should be accessible, affordable, comfortable, door-to-door, and available at a frequency that allows for spontaneous use and the ability to get to a wide range of destinations. It is therefore important to help older adults regain and sustain their postpandemic daily and community-based activities by improving the use of mobility options that are both flexible (usable where and when they want) and safe (reducing the risk of falls, incidents, and travel-related anxiety). For example, going to a doctor's appointment might include being able to go downstairs, remain calm despite the stress of not arriving at the hospital on time, and find one's way to the doctor's office, which may require physical assistance, comfort, or help with navigating. Transportation for seniors should thus go beyond help leaving the house: it must ensure that they are independent and free to choose where, when, and how to get to desired locations while reducing the physical and psychological risks and discomfort associated with moving around.

Starting Point

In June 2018, a community-based workshop was organized to identify and respond to the challenges of aging in place and mobility in Sherbrooke, Canada. More than 50 people, including 20 older adults, participated in this workshop, which was co-organized by members of LIPPA, the French abbreviation for the Laboratoire d'innovations par et pour les ainés (the laboratory of innovations by and for older adults). LIPPA's mission is to create a more inclusive society by developing innovative and sustainable solutions by and for older adults [16].

The findings from a community-based workshop supported by LIPPA guided the development of this study. Two goals emerged from the workshop: promoting better intergenerational housing and fostering greater mobility for seniors. Discussions on the latter goal produced innovative ideas regarding how to better meet older adults' transportation needs. Participants highlighted the difficulty older adults face in getting information about the different services available and knowing when and how to use them. They expressed the need to give older adults access to existing transportation services through a one-stop platform. Participants also stressed the need to speak with a real person; this aspect should be considered when designing the

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platform to ensure it is used by older adults who are not familiar with the technology. The gap in access to transportation services to support social and community-based activities, as well as the importance of building solutions based on existing services to avoid duplication, are consistent in reviews of the literature [13,17-20]. Thus, at the end of this workshop, researchers from LIPPA joined forces to address these needs.

Objectives

The aim of this study is to develop Mobilainés (a portmanteau of the French words for "mobility" and "older adults"), a mobility as a service (MaaS) platform [21] that incorporates different modes and forms of transportation services, to help older adults move around where, when, and how they wish. This study uses a "Living Lab" approach [22]. Living Labs foster the creation of environments where stakeholders form public-private-people partnerships to develop and test new technologies in real life contexts. To promote older adults' functional autonomy and ability to make decisions based on their own values and realities, Mobilainés requires knowledge development and the combination of diverse experiences, which naturally calls for a Living Lab approach. Compared to other transportation planning tools [23], Mobilainés will be unique in supporting older adults as they use various means of transportation adapted to their needs and preferences. More specifically, it considers personalized parameters that are often neglected in existing transportation planning tools [24] (eg, lifestyle habits and feeling safe when taking a trip), in addition to more general information easily accessible in current databases (eg, time and location). At present, using app-based travel information is considered the most realistic way to provide real-time information to address the needs of older adults. However, a large number of older adults [23] do not find transportation planning apps easy or intuitive to use. Mobilainés thus aims to include a technological interface, such as the web, with human support (eg, via telephone) to take into account the variability in digital literacy in an aging population. The functionality of our approach will also consider the aging process and region-specific issues in terms of human machine interactions, such as by using enhanced image contrast and voice commands and providing options such as calculating the time according to walking speed, giving the proximity of bus shelters and benches (for rest), and avoiding outdoor stairs. For example, Mobilainés could be designed to help an 81-year-old woman living in an urban area find a seat on the bus or avoid walking on icy sidewalks while planning a trip to the grocery store. Mobilainés does not seek to create a new mode of transportation; the goal is to merge existing transportation options in the same one-stop location to increase their usability and help older adults make decisions by providing useful information and recommendations based on available data, such as the roads most frequently cleared of snow in Sherbrooke. To support older adults in selecting and using the means of transportation that best fit their needs and preferences, this study had 3 objectives. Objective 1: define older adults' mobility needs and preferences in order to conceptualize the one-stop platform. Objective 2: cocreate a prototype of the one-stop platform. Objective 3: test the prototype with users in a real-life context.

Methods

Design and Procedures

With LIPPA's support and expertise, a Living Lab co-design approach is being used for this study. Five key elements usually define the Living Lab approach [25-27]: (1) the cocreation process, (2) intersectoral collaboration, (3) engagement of citizen-users throughout the process, (4) open-system development of innovative solutions, and (5) real-life context. Mobilainés incorporates these elements as it brings together intersectoral partners, including transportation providers and various community organizations, to rethink how to plan trips with older adults so that they feel more comfortable and safer when moving around. To support the future use of Mobilainés [28], it is crucial to secure older adults' commitment at every stage of the process. Engagement, seen as a process that fosters the motivation to carry out a common project [29], can be increased by communication activities that encourage productive dialogue [30]. Participants in this productive dialogue are able to be objective about their own conceptualizations and make connections with conceptualizations that also benefit others and the project. For example, a dialogue becomes productive when individuals are able to make new distinctions using communication methods that foster this objectivity, such as workshops, presentations, and the use of lay language to convey information.

Research Team

Our multidisciplinary team is composed of researchers with expertise in rehabilitation, communication, computer science, social work, and telehealth. Two master's students and two PhD students in communication, gerontology, and computer science are also involved in specific aspects of the study, in accordance with their academic fields and degrees. The first authors and the project coordinator are currently meeting biweekly to discuss data collection and analysis and present results, as well as coordinate experts' and partners' contributions and timelines for everyone concerned.

Steering Committee

A steering committee of 8 stakeholders from the public, scientific, private, and community sectors, as well as older citizens, has been tasked with monitoring the study's progress, reviewing data collection methods and results, and deciding and prioritizing design aspects of Mobilainés through each study phase, ensuring its sustainability and respecting the citizen-centered Living Lab approach. Governance and ethical issues, such as intellectual property, are also being discussed. The committee meets quarterly, though the frequency varies depending on need as perceived by the members. As full partners in the process, older adult members help keep this population's perspectives at the center of the creative process and ensure that their emotions, experiences, and limitations are considered in all decisions [31-33]. The steering committee contributes to responding to the needs and expectations of every partner around the table. Sessions are held in person or via videoconference and are audiotaped for data collection purposes. To maintain long-term engagement, visual tools are used at each meeting and constantly updated to provide information on the phase and

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timeline of each objective and a summary of data collection and results. Committee members are also invited to complete a survey at the end of each meeting to monitor their engagement level. The results of each phase are presented at yearly meetings to obtain specific feedback and clarify the members' willingness to continue contributing to the project.

Co-design Workshops

To support a co-design process throughout the study, intersectoral partners and older adults are invited to participate in in-person workshops every 2 or 3 months [34] using different cocreation methods and tools. We are using LIPPA's well-established connections with local organizations to recruit older adults who present a wide variety of mobility profiles, experiences, and needs. At the beginning of each co-design workshop, a short video explaining the objectives of Mobilainés is presented to help participants understand the project as they "build the unknown" [35]. A special effort is made to clarify the roles, needs and contributions of all partners [36]. During the workshops, it is crucial to pay attention to the way older adults are involved in the process [37]. Online collaborative tools, such as Miro (Miro LLC), are used and shared on screen so that participants can see how they contribute to the workshop objectives. These co-design workshops are led by researchers who are familiar with the cocreation process and are audio- and videotaped for data collection purposes.

Study Phases

Because the Living Lab approach is not linear, the innovation design has 3 phases, with each phase including several iterative subphases. This design incorporates the 3 main phases typically used in Living Labs: exploration, experimentation, and evaluation [38].

Phase 1 (Exploration): Defining Older Adults' Mobility Needs and Preferences in Order to Conceptualize the One-Stop Platform

The aim of Phase 1 is to support the conceptualization of the one-stop platform by documenting the realities, needs, and expectations of older adults and transportation service providers and their satisfaction with existing mobility planning tools. This exploration phase includes 5 subphases. Phase 1.1 will identify facilitators and barriers to the mobility of older adults in Sherbrooke, and more specifically, documentation of their experience with planning trips and moving around. Phase 1.2 will determine the status of current transportation services as well as existing trip planning platforms and their functionality (including their content and interface). Phase 1.3 will define the criteria for the ideal Mobilainés platform [28]. Phase 1.4 will identify potential functionality to enable meeting the identified needs. Finally, phase 1.5 will bring together the most relevant partners in order to create the ideal platform.

In order to utilize the most up-to-date knowledge and experiences, the research team is gathering (1) evidence from recent scientific and gray literature by performing 2 scoping reviews [39] to identify (a) facilitators and barriers to older adults' mobility and (b) existing tools for user interface and experience; (2) data from surveys completed by the steering committee and older citizens (n=8) to prioritize the platform criteria; and (3) results from 3 steering committee meetings as well as 5 in-person workshops that include transportation service providers, community-based and public health stakeholders (n=8), and older citizens (n=8); telephone interviews are also being conducted with very frail adults (n=8). Sustainable environment experts are also involved, to assess how environmental factors and social awareness can have a positive impact on the choice of transportation methods.

Phase 2 (Experimentation): Cocreating a Prototype One-Stop Platform

The aim of Phase 2, also ongoing, is to produce preliminary versions of the components of Mobilainés (eg, functionalities of the web application and telephone support). The necessary experts will be gathered and the objectives of 5 subphases will be established. Phase 2.1 will be the development of 4 profiles of typical older-adult end users of the platform to produce personas based on data gathered in Phase 1 [40]. Phase 2.2 will be recruitment, with the help of our partners, of 12 older adults embodying these personas (these 4 personas reflect older adults' differing needs and preferences, such as the level of use and access to transportation planning tools when planning trips and the frequency and assistance required to go out). Phase 2.3 will be the production of usage scenarios and mockups (static designs of the web application) to present Mobilainés's potential functionalities (content and interface) and the different ways older adult end users might utilize them (Miro, an online collaborative whiteboard, will be used to support the ideation process and create a first mockup, which will then be programmed in React, a JavaScript library [Meta Platforms, Inc]). Phase 2.4 will be testing of the scenarios and mockups with older adults (n=12), who will rate the features of Mobilainés in relation to their needs and preferences. Phase 2.5 will be refinement of the features of the one-stop transportation planning service, based on the input of the older adults. Decision-making tools, such as the "new, useful, feasible" (NUF) matrix [41], will help the steering committee choose between several mockup options according to their novelty, usefulness (or satisfaction [42]), and feasibility.

In this phase, different scenarios representing realistic uses of Mobilainés will be created to refine its functionality (eg, its ability to display interactive maps showing the most age-friendly routes, the ease of use of its interface, and its inclusion of fall prevention workshops), the accessibility of its interface (eg, telephone support and use of technology), and to provide information about how the preliminary prototype matches older adults' needs.

Phase 3 (Evaluation): Pretesting the One-Stop Platform Prototype

Phase 3 will include 5 subphases. In phase 3.1, technology experts involved in the project will implement the technology platform functionality of Mobilainés, based on the mockups and scenarios developed in phase 2. Prototyping of the Mobilainés platform will rely on the use of technology for data gathering (eg, timetables, real-time location information, and user-generated content) [43]. The Mobilainés MaaS platform uses data acquired from various sources, including OpenStreetMap [44], the Google Maps platform [45], the

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Société de transport de Sherbrooke (the Sherbrooke transportation company) [46], and open-source data from the City of Sherbrooke [47]). These data will be processed and utilized to meet older adults' mobility needs. The literature on journey planning algorithms will be reviewed, and algorithms will be tested to select the algorithm best adapted to older adults' needs and preferences, as identified in Phase 1. Based on the available data and identified needs, the algorithm will find the most well-adapted and personalized itinerary to the given destination. Service agreements and protocols for human support (eg, telephone) will also be determined. In phase 3.2, older adults matching the personas identified in Phase 2 will test the prototype's usability in specific scenarios. Usability tests of the web application will be performed iteratively in 2 sessions (testing initial and revised versions) with targeted end users (n=8). Participants will test 3 usage scenarios in which they have to navigate the web portal interface and obtain travel information for a specific destination while inputting specific preferences. Interactions with the web portal application will be captured with screen recording software. Facial expressions and verbal comments will be recorded using an external camera. Eye movements (saccades and fixations) will be recorded with an eye tracking system (Invisible; Pupil Labs). Task performance in the 3 case scenarios (including aspects such as critical errors and the task completion rate) will be analyzed [48]. A retrospective think-aloud session with gaze path simulation [49] combining the captured streams (screen, face, and gaze) will be used to debrief the participants and identify usability issues. Eye tracking metrics (such as fixation duration) will be extracted from eye movements using Blickshift analytics (Blickshift GmbH) and triangulated with the debrief results. At the end of the session, participants will also complete the System Usability Scale [50], a questionnaire frequently used to measure efficacy and satisfaction with usability when users perform specific tasks, as well as a questionnaire based on the Unified Theory of Acceptance and Use of Technology model, used to measure the perceived performance, expectancy, facilitating conditions, and social influence of a new technology [51]. Participants will then be invited to join a focus group to further document their satisfaction (quantified as like or dislike) with the navigation, information, and sensory design. Phase 3.3 will involve refinement of the prototype according to the results obtained in phase 3.2. Phase 3.4 will be testing of the Mobilainés prototype in real environments. Older participants (n=30) will be recruited through collaboration with local organizations and assigned different mobility profiles (see phase 2) to reflect a variety of needs, preferences, and characteristics, such as gender, income, rural or urban living area, and physical limitations. More specifically, we will perform pre-post measures after 6 and 12 weeks to identify changes resulting from use of the prototype in (1) older adults' habits for trip frequency and destination, (2) mobility experience, such as moving around satisfactorily, getting to activities at the desired time, and feeling safe and comfortable when moving around, (3) participation in meaningful activities, and (4) empowerment (Table 1). We will use a combination of qualitative methods, such as semi-structured interviews and logbooks, and quantitative methods, such as actigraphy, geolocation, and questionnaires [52]. The participants will be asked to record their use of Mobilainés and the occurrence of adverse events, such as the death of a proxy or a major health change, in a logbook. To minimize seasonal effects on the measures, the participants will be divided into 3 groups of 10. Each group will be tested during fall, spring, winter, or summer. With the participants' consent, individual geolocation data will be collected using GPS watches; participants may deactivate this data capture upon request. GPS coordinates will be used to document travel details, such as time outside the home, distance and time of travel, and mode of travel, and correlate this with use of the Mobilainés prototype, which will record inquiries made by each user. To prevent potential personal identification, individual geolocation data will not be linked to a geographic information system nor be presented or summarized at the individual level in any communications presenting the results [53].

The final phase, phase 3.5, will involve discussion of ways to support the adoption and implementation of Mobilainés. More specifically, to facilitate the transition toward scaling up the technologies emerging from Mobilainés, public and private sector partners will support the steering committee in establishing sustainability modalities. This final phase will refine the pretested prototype and the protocols for providing services to older adults. It may also uncover gaps in current transportation services that need to be filled to ensure a satisfactory mobility experience (eg, an intersection with traffic lights might have insufficient time for an older adult with a walking aid to cross the street).

Table 1. Prepost measurement variables and assessment methods.

Variables	Habits	Experience	Social participation	Empowerment
Quantitative measures				
Technology-based capture: actigraphy and geolocation [52]	✓			
French Canadian version of the Life-Space Assessment Questionnaire [54]	✓			
Health Care Empowerment Questionnaire [55]				✓
Qualitative assessment				
Semistructured interviews		✓	✓	
Logbooks		✓		✓

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Data Analyses

Matrices will be used to perform mixed method analyses of the multiple types of data generated throughout the iterative processes of conceptualizing and creating the prototype (objectives 1 and 2) and by the pre-post qualitative and quantitative tests of the prototype (objective 3).

Qualitative Analysis

The workshop data will be produced, explored, and thematized using support interfaces, such as boards, post-its, drawings, and models. This production, exploration, and thematization process is quite widespread in co-design approaches since it allows everyone's point of view to be considered, for improvements to be made collectively, and for meaning to be derived while avoiding desirability and cognitive convergence biases [36]. Data are reviewed to identify points of agreement and disagreement, which leads to a better understanding of how ideas change during group discussions [35]. This process allows the research team to (1) identify themes or comments that are not captured during the workshops; (2) confirm and consolidate existing themes; (3) explore the robustness of the themes; and (4) validate the conceptual tightness of the themes [36]. Themes emerging from the workshops will be compared with a systematic analysis of the data to ensure the reliability and validity of the results. Thematic analyses of the qualitative data streaming from the steering committee meetings and individual interviews will also be conducted during each study phase, as well as during the scoping review (phase 1.2).

Quantitative Analysis

Descriptive analyses will be performed to determine participant characteristics and context, as well as to examine the quantitative data streaming from surveys and questionnaires used in each study phase. In addition, statistical analyses (paired *t* tests) will be conducted to explore changes in participants' behavior as a result of using the prototype (pre-post measures—phase 3.4). SPSS (version 12; IBM Corp) will be used.

Data Triangulation

Data sources will be triangulated to address each subphase objective. For example, data from surveys, workshops, and literature reviews on age-friendly technologies and transportation planning apps will be combined to support the identification of the best functionalities to include [56,57] in Mobilainés (ie, this information will be used to compile "dos and don'ts") (phase 1.4). Triangulation of the quantitative and qualitative data reduces the biases associated with each of these methods. For example, for the final tests (phase 3.4), participants may not be aware that they travel as often or for as long as they do or they may hesitate to report behavior they are ashamed of (such as walking slowly or avoiding busy routes), but this can be captured by actigraphy or geolocation. On the other hand, these methods may not capture significant problems encountered by older adults when moving around (eg, if they need assistance to fold a walker and put it in a taxi). Matrices in Excel (Microsoft Corp) will be used to merge qualitative and quantitative data [58]. A research assistant will conduct this analysis, and at least one other research team member will covalidate the qualitative data.

Ethical Considerations

The Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux de l'Estrie—Centre hospitalier universitaire de Sherbrooke (Integrated health and social services center of the Eastern Townships and the University of Sherbrooke hospital) approved the study in September 2019 (approval number 2020-3389). Older adults and other members of the steering committee are considered official partners in the project rather than research participants. A LIPPA coordinator is available to support their participation in the steering committee and other cocreation activities. To promote equity between partners and recognize the specific contribution of older adults throughout the project, the same financial compensation (to cover meeting-related transportation expenses) will be offered to all steering committee members and others involved in the co-design sessions [59]. Since the cocreation process is dynamic and iterative, the research team may ask the Research Ethics Committee to approve modifications to the protocol in phases 2 and 3.

Results

This ongoing study began in September 2019. The first 2 phases will be completed by September 2022. Due to the pandemic, steering committee meetings were conducted online from March 2020 to June 2021, but all workshops took place in person, complying with public health measures. The study is scheduled for completion by mid-2023. Years 1 and 2 were used to define the mobility needs and preferences of older adults in order to conceptualize the one-stop platform. Year 3 was used to cocreate the prototype one-stop platform. Year 4 will be used to test the prototype with users in a real-life context. In the spirit of open innovation, LIPPA will also share the results of each phase on its website [16]. Possible solutions that were not used will also be disseminated to allow other knowledge users to explore their possible implementation in other contexts.

Discussion

Expected Findings

The development of this one-stop platform transportation planning service will use a participatory and innovative methodology. Our Living Lab approach differs from traditional research on aging by facilitating intersectoral knowledge sharing and co-design of innovative solutions by and with older adults. As this approach improves adoption of the resulting innovation and its acceptability to users, Mobilainés is expected to produce practical scientific and socioeconomic impacts that benefit both individuals and society. More specifically, Mobilainés seeks to provide multimodal interfaces, such as web and telephone support, and functions, such as helping users avoid icy paths and sidewalks, that are based on quantitative and qualitative data from users with various profiles. These innovations will help to improve responses to a wide range of needs (based on disability level and technological knowledge), preferences (such as the desire to move around in familiar areas or take part in social interaction when taking a trip), and resources (such as income or learning ability) of a broad spectrum of older adults. According to Metz [60], available, effective, and affordable

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transportation facilities provide access to people and places necessary to maintain good quality of life. By promoting transportation services more adapted to the needs of older adults, Mobilainés will contribute to their quality of life by enabling active participation in the community, such as going to the shopping center, grocery store, or theater, and other activities significantly impacted by the pandemic. Mobilainés is also expected to help meet the needs of older adults for socialization while reducing the harmful effects of preventable incidents and the less visible consequences of sedentary lifestyles, isolation, and exclusion. For example, Mobilainés could help (1) reduce falls and car accidents by helping older adults avoid icy routes and sidewalks, (2) reduce inactivity by enabling older adults to walk outside more often, (3) reduce loneliness by helping older adults meet people, and (4) reduce the stigma affecting some modes of transportation [61]. In a postpandemic context, after lockdowns increased deconditioning and broke social ties, it is crucial to address these risks while considering health issues. Finally, over the long term, Mobilainés may act as a catalyst to change the built environment and society. For example, data collected from users may point to a lack of bus shelters in a particular area; knowing this should help to improve older adults' mobility experience and support an informed decision on their transportation options. Although studies on older adults' mobility in smart cities have increased in recent years in the United States, Europe [62,63], and Asia [7], it is still an emerging research area in Canada.

Strengths and Limitations

As Mobilainés is being developed in a Quebec community with a wide variety of older adult demographics (eg, low vs high income and urban vs rural location [64]), our findings could be applicable to other communities. Although older adults face barriers that may differ from one place to another based on the steepness of the terrain, traffic density, and available transportation services, their mobility needs are similar, including going shopping, visiting relatives, going to leisure activities or places of work, and volunteering. By focusing on the needs expressed in co-design sessions by a broad spectrum of older adults (eg, by including those with high or low technological literacy) and reporting the progress of the study in real time on our website [16], Mobilainés has great potential for transferability, as both the methodology and the solutions we develop are potentially reproducible and exportable [65,66]. In addition, as one of the main challenges of research innovation is sustainability after the study is complete [65,66], our research team is seeking to increase the survivability of Mobilainés by addressing this important issue with members of the steering committee in the initial phases of the study.

Although a Living Lab approach is well suited to developing innovative solutions to complex social issues [67,68], including aging, it poses some challenges and creates some tensions [69], especially when it involves more vulnerable populations or marginalized situations [70]. For example, Living Lab studies that focus on older adults must take into account slower rates of innovation, communication and relationship issues, and the locations and types of co-design workshops [71,72]. Thus, in addition to the use of simple visual tools and videos developed by our research team [16], some co-design workshops will take place (when allowed by pandemic health measures) in the facilities of local organizations to foster partner engagement and participation by older adults [72]. In the same vein, our findings could extend to informing future co-design approaches and methods used to involve and engage older people in the process of designing technologies, such as employing videos to introduce people to different stages of the design and development process.

Conclusion

With the proliferation of technological solutions brought about by the pandemic, there is a need to ensure that the platform will not be just another innovation that older adults will not use. To avoid this potential pitfall, Mobilainés will merge existing transportation options to support the use of services currently in place instead of adding new ones. Co-created by and for older adults, Mobilainés should also support their future use of the platform and potentially reduce the costs associated with multiple development cycles. Mobilainés differs from current platforms by helping older adults enhance their mobility experience, knowing that a positive experience will keep them motivated to go out again, especially in a postpandemic context, where feeling safe may be even more important than before. Mobilainés thus aims to become a crossroads where experience, knowledge, and innovation meet with the goal of fostering autonomy and freedom in older adults' decision-making regarding transportation while reducing the physical and psychological risks of being harmed when moving around. We live in an era in which re-engagement in the community needs to be supported, and Mobilainés will contribute to a more inclusive society by improving older adults' access to transportation, now and in the future, and by accommodating their current and anticipated needs.

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Conflicts of Interest

None declared.

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Abbreviations

LIPPA: Laboratoire d'innovations par et pour les aînés
MaaS: Mobility as a Service
NUF: New, useful, feasible

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Protocol

Implementing a Personalized Integrated Stepped-Care Method (STIP-Method) to Prevent and Treat Neuropsychiatric Symptoms in Persons With Dementia in Nursing Homes: Protocol for a Mixed Methods Study

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Abstract

Background: Neuropsychiatric symptoms occur frequently in many nursing home residents with dementia. Despite the availability of multidisciplinary guidelines, neuropsychiatric symptoms are often inadequately managed. Three proven effective methods for managing neuropsychiatric symptoms were integrated into a single intervention method: the STIP-Method, a personalized integrated stepped-care method to prevent and treat neuropsychiatric symptoms. The STIP-Method comprises 5 phases of clinical reasoning to neuropsychiatric symptoms and 4 stepped-care interventions and is supported with a web application.

Objective: This study aims to identify the facilitators and barriers in the implementation of the STIP-Method in nursing homes.

Methods: A mixed methods design within a participatory action research was used to implement the STIP-Method in 4 facilities of 2 Dutch nursing home organizations. In total, we aimed at participation of 160-200 persons with dementia and expected an intervention fidelity of 50% or more, based on earlier studies regarding implementation of effective psychosocial interventions to manage neuropsychiatric symptoms. All involved managers and professionals were trained in the principles of the STIP-Method and in using the web application. An advisory board of professionals, managers, and informal caregivers in each facility supported the implementation during 21 months, including an intermission of 6 months due to the COVID-19 pandemic. In these 6-weekly advisory board meetings, 2 researchers stimulated the members to reflect on progress of the implementation by making use of available data from patient records and the web application. Additionally, the 2 researchers invited the members to suggest how to improve the implementation. Data analysis will involve (1) analysis of facilitators and barriers to the implementation derived from verbatim text reports of advisory board meetings to better understand the implementation process; (2) analysis of patient records in accordance with multidisciplinary guidelines to neuropsychiatric symptoms: personalized, interdisciplinary, and proactive management of neuropsychiatric symptoms; (3) evaluation of the web application in terms of usability scores; (4) pre-

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and postimplementation analysis of patient records and the web application to evaluate the impact of the STIP-Method, such as changes in neuropsychiatric symptoms and informal caregiver burden.

Results: We enrolled 328 persons with dementia. Data collection started in July 2019 and ended in December 2021. The first version of this manuscript was submitted in October 2021. The first results of data analysis are expected to be published in December 2022 and final results in June 2023.

Conclusions: Our study may increase understanding of facilitators and barriers to the prevention and treatment of neuropsychiatric symptoms in nursing home residents with dementia by implementing the integrated STIP-Method. The need for well-designed implementation studies is of importance to provide nursing homes with optimal tools to prevent and treat neuropsychiatric symptoms.

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KEYWORDS

dementia; neuropsychiatric symptoms; caregiver; implementation; psychosocial intervention; nursing homes

Introduction

Background

Neuropsychiatric symptoms such as depression, anxiety, apathy, agitation, and aggressive behavior are highly prevalent in persons with dementia. The prevalence rates of clinically relevant neuropsychiatric symptoms are over 70% [1,2] and the cumulative 2-year prevalence is about 97% [3]. In persons with dementia, neuropsychiatric symptoms are associated with psychological distress, increased mortality, greater functional impairment, lower quality of life, increased emergency department visits, hospitalizations, and long-term care admissions as well as high caregiver burden [4-9].

Although psychotropic medication is often prescribed to manage neuropsychiatric symptoms in persons with dementia, this type of medication is associated with limited effect and considerable side effects [10,11]. National and international guidelines on the management of neuropsychiatric symptoms recommend psychosocial, personalized, and interdisciplinary interventions for first-line treatment to reduce the inappropriate prescription of psychotropic medication [12-15]. Person-centered care, that is, care that fits wishes, needs, and capabilities of persons with dementia and their (informal) caregivers, is the basic principle in the Dutch guideline “Problem behavior in people with dementia” [15]. Several psychosocial multicomponent interventions have been developed to prevent and treat neuropsychiatric symptoms in persons with dementia and are effective according to the Dutch guideline [15]: Integrative reactivation and rehabilitation (IRR) [16]; Grip on Challenging Behavior (Grip) [17]; and the Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia (STA OP!) [18]. As shown in Table 1, these interventions all consist of a continuous loop of detection; analysis; treatment of physical, cognitive, and psychosocial problems; and evaluation. At the same time, these interventions slightly differ from each other. Multimedia Appendix 1 [12, 16,19-33] includes a detailed description of the 3 methods.

Two recent consecutive audits of quality of care in nursing homes carried out by Dutch Health Inspectorate with an interval of 2 years both showed late, inadequate, or incorrect management of neuropsychiatric symptoms despite the existence of national guidelines and advices based on the first audit [34,35]. A broad analysis of neuropsychiatric symptoms is still insufficiently implemented. As a result, possible interventions are poorly implemented [35]. Although IRR, Grip, and STA OP! have been developed and proven to be effective when actually applied as intended, these programs are not broadly implemented within Dutch nursing homes beyond the research setting [35]. Even though the intervention fidelity of IRR, defined as the adherent and competent delivery of an intervention as set forth in the research plan [36], was rather high (90%) within the studied nursing homes, it showed a limited transferability to nursing homes outside the research setting because of a lack in necessary knowledge and skills. Within Grip, all necessary forms of the program were used in only a small percentage of persons with dementia [37]. The intervention STA OP! was performed in only a small proportion (39%) of persons with dementia [18]. An overview of determined facilitators and barriers to implementation is presented in Table 2. The low level of intervention fidelity of these Dutch programs is in line with results of international studies on intervention fidelity of effective psychosocial interventions to manage neuropsychiatric symptoms. For example, the effective DEMBASE program in Japan was fully implemented in 52% of persons with dementia [38]. The overall intervention fidelity of Dementia Care Mapping was poor [39]. Only 13% of nursing homes completed the fully protocol to an acceptable level [39].

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Table 1. Overview of characteristics of 3 effective methods to manage neuropsychiatric symptoms, as described in Bakker et al [16], Zwijsen et al 2014 [17], and Pieper et al 2018 [18].

Characteristics	IRR[a]	Grip[b]	STA OP![c]
Proactive method (start when admitted to nursing home)	✓		
Reactive method (start when problems are signaled by nursing staff)		✓	✓
Cyclical process (detection, analysis, treatment, evaluation)	✓	✓	✓
Physical functioning	✓	✓	✓
Assessment and management of pain			✓
Cognitive functioning	✓	✓	✓
Psychosocial functioning	✓	✓	✓
Stepped-care model (stepping up interventions from the least to the most intensive and stepping down, linked to patients' needs)			✓
Matched-care model (client and therapy are matched, based on intake information about specific problems and patient characteristics)	✓		
Interdisciplinary collaboration	✓	✓	✓
Involvement of informal caregiver	✓	✓	
Treatment of informal caregiver	✓		
Standard involved disciplines	Nurse, elderly care physician, clinical psychologist, social worker	Nurse, psychologist, elderly care physician	Nurse, psychologist, social worker, elderly care physician, occupational therapist, physical therapist
Indicative involved disciplines	For each patient, at least two of the following therapists are involved: music therapist, psychomotor therapist, creative therapist, physical therapist, occupational therapist, speech therapist, dietician	Other disciplines are involved if needed. For example, occupational therapist	N/A[d]

[a]IRR: integrative reactivation and rehabilitation.

[b]Grip: Grip on Challenging Behavior.

[c]STA OP!: Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia

[d]N/A: not applicable.

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Table 2. Overview of facilitators and barriers of implementation, as described in Zwijsen et al [37], Hakvoort et al [40], and Pieper et al [41][a].

	Grip[b]	STA OP![c,d]
Facilitators for implementation	• Support in power, for example, management board of directors • Enhanced awareness: positive attitude toward change • Group size: 10-15 participants for training sessions	• Support in power, for example, presence of persons with a motivational leadership style • Enhanced awareness: positive attitude toward change
Barriers for implementation	• Staff turnover • High workload • Involvement in multiple projects or new innovations • Canceled meetings • Organizational changes • Large number of forms to be filled in • Lack of digitalized forms • Lack of information for informal caregivers	• Staff turnover • High workload • Involvement in multiple projects or new innovations • Absence of essential disciplines

[a]Facilitators and barriers were not investigated for integrative reactivation and rehabilitation.

[b]Grip: Grip on Challenging Behavior.

[c]STA OP!: Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia.

[d]Group size was not indicated as a facilitator or a barrier for implementation within STA OP!

Recent studies have shown that interventions should be aimed at both persons with dementia and their informal caregivers. Specific interventions for informal caregivers have long-lasting effects on depression and anxiety symptoms, increase quality of life, and are cost-effective [42]. When implementing a multicomponent care improvement intervention, it is important to understand the implementation process to improve sustainability in clinical practice [12,43,44] to prevent and treat neuropsychiatric symptoms. Although factors for IRR, Grip, and STA OP! have been investigated, nursing homes did not succeed in implementing these methods.

If taken into account the known facilitators and barriers, to what extent will effective methods be implemented? Are there other facilitators and barriers that have not been taken into account? Therefore, the researchers involved in IRR, Grip, and STA OP! (TJEMB, MS, and WPA) and experts on implementation and management of neuropsychiatric symptoms (DLG, JTS, SUZ) collaboratively developed a joint multicomponent intervention, the STIP-Method: a personalized integrated stepped-care method to prevent and treat neuropsychiatric symptoms in persons with dementia in nursing homes, which is compliant with the current Dutch guidelines to manage neuropsychiatric symptoms [15]. In addition to the overarching elements of the existing 3 methods, the stepped-care model was integrated into the STIP-Method. Stepped care can be defined as a staged, evidence-based system comprising hierarchically delivered interventions linked to patients' needs: from the least to the most intensive, and stepping down or up when needed [45,46]. The integral STIP-Method especially focuses on interdisciplinary collaboration and shared decision making. Shared decision making between professionals and persons with dementia and informal caregivers is of proven importance to achieve real person-centered care [47]. Finally, the STIP-Method is supported by the use of a web application that finds its roots in Sweden: BPSD Care, in which BPSD stands for Behavioural and Psychological Symptoms of Dementia. In Sweden, it forms a nationwide quality registry that is globally acknowledged as an innovation in the psychosocial dementia care program context [48]. Adaptations of the BPSD-registry program have been developed in both Denmark [49] and Japan [50-52]. The use of BPSD Care has been shown to be supportive in significantly reducing neuropsychiatric symptoms, increasing quality of life in persons with dementia [53], and leading to a lower sense of burden among professionals [51].

Objectives

This study aims to identify the facilitators and barriers in the implementation of the STIP-Method in nursing homes. Based on earlier studies on intervention fidelity of effective psychosocial interventions to prevent and treat neuropsychiatric symptoms [18,37], we hypothesize that the STIP-Method will be delivered according to protocol to 50% or more persons with dementia (intervention fidelity). Additional aims are to evaluate to what extent the STIP-Method is delivered according to protocol (intervention fidelity), to evaluate the impact of the implementation of the STIP-Method on neuropsychiatric symptoms, restraint use, aggression incidents, and use of psychotropic medication. Furthermore, we assess the contribution of the BPSD Care web application to the management of neuropsychiatric symptoms. We expect the study will deliver an in-depth understanding of facilitators and barriers to the management of neuropsychiatric symptoms to positively influence these implementation aspects through (1) emphasis on interdisciplinary collaboration and involvement of informal caregivers, (2) implementation of the web application BPSD Care, and (3) considering the facilitators and barriers regarding the interdisciplinary implementation of Grip and STA OP!

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Methods

Study Design

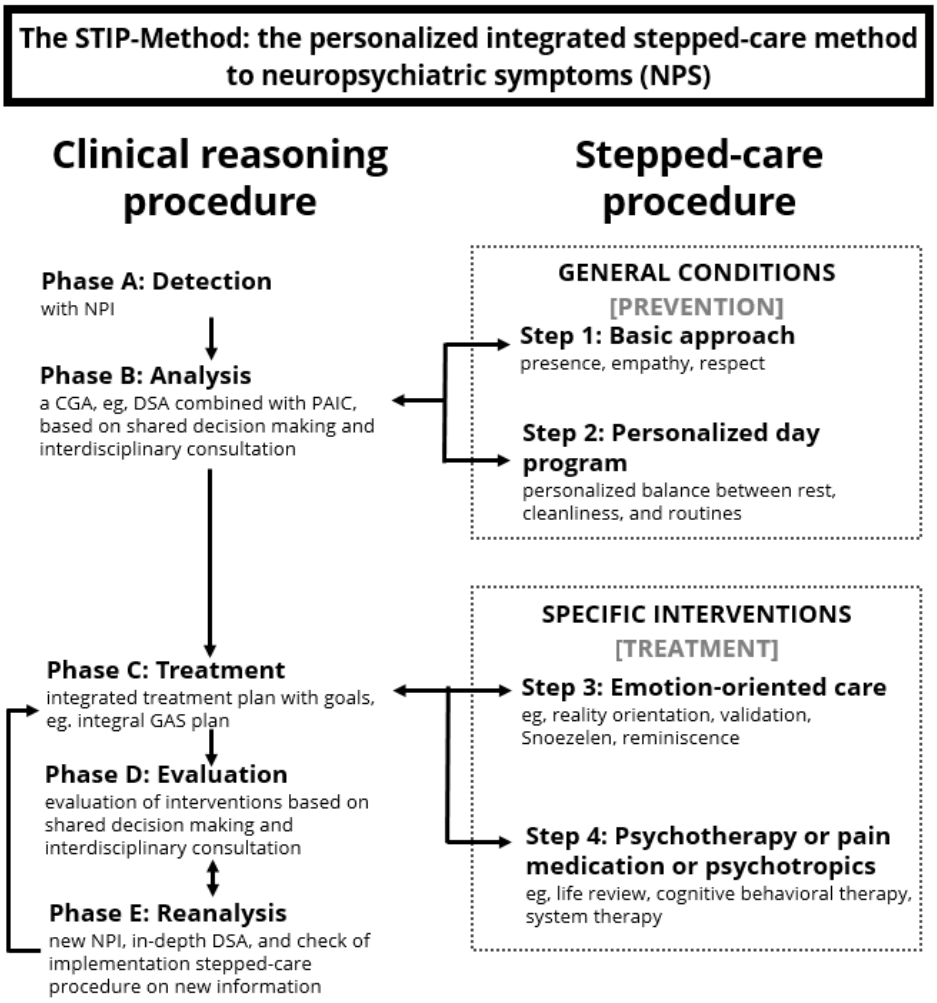
We used a mixed methods design within a participatory action research. Principles and processes of participatory action research were used during the implementation of the STIP-Method, and mixed methods were applied through data collection stages (qualitative and quantitative). Participatory action research involves a cyclical process of fact finding, action, and reflection, leading to further inquiry and action for change [54]. This approach has frequently been proven to be effective in involving persons with dementia and informal caregivers and blends research with action [55]. Table 2 shows the enhanced awareness of the method as a facilitating factor in implementing Grip and STA OP! To raise awareness, it is essential that all disciplines experience a sense of urgency and autonomy with regard to management of neuropsychiatric symptoms [37,40,41]. To provide this sense, it is vital to actively involve the target group in the implementation process. Therefore, researchers actively collaborated with professionals, managers, and informal caregivers to support the implementation of the STIP-Method. During implementation, explicit attention was given to the lessons learned from the implementation of IRR, Grip, and STA OP!, so as to understand whether implementation will be improved when these lessons were taken into account. When implementation will not be improved, understanding of the underlying causes is of great importance. Qualitative methods were used to examine facilitators and barriers in the implementation of the STIP-Method. Inductive content analysis was performed using the data directly to define codes and themes, which is further explained in the "Analysis" section [56]. Quantitative methods were used to evaluate the impact of the implementation of the STIP-Method and to assess the contribution of the BPSD Care web application to the management of neuropsychiatric symptoms. Data were collected between July 2019 and December 2021 in the Netherlands with a 6-month intermission due to the COVID-19 pandemic.

Intervention: The STIP-Method

Overview

The STIP-Method consists of 2 types of procedures: clinical reasoning comprising 5 phases, and a stepped-care procedure comprising 4 interventions (Figure 1). The intervention is supported with the BPSD Care web application to facilitate the clinical reasoning procedure.

Figure 1. The STIP-Method. CGA: Comprehensive Geriatric Assessment; DSA: dynamic system analysis; GAS: Goal Attainment Scaling; NPI: Neuropsychiatric Inventory; PAIC: Pain Assessment in Impaired Cognition.



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Clinical Reasoning Procedure

The clinical reasoning procedure is made up of 5 phases (A, B, C, D, and E). Phase A involves identifying and assessing neuropsychiatric symptoms using the Neuropsychiatric Inventory (NPI) [33]. In addition, activities of daily living are assessed via the Barthel Index [57,58], cognitive functioning with the Mini-Mental State Examination (MMSE) [59], and pain perception via the Pain Assessment in Impaired Cognition (PAIC) [60]. In phase B, the analysis phase, factors behind specific behavior are explored based on an extended biography together with the person with dementia or informal caregiver. A broad needs assessment is performed that focuses on basic needs, pain, and physical and psychosocial needs, for example, based on the 7 domains of the Dynamic System Analysis: biology, cognition, personality characteristics, emotional aspects, communication, social context, and life history [61,62]. In phase C, treatment, an integrated treatment plan comprising all involved disciplines is drawn up and carried out. This plan incorporates the relevant themes, goals to be achieved, and interventions to be used per discipline. Subsequently in phase D the integral treatment plan is evaluated in an interdisciplinary manner, with consideration for perceptions of both persons with dementia and their informal caregivers. If the interdisciplinary team concludes that goals in the integral treatment plan are not achieved, an in-depth reanalysis will follow in phase E. For example, when an NPI score does not decrease after the intervention, the patient's symptoms are assumed to persist. In case of new aspects, the 5 phases of the clinical reasoning process are run through again.

Stepped-Care Procedure

Within the stepped-care approach, 4 steps (1-4) of increasing intensity of interventions are distinguished [63,64]. Based on the broad analysis, potentially suitable interventions are examined. Steps 1 and 2 are general conditions for all persons with dementia. Step 1 concerns an appropriate basic approach with presence, empathy, and respect. In step 2 the focus is on a tailor-made daily program that takes into account concrete preferences, hobbies, and activities of persons with dementia based on an in-depth biography. If the effect of these steps is insufficient, specific interventions of steps 3 and 4 can be applied. These steps can also follow immediately after phase B, the analysis phase. In step 3 emotion-oriented care is used to support persons with dementia in coping with the cognitive, emotional, and social consequences by connecting to their individual abilities and subjective experience. Included methods are reality orientation, reminiscence, Powerless in Daily Living (PDL care), and 'Snoezelen' (a method to actively stimulate the senses of hearing, touch, vision, and smell in a resident-oriented, nonthreatening environment [65]). PDL care is a type of demand-oriented care that is given multidisciplinary, whereby tools and methods from occupational therapy and physiotherapy are integrated into the care procedures of nurses and therapists [66]. Step 4 refers to a personalized form of (a selection of) 11 available psychotherapeutic interventions from the IRR program focusing on persons with dementia and informal caregivers [16]. Multimedia Appendix 1 includes a detailed description of these psychotherapeutic interventions. It is a common misconception that persons with mild to severe dementia cannot be treated. Of course the cognitive status of a person with dementia plays a role in determining appropriate psychotherapeutic interventions.

BPSD Care Web Application

The web-based BPSD registry is translated into Dutch and is launched under the title "BPSD Care web application." This web application supports the process of clinical reasoning by providing a visualization of longitudinal change in neuropsychiatric symptoms to inform interdisciplinary decision making [38]. Visual feedback to motivate professionals was suggested to be a vital facilitator for implementation in Japan [38]. The registry relies on outlining the frequency, severity, and emotional burden of neuropsychiatric symptoms using the NPI scale (phase A), providing a comprehensive checklist for possible causes of neuropsychiatric symptoms and various scales (MMSE, Barthel Index, and PAIC) to better explore the factors behind specific behavior (phase B). Furthermore, the registry offers evidence-based care plan proposals to reduce neuropsychiatric symptoms and supports monitoring results of the employed interventions in a convenient way. The web application is used adjacent to the regular patient records in nursing home organizations.

Setting

The STIP-Method was implemented in 4 facilities from 2 Dutch nursing home organizations. Implementation lasted 21 months (from October 1, 2019, to July 1, 2021), including an intermission of 6 months due to the COVID-19 pandemic. In 2017 and 2018, professionals and management employed in these 2 nursing home organizations were trained in step-by-step management of neuropsychiatric symptoms using the stepped-care method. Although the board, management, and professionals of both nursing home organizations indicated that professionals had improved their knowledge about neuropsychiatric symptoms after training, they indicated that they still inadequately involve persons with dementia and informal caregivers in the treatment process. Both organizations recognized the necessity to improve management of neuropsychiatric symptoms and consequently, the STIP-Method was implemented in these 2 organizations.

Implementation

Training

All managers and professionals of the 4 nursing homes were trained in the principles of the STIP-Method. The training course guided (1) neuropsychiatric symptoms and determining underlying factors in persons with dementia; (2) coordination between professionals and collaboration with persons with dementia and informal caregivers; (3) the use of web application BPSD Care; and (4) implementation of agreed interventions with an emphasis on stepped-care procedure steps 1 and 2. Interventions from steps 3 and 4 were discussed briefly. The training was provided by involved researchers during 4 sessions of 3 hours and was organized at their own facility. A group size between 10 and 15 participants for training sessions was maintained (facilitating factor of the Grip study) [40]. In-depth training is necessary to master stepped-care procedure steps 3 and 4. Participants were encouraged by the researchers to attend

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an available elaborate training course for steps 3 and 4. This course was provided beyond the scope of this study.

Advisory Boards

The implementation of the STIP-Method was supported by means of (1) advisory boards, (2) collective advisory board meetings, and (3) a project group. Based on the identified facilitators in the Grip and STA OP! studies [40,41], the advisory boards consisted of, on average, 8 members: a psychologist, an elderly care physician, a manager, 2 informal caregivers, and 2 or 3 members of the nursing staff. The advisory board meetings were held in each facility once every 6 weeks and lasted 90 minutes. Progress of implementation was discussed based on data from patient records and the BPSD Care web application. The meetings were moderated by 2 researchers (TJEMB and a researcher outside the study group) to facilitate the process of identifying facilitators and barriers. The agenda for the meetings was determined by the members of the advisory boards, enabling them to discuss what was important to them to further improve the implementation. In addition, a collective advisory board meeting was planned every 24 weeks for the 4 advisory boards to learn from each other's experiences. Furthermore, a project group of professionals, managers, and board members of each organization met every 12 weeks to discuss progress and to make adjustments at organizational level where necessary (facilitator of the Grip Study [40]).

Support by Two Researchers

During the whole intervention period, 2 researchers (1 implementation specialist and 1 STIP-Method content specialist [TJEMB]) supported and stimulated participants of the advisory boards to reflect on available data from patient records and the web application BPSD Care. Additionally, researchers encouraged participants of advisory boards to seek for ways to increase implementation.

Study Population

To identify differences in implementation aspects in and between nursing home organizations, both organizations have chosen 2 participating facilities. On average, a nursing home facility houses 40-50 persons with dementia. Taking into account the number of beds and turnover of nursing home residents, 160-200 persons with dementia were expected to be included within the 4 facilities.

Recruitment

Within each nursing home facility, managers were asked to send an invitation letter, a participant information letter, and a consent form to the legal representatives of persons with dementia. The representatives were asked to allow researchers to access the patient records. Representatives could give permission by signing and returning the written informed consent form to the nursing home in a prestamped envelope. After 4 weeks, a reminder was sent to the managers to motivate their team members to contact representatives about the informed consent forms. Participants had the right to withdraw from participation at any time. No financial incentive to participate was provided.

Besides recruitment of persons with dementia, each participating nursing home facility had to form an advisory board. Managers had the freedom to decide whom to invite to the advisory board meetings. Informal caregivers received financial compensation because of the effort required to attend the meetings.

Inclusion and Exclusion Criteria

Persons with dementia were included if they met the following criteria: (1) dementia diagnosis; and (2) residing on psychogeriatric wards of nursing homes. Informal caregivers had to be able to understand and communicate in Dutch.

Data Collection

Methods to Identify Facilitators and Barriers in the Implementation of the STIP-Method

During the advisory board meetings, participants were invited to share suggestions for facilitators and barriers at organizational and facility levels. Additionally, board members and managers were interviewed after implementation in order to challenge them to reflect on their role during the implementation process and to identify their perceived facilitators and barriers. Finally, after the implementation period, we collected experiences from participants of advisory board groups by conducting an online survey to assess the contribution of advisory board groups toward the implementation of the STIP-Method. Topics were frequency, composition of the advisory board meetings, and usefulness of the meetings.

Instruments to Assess Intervention Fidelity

To evaluate if the STIP-Method was implemented in a personalized, interdisciplinary, and proactive manner, we assessed all patient records and registries in the BPSD Care web application at the start and the end of the implementation. Consideration was given to the availability and date of completion of 5 phases of clinical reasoning and 4 stepped-care interventions. Whether the care was personalized was evaluated by checking if an appropriate basic approach with presence, empathy, and respect (step 1) was used and if a tailor-made daily program was drawn up (step 2). With regard to interdisciplinary collaboration, we assessed whether and to what extent an integral treatment plan was applied. During a consensus meeting of the involved researchers of IRR, Grip, and STA OP!, it was decided to define proactive implementation as 2 weeks after admission to the nursing home, based on earlier research and previous experiences [16]. Furthermore, a qualitative analysis was carried out on 50 patient records at baseline and 50 after implementation. We used a specific quality standard based on the Dutch multidisciplinary guideline on problem behavior in dementia [15]. With regard to the qualitative analysis, the 9 elements of the STIP-Method were graded using a 4-point scale (missing, insufficient, sufficient, and good). The definitions of these grades are outlined in Table 3. All observations were independently scored by 2 researchers (HMFV and a researcher outside the study group) to monitor interrater reliability.

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Table 3. Qualitative analysis of patient records.

Definition	Good (=standard)	Sufficient	Insufficient
Clinical reasoning phases			
A: Detection	• Neuropsychiatric inventory is fully completed • Results are discussed in an interdisciplinary manner	Does not fully meet the standard	Does not meet the standard at all
B: Analysis	• Biography consists of concrete information on physical, psychological, and social domains • Biography is up to date • Broad analysis includes at a minimum a physical examination, neuropsychological factors, biography, information about personality and contextual factors	Does not fully meet the standard	Does not meet the standard at all
C: Treatment	• Integral treatment plan (with informal caregiver, psychologist, professionals, and elderly care physician) involves at least physical, psychological, and social domain • Attention for informal caregiver aspects within the social domain • Focus on factors extracted from broad analysis • Measurable treatment goals and interventions	Does not fully meet the standard	Does not meet the standard at all
D: Interdisciplinary evaluation: behavior visits[a], multidisciplinary consultations, and care plan reviews[b]	• Evaluation of goals and degree of implementation of actions • Information about progress and satisfaction of persons with dementia and informal caregiver is available • Appointment for next evaluation is available	Does not fully meet the standard	Does not meet the standard at all
E: Reanalysis	• Not further defined: reference to phases A and B		
Stepped-care interventions			
1: Basic approach	• Results from broad analysis • Describes how real contact, with presence, empathy, and respect, can be made with persons with dementia • Is based on the needs of the person with dementia and informal caregiver	Does not fully meet the standard	Does not meet the standard at all
2: Personalized day program	• Results from broad analysis • Fits well with the needs of the person with dementia • Concrete preferences, hobbies, and activities are taken into account • Consists of concrete actions and activities • Easy to find in patient record	Does not fully meet the standard	Does not meet the standard at all
3: Emotion-oriented care	• Results from broad analysis • Responds to underlying needs and causes • Easy to find in patient record • Drawn up on an interdisciplinary manner	Does not fully meet the standard	Does not meet the standard at all
4: Psychotherapeutic interventions	• Interventions to target the diagnosed physical function problems • Focus on emotional experience, personality, traumatic life experiences, social functioning (including informal caregiver burden)	Does not fully meet the standard	Does not meet the standard at all

[a]Visits related to neuropsychiatric symptoms and with the presence of at least a psychologist, an elderly care physician, and a registered or practice licensed nurse.

[b]Reviews of the care plan with the presence of an elderly care physician and a registered or practice licensed nurse.

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Instruments to Assess the Impact of the Implementation of the STIP-Method

During the implementation period, the progress of the NPI scores among persons with dementia was used to assess the impact of the implementation on the level of frequency, severity, and informal caregiver burden of neuropsychiatric symptoms. In addition, the number of freedom-restricting measures, aggression incidents, and the prescription of psychotropic medication were used.

Instruments to Assess to What Extent the BPSD Care Web Application Does Contribute to the Facilitation of Clinical Reasoning and the Management of Neuropsychiatric Symptoms

At baseline and after implementation, all involved professionals were requested to fill in a digital, self-constructed questionnaire to evaluate ongoing implementation of the STIP-Method, including the BPSD Care web application. Participants rated the usability of the web application on items of the System Usability Scale, a validated 10-item questionnaire with a 5-point response scale ranging from strongly disagree (1) to strongly agree (5) that lead to a score between 1 and 100 [67]. Job satisfaction was measured by 7 questions derived from the Dutch employee satisfaction survey from ActiZ (Dutch Association for Health Care Providers in Elderly Care) [68]. The Employee Net Promotor Score was used to summarize caregiver satisfaction and is based on a single question: “How likely is that you would recommend our organization to a friend or colleague?” Participants gave an answer ranging from 0 (not all likely) to 10 (extremely likely). The score is calculated as the percentage of “promotors” (individuals scoring a 9 or 10) minus the percentage of “detractors” (individuals answering 0-6) [69]. To assess the general usability of the STIP-Method, questions regarding 5 phases of clinical reasoning and 4 stepped-care interventions were added with a 5-point response scale ranging from not useful (1) to very useful (5). Furthermore, a multiple-choice question was asked to assess the purpose of using the web application. In addition, verbatim text reports of advisory board meetings were used to assess the contribution of the web application to the management of neuropsychiatric symptoms. An extended overview of the used assessment instruments is shown in Table 4. Figure 2 depicts a timeline for implementation and data collection.

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Table 4. Overview of concepts, measures, and measurements to assess the implementation of the STIP-Method, a personalized integrated stepped-care method.

Source and assessment	Measurement instrument	Time of measurement	
		Start implementation	End implementation
Advisory board meetings			
• Facilitators and barriers	• Advisory boards at each facility[a]		
	• Collective advisory board meeting (all 4 facilities)[b]		
	• Project group[c]		
Patient records			
• Availability and date of completion of 5 phases of clinical reasoning + 4 stepped-care interventions	• Quality standard: STIP-Method	✓	✓
• Quality check patient records with a 4-point scale (good, sufficient, insufficient, and missing)	• Quality standard: STIP-Method	✓	✓
BPSD[d] Care			
• Neuropsychiatric symptoms	• Neuropsychiatric Inventory	✓	✓
• Broad needs assessment	• Inventory of causes based on Dynamic System Analysis	✓	✓
• Cognitive functioning	• Mini-Mental State Examination	✓	✓
• Activities of daily living	• Barthel Index	✓	✓
• Pain	• Pain Assessment in Impaired Cognition	✓	✓
Pharmacists' electronic patient records			
• Medication use	• Use of the ATC[e] classification system on psychotropic medication: antipsychotics (N05A), anxiolytics (N05B), hypnotics (N05C), antidepressants (N06A), anti-dementia medication (N06D), and anti-epileptic medication (N03)	✓	✓
Patient records			
• Demographics	• Organization and facility	✓	✓
	• Type of dementia	✓	✓
	• Date of admission to nursing home	✓	✓
	• Demographics: sex, date of birth	✓	✓
	• Restraint use	✓	✓
	• Reported aggression incidents	✓	✓
Online survey			

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Source and assessment	Measurement instrument	Time of measurement	
		Start implementation	End implementation
• Evaluation of the STIP-Method	• Short evaluation of ongoing implementation of the STIP-Method, including the BPSD web application. To assess feasibility, satisfaction, job satisfaction	✓	✓
• Process evaluation advisory board meetings	• Evaluation of using advisory board groups. Focusing on frequency, composition, utility, and effects		✓
Semistructured interview			
• Process evaluation of the STIP-Method	• Board members and local project leaders		✓

[a]Every 6 weeks (12 in total).

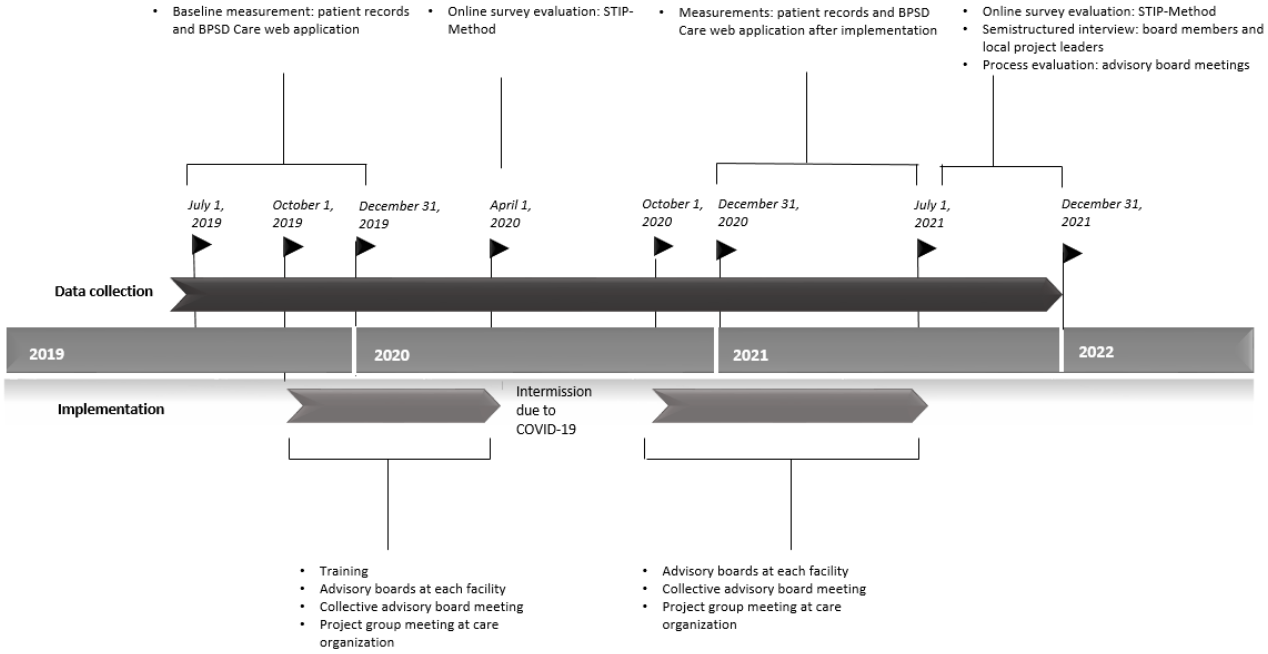
[b]Every 6 months (4 in total).

[c]Every 3 months (8 in total).

[d]BPSD: Behavioural and Psychological Symptoms of Dementia

[e]ATC: Anatomical Therapeutic Chemical.

Figure 2. Timeline for implementation and data collection. BPSD: Behavioural and Psychological Symptoms of Dementia.



Analysis

Data extracted from patient records were coded with unique identification numbers to guarantee privacy. All analyses will be undertaken at the level of nursing home and persons with dementia. All advisory board meetings were audio-recorded. Verbatim transcription will be done by a researcher (HMFV) with the support of research assistants. The transcripts will be coded using content analysis, facilitated by the qualitative analysis software ATLAS.Ti.9. Two researchers (HMFV and CZ) will code in vivo the first 3 advisory board meetings together to reach clarity about how to code the board meetings consistently. Hereafter, the researchers will discuss any conflicting codes and ambiguous statements to come to an agreement about the final coding scheme. Then, the identified facilitators and barriers will be categorized into main themes.

Ethics Approval

The study started after being reviewed by the Medical Ethics Committee of the Erasmus University Rotterdam, under file number MEC-2019-0343.

Dissemination Plan

At the completion of the study, we will present the findings at national and international scientific conferences; professional events for stakeholder group; and at our professional website. Findings will be presented in a summarized form with no identifying information. We will also publish the results in

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peer-reviewed journals, open access publications, and lay magazines.

Results

We enrolled 328 persons with dementia. Data collection started in July 2019 and ended in December 2021. The first version of this manuscript was submitted in October 2021. The first results of data analysis are expected to be published in December 2022 and final results in June 2023.

Discussion

Relevance

This protocol describes a mixed methods study within a participatory action research to implement the STIP-Method to manage neuropsychiatric symptoms in persons with dementia in nursing homes. The STIP-Method is developed from 3 already proven effective methods to manage neuropsychiatric symptoms. Previous research on the implementation of these 3 methods showed a low level of intervention fidelity. A better understanding of the implementation process is necessary to improve sustainability in clinical practice to improve the management of neuropsychiatric symptoms [12,43,44]. We expect the study will deliver an in-depth understanding of facilitators and barriers to the management of neuropsychiatric symptoms to positively influence these factors. Although not an effect study, it aims to measure impact in real-life care settings related to the intervention fidelity.

Strengths and Limitations

A strength of this study is that the STIP-Method is more comprehensive, as it uses the key elements from the underlying effective interventions. Furthermore, we aimed to gain insight into the best manner of implementation by using an advisory board of, among others, informal caregivers. A possible limitation is a potential tension in nursing homes between urgency as recognized in the participating organizations and the increased difficulty to implement an intervention with more elements than the already known stepped-care interventions. In addition, BPSD Care was used as an application adjacent to patient records. Within the Grip study, managers prior to implementation indicated a tool adjacent to patient records as a barrier [40]. However, within the Grip study, using 2 systems did not cause any problems. The lack of a connection between systems may be a barrier in our study.

Conclusions

We anticipate that our results can be used to improve the intervention fidelity of multicomponent interventions to prevent and treat neuropsychiatric symptoms in persons with dementia. These improvements may enhance quality of life for persons with dementia and their informal caregivers and may improve job satisfaction and the attractiveness of their profession.

Acknowledgments

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Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request. We will use the DataverseNL, a publicly accessible data repository platform.

Authors' Contributions

HMFV is the first author of the manuscript and participated in the design of the study. WPA, TJEMB, and CZ were responsible for the study and intervention designs. All authors have read and approved the final manuscript and contributed to the drafting and revision of the manuscript.

Conflicts of Interest

The researchers involved in integrative reactivation and rehabilitation (IRR), Grip on Challenging Behavior (Grip), and Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia (STA OP!) (TJEMB, MS, and WPA) and experts on the implementation and management of neuropsychiatric symptoms (DLG, JTS, and SUZ) collaboratively developed a joint multicomponent intervention, the STIP-Method, and provided input to the process of development. MN was involved in the development of the web application. All authors have declared that they have no competing interests.

Multimedia Appendix 1
Description of existing effective methods: 1. Integrative reactivation and rehabilitation (IRR), 2. Grip on challenging behavior (Grip) and 3. Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia (STA OP!); similarities and differences.
[DOCX File , 382 KB - resprot_v11i6e34550_app1.docx]

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Abbreviations

BPSD: Behavioural and Psychological Symptoms of Dementia
Grip: Grip on Challenging Behavior
IRR: integrative reactivation and rehabilitation
MMSE: Mini-Mental State Examination
NPI: Neuropsychiatric Inventory
PAIC: Pain Assessment in Impaired Cognition
STA OP!: Stepwise, Multidisciplinary Intervention for Pain and Challenging Behavior in Dementia

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Corrigenda and Addenda

Correction: Understanding and Addressing Variation in Health Care–Associated Infections After Durable Ventricular Assist Device Therapy: Protocol for a Mixed Methods Study

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In "Understanding and Addressing Variation in Health Care–Associated Infections After Durable Ventricular Assist Device Therapy: Protocol for a Mixed Methods Study" (JMIR Res Protoc 2020;9(1):e14701), the authors noted one error.

In the originally published paper, the *Acknowledgments* section inadvertently included the following incorrect statement:

> *Additional funding was provided by the National Institutes of Health (grant number T32-HL-007853).*

In the corrected version, this statement has been removed.

The correction will appear in the online version of the paper on the JMIR Publications website on June 23, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Protocol

Hearing Loss in Patients With Morquio Syndrome: Protocol for a Scoping Review

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Abstract

Background: Mild to moderate hearing loss is common in patients with mucopolysaccharidosis (MPS) IVA. The hearing loss can be conductive, sensorineural, or mixed. However, in these patients, the mixed form is frequent, attributed to the combination of conductive and neurosensory elements, with slowly progressive evolution. Conductive hearing loss may be secondary to recurrent upper respiratory tract infections, serous otitis media, and deformities of the ear ossicles due to the accumulation of glycosaminoglycans (GAGs). Meanwhile, the sensorineural form is mainly attributed to the accumulation of GAGs in the auditory system.

Objective: The aim of this scoping review is to understand the extent and type of evidence in relation to the physiopathology, classification, epidemiology, and clinical management of hearing loss and the effect of therapy for hearing loss in patients with MPS IVA.

Methods: This scoping review includes participants across all genders and of no particular age group who are diagnosed with MPS IVA and develop hearing loss as a comorbidity. No exclusion criteria (country, language, or document type) will be applicable. The information sources will include experimental and quasi-experimental, analytical observational, observational, and qualitative studies. Unpublished literature will not be covered. Grey literature will be covered. A total of 2 independent reviewers will participate in the process of screening the literature, paper selection, and data extraction, and this process will be performed blindly. When all manuscripts have been selected, disagreements that arise between the 2 reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. Results will be reported with descriptive statistics and information will be displayed in a diagrammatic or tabular manner, as explained in the JBI guidelines.

Results: The literature search was performed in November 2021 in MEDLINE, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), the Cochrane Library, ScienceDirect, Google Scholar, and OpenGrey; a total of 780 results were retrieved. Completion of the review is expected in mid-2022.

Conclusions: This scoping review will be the first to describe the extent of the information regarding the development of hearing loss in the MPS IVA population. The data gathered by this review may lead to an understanding of the grade of hearing loss in this population and allow for the assessment of possible interventions according to the disease pattern.

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KEYWORDS

Morquio syndrome; hearing loss; rare diseases; scoping review

Introduction

Background

Mucopolysaccharidosis (MPS) IVA, also known as Morquio syndrome, is a lysosomal storage disease caused by the loss of function of the enzyme N-acetylgalactosamine-6-sulfate sulfatase, which is required for the catabolism of glycosaminoglycans (GAGs), such as keratan sulfate and chondroitin 6-sulfate [1]. Biochemically, MPS IVA is characterized by an accumulation of GAGs within lysosomes and elevated GAG crystals in the urine, blood, and cerebrospinal fluid. GAG accumulation causes progressive damage in a wide variety of tissues, manifesting clinically as joint stiffness, bone malformation, growth retardation, restrictive lung disease, and liver, eye, heart, and dental abnormalities. Remarkably, patients with MPS IVA do not present primary neurological manifestations, although they can present behavioral problems, anxiety, and depression [2,3].

The life expectancy of patients with MPS IVA ranges from 8 to 43 years. Respiratory failure is the primary cause of death in patients with MPS IVA, followed by cardiac failure, posttraumatic organ failure, postoperative complications, and myocardial infarction [4]. Nevertheless, due to recent medical and surgical advances, the survival of these patients has improved. Hearing impairment is a common problem among patients with MPS IVA, and many of them exhibit permanent and severe hearing loss throughout life [5], so there is likely an increase in cases of moderate to severe hearing loss in the longest living patients [4]. In response, this scoping review will be conducted to obtain all published literature addressing the physiopathology, hearing loss classification, epidemiology, clinical management, and effect of therapy for hearing loss in patients with MPS IVA. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted, and no completed or undergoing systematic reviews or scoping reviews on the topic were identified.

Review Question

What is the current state of evidence on the physiopathology, classification, epidemiology, and management or treatment of hearing loss and the effect of therapy for hearing loss in patients with MPS IVA?

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [6].

Eligibility Criteria

Participants

Studies that include participants of both genders and of no particular age who are diagnosed with MPS IVA and who developed hearing loss as a comorbidity will be selected.

Inclusion Criteria

The following studies will be selected for this review:

- Studies including patient hearing loss details, such as physiopathology, classification of hearing loss (neural, sensory, or sensorineural), and epidemiology (data on hearing loss in patients with MPS IVA according to age and gender)
- Studies providing information about the effects of replacement therapy on hearing loss in patients with MPS IVA
- Studies providing information about the medical management of patients with hearing loss due to MPS IVA and complications

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time series studies. In addition, observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion. This review will also consider observational study designs, including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies will also be considered for inclusion.

Search Strategy

The search strategy will aim to identify published studies. Unpublished literature will not be included. The search strategy will focus on published studies without discriminating based on publication date or language. The key terms used in the article titles and abstracts as well as the articles' index terms were used to develop a full search strategy for the following databases: MEDLINE, LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde), Web of Science, the Cochrane Library, Trip Medical Database, Embase, ScienceDirect, and Google Scholar. Furthermore, a second search will be done to identify grey literature in OpenGrey and the Grey Literature Report.

To identify relevant articles, we established the following systematic search strategy using MeSH (Medical Subject Headings) keywords: "Hearing Disorders" OR "Hearing Loss" AND "Mucopolysaccharidosis IV" or "Hearing Disorders" OR "Hearing Loss" AND "Mucopolysaccharidosis IV".

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The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. Search terms will be created by the entire team of reviewers, though the search will be conducted by 1 person. The reference list of all included sources of evidence will be screened for additional studies. Studies published in any language will be included.

Study Selection

All identified citations will be collated and uploaded into Rayyan QCRI23 (Rayyan Systems Inc) and duplicates will be removed. Titles and abstracts will then be screened by 3 independent reviewers for the application of the selection criteria. Then, the full text of the selected studies will be assessed in detail to verify inclusion. Reasons for the exclusion of studies at this stage that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) flowchart [7].

Data Extraction

A data extraction instrument was created (Multimedia Appendix 1). A total of 2 researchers will extract the data from each record. Extraction fields include the following: the country where the study was conducted, year of publication, data characterization (physiopathology, diagnostic, epidemiology, management or treatment, and complications), study design, medical history, clinical diagnosis, diagnostic test and results, and clinical interventions. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer(s).

Data Analysis and Presentation

This will likely be a descriptive tabulation of all pertinent information regarding hearing loss in patients with MPS IVA, including physiopathology, risk factors, epidemiology, diagnosis, and prevention. Findings and recommendations, methods incorporated and their usefulness, and study limitations will also be captured. All knowledge gathered will be summarized and discussed.

Reference Searches

Snowballing or citation tracking criteria will be used to identify important articles relevant to the topic of interest; this will also be done by using the reference list of a paper or citations of a paper by other articles to identify additional manuscripts relevant to the topic of the study. After identifying potential new manuscripts and citations, a backward snowballing search will be done by reviewing the reference list and excluding papers that do not fulfill the basic criteria for inclusion. Subsequently, papers from the list that have already been examined will be removed. If a paper meets the inclusion criteria, potential new manuscripts will be identified by checking the reference list of the included paper [8]. Following that, forward snowballing will be done by identifying new papers from the reference list of included papers with a similar approach as backward snowballing.

Results

The search was performed on March 2, 2022, in MEDLINE, LILACS, the Cochrane Library, ScienceDirect, Google Scholar and OpenGrey; a total of 780 results were retrieved. Completion of the review is expected in mid-2022. All potential manuscripts will be imported into the reference management software Rayyan QCRI23. The results of this scoping review will identify and describe the epidemiology, physiopathology, classification, and clinical management of hearing loss in patients with Morquio syndrome. Additionally, it will also identify the known available effect of the current therapies (enzyme replacement therapy [ERT] and hematopoietic stem cell transplantation [HSCT]) on hearing loss in patients with MPS IVA.

Discussion

The clinical spectrum of hearing loss in MPS IVA is wide and not well described yet. There has been limited research on the audiological assessment of patients with MPS IVA. However, some studies have suggested that the prevalence of hearing loss in this population varies between 67% to 94% [9-11]. According to this research, hearing loss can present in different forms, conductive, sensorineural, or mixed, and its severity can vary from mild to profound hearing loss. Furthermore, MPS IVA presents with recurrent otitis media [5,11]. Similar to other disorders, conductive hearing loss occurs at an early age, while sensorineural or mixed hearing loss develops later on in life [11]. The conductive component of hearing loss is likely caused by the synergistic presentation of recurrent otitis media and accumulation of GAGs on the tympanic membrane and the ossicular chain [5]. The physiopathology of sensorineural hearing loss is unknown, but a few studies have identified the possibility of hair cell loss contributing to sensorineural hearing loss, and animal models have described the role of the accumulation of keratan sulphate in the inner ear [5,12].

The efficacy of ERT on the audiological disorder of MPS IVA is still unknown, though a case report described an improvement with ERT therapy [13]. However, further studies with larger samples are needed to determine the efficacy of ERT on hearing improvement [14]. On the other hand, the role of HSCT therapy in treating hearing loss has not yet been determined [15-17]. A recent study has demonstrated the effect of cochlear implants on the improvement of postlingual hearing loss [18].

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Data extraction instrument.
[XLSX File (Microsoft Excel File), 13 KB - resprot_v11i6e32986_app1.xlsx]

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Abbreviations

ERT: enzyme replacement therapy

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GAGs: glycosaminoglycans
HSCT: hematopoietic stem cell transplantation
LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde
MeSH: Medical Subject Headings
MPS IVA: mucopolysaccharidosis IVA
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews

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Protocol

Ageism and Artificial Intelligence: Protocol for a Scoping Review

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Abstract

Background: Artificial intelligence (AI) has emerged as a major driver of technological development in the 21st century, yet little attention has been paid to algorithmic biases toward older adults.

Objective: This paper documents the search strategy and process for a scoping review exploring how age-related bias is encoded or amplified in AI systems as well as the corresponding legal and ethical implications.

Methods: The scoping review follows a 6-stage methodology framework developed by Arksey and O'Malley. The search strategy has been established in 6 databases. We will investigate the legal implications of ageism in AI by searching grey literature databases, targeted websites, and popular search engines and using an iterative search strategy. Studies meet the inclusion criteria if they are in English, peer-reviewed, available electronically in full text, and meet one of the following two additional criteria: (1) include "bias" related to AI in any application (eg, facial recognition) and (2) discuss bias related to the concept of old age or ageism. At least two reviewers will independently conduct the title, abstract, and full-text screening. Search results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) reporting guideline. We will chart data on a structured form and conduct a thematic analysis to highlight the societal, legal, and ethical implications reported in the literature.

Results: The database searches resulted in 7595 records when the searches were piloted in November 2021. The scoping review will be completed by December 2022.

Conclusions: The findings will provide interdisciplinary insights into the extent of age-related bias in AI systems. The results will contribute foundational knowledge that can encourage multisectoral cooperation to ensure that AI is developed and deployed in a manner consistent with ethical values and human rights legislation as it relates to an older and aging population. We will

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publish the review findings in peer-reviewed journals and disseminate the key results with stakeholders via workshops and webinars.

Trial Registration: OSF Registries AMG5P; https://osf.io/amg5p

International Registered Report Identifier (IRRID): DERR1-10.2196/33211

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KEYWORDS

artificial intelligence; ageism; age-related biases; gerontology; algorithms; search strategy; health database; human rights; ethics

Introduction

Artificial intelligence (AI)—defined as "[the] designing and building of intelligent agents that receive percepts from the environment and take actions that affect that environment" [1]—has emerged as a major driver of technological development in the 21st century [2]. Although AI is often viewed as a neutral force, many widely deployed AI applications encompass the racial and gender biases that pervade society [3]. This is partly because AI models use input data that is mostly human-curated and thus are susceptible to encompass implicit and explicit bias as the basis for prediction—in other words, "bias in, bias out." The following are some examples of AI bias. A widely used algorithm for population health management in the United States underestimated the health risks of Black patients due to their limited access to health care as a consequence of systemic racism [4]. Word2vec, a publicly available embedding algorithm, amplified the gender biases inherited from its training data by forming associations between words related to gender and occupation—in particular, "men" to "computer programmer" and "women" to "homemaker" [5]. Research also suggests that AI-driven algorithms show women fewer advertisements for high-paying jobs since these jobs have a historical context of being occupied by men [5].

An aging global population [6] brings new social challenges, most notably with regards to ageism and social exclusion. Ageism is an age-related bias that is conceptualized to include (1) prejudicial attitudes toward older adults and the process of aging, (2) discriminatory practices against older adults, or (3) institutionalized policies and social practices that foster the attitudes and actions in relation to (1) and (2) [7]. The World Health Organization recently published a policy brief entitled "Ageism in Artificial Intelligence in Health" [8]. However, ageism in AI extends beyond the confines of health care and health-related data and has been described as *digital ageism* [9]. Ageist attitudes, beliefs, and practices may be overt or covert; for example, these conditions may be created through the bias of omission or exclusion [10]. Although most commonly directed toward older people [11-14], ageism can also be directed at younger individuals [15]. The concept and extent of digital ageism, however, are not well established in the literature on bias in AI. This review aims to address this knowledge gap by examining bias in AI systems against older adults.

There is an increasing presence of technology and AI in our daily lives, with substantial applications in health care [16], education [11], employment [17-19], finance [20,21], and law [22,23], generating a "digital world" from the 2.5 quintillion bytes of data created daily [24]. However, due to structural barriers, such as limited internet access, older adults can be socially and digitally excluded [25,26]. The exclusion of older adults means that their needs and desires are not considered or reflected in the technology pipeline, spanning from hardware design [27-29] to AI systems development, which can negatively impact their desire to adopt the technologies [30,31]. For instance, in studies analyzing smartphone design and use, older adults are commonly excluded [32], and when they are included, they are classified into a broad and vague age category, such as "50+" or "60+" [33,34]. This can contribute to misconceptions held by developers that lead them to view older people as a monolith rather than a heterogenous group [35], particularly regarding ageist stereotypes in the technology design process that characterize aging as a state of inevitable decline that will require costly care [35-37]. Consequently, technology developers assume that older people will need and want health technologies to compensate for declining abilities [36], resulting in the development of technologies that are suboptimized for older adults' abilities and needs. Cumulatively, a digital experience that is inaccessible and unrelatable is created [38].

Technologies that are created on the basis of inaccurate assumptions about older people can cause users (ie, older people) to internalize negative stereotypes, reducing their self-efficacy and willingness to engage with technologies in general [35]. A decreased use of technology by older adults compared to younger populations can disincentivize developers to consider older adults as end users for future designs [38], thereby contributing to a vicious cycle that excludes older adult and sustains ageism. The result of these multilayered barriers, including barriers to access and ageism throughout the technology development pipeline, is that older people collectively produce less data for AI training [39]. These imbalanced data sets with underrepresented key segments raise questions and concerns about how older people are perceived in the "digital world" and the implications of deploying ageist AI systems.

The goals of this study are interdisciplinary in nature and aim to explore how age-related bias is encoded and amplified in AI systems and understand any corresponding societal, legal, and ethical implications. This review will address the following research questions:

1. What is known about age-related bias in AI technology?
2. How do AI systems encode, produce, or reinforce age-related bias?
3. What literature exists on the extent of age-related bias in AI systems?

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4. What is the state of knowledge on older people's experiences of age-related bias in AI systems?
5. What are the social, legal, and ethical implications of age-related bias in AI systems?

This study will contribute to the global conversation about bias in AI systems and the associated concerns of fairness [40-44] by broadening the dialogue on race and gender biases to include the impacts of age-related bias on older people. The foundational knowledge gained through this study will be used to identify related challenges and opportunities in the subfield of AI and age-related bias, establish a multiphase research program aimed at defining ageism in AI, and develop a deeper understanding of ageism in the context of AI predictive modelling.

Methods

Methodology and Framework

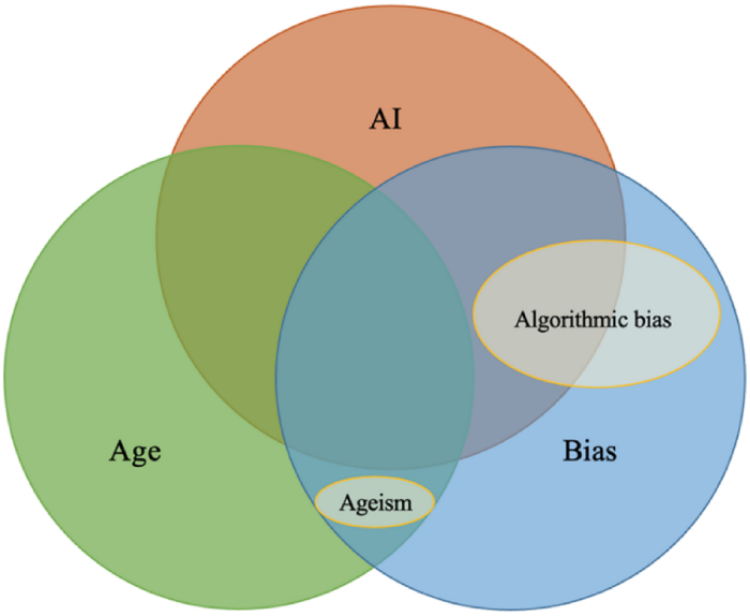
This scoping protocol was developed using guidance from the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) reporting guideline [45]. A scoping review methodology is optimal for our exploratory aims of synthesizing the evidence and assessing the scope of the literature on ageism in AI [45]. Bias assessment in AI is an emerging field, especially for age-related bias. The study will follow the methodological framework developed by Arksey and O'Malley [46] and further enhanced using the recommendations by Levac et al [47]. This framework has 6 stages that aim to achieve both in-depth and broad coverage of all the available literature [46]. This scoping review has been registered in the Open Science Framework (OSF) database [48].

Step 1: Identifying the Research Question(s)

As scoping review questions are recommended to be broad [47], the research team approached the literature using an interdisciplinary lens to include legal, ethical, technical, and social perspectives and queries. The authors include gerontologists, legal scholars, engineers, ethicists, a computer scientist, a philosopher, and a public health graduate student. Collaborators on the project are philosophy scholars and members of provincial- and national-level Canadian organizations interested in aging and technology. Through discussion, the team generated the research questions stated above.

Under an information specialist's guidance, the research team developed a search strategy consistent with scoping review methodology [47]. The team and collaborators articulated three distinct concepts: (1) AI [1]; (2) age-related bias (ageism) [7]; and (3) algorithmic bias, defined as bias in the algorithms (Figure 1). In contrast to previous work [38], the search strategy for this study included all types of AI and its application across all devices used by humans (eg, AI used on mobile devices, computers) and encompassed multiple disciplines (eg, health-related, business) to ensure a comprehensive search.

Figure 1. Main concepts included in the search strategy. AI: artificial intelligence.



Step 2: Identifying Relevant Studies

Peer-Reviewed Literature

This section will describe the completed search strategy for the scoping review. The search strategy was informed by test searches in Scopus, Medline, IEEE Xplore, ACM Digital Library and Google Scholar with the key search terms "artificial intelligence" and "ageism." The first 200 results in each database were screened by checking their title and abstract for relevant records. There were no relevant search results that explicitly discussed AI and ageism, so the concept "ageism" was expanded and changed to "age" to capture more records discussing aging as suggested by the information specialist. Next, individual key terms were searched to gather synonyms, and a synonym list was generated (see Multimedia Appendix 1). Due to the high number of "artificial intelligence" and "age" synonyms, these terms were categorized into broad topics under each term. For example, the 57 synonyms found for AI were categorized into synonyms that were specifically related to the following topics:

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AI techniques (eg, machine learning), general technology using or intersecting with AI (eg, big data, informatics, data science), and AI applications related to health technologies (eg, biomedical technology). The synonyms of age were categorized into terms related to bias (eg, age-related bias, ageist), older adults as a demographic or population (eg, aging person, seniors), and a field of study (eg, gerontology). The list of all the synonyms and their categories as well as their frequency of appearance in the searches can be found in Multimedia Appendix 1.

We conducted test searches by combining synonyms of our key concepts in Scopus, a multidisciplinary database that matched the nature of our study, to examine which synonym combinations could generate relevant records. After searching for all the synonyms proposed, we found 5 key papers that discussed age-related algorithmic bias, 53 relevant articles, and 29 additional synonyms occurring in the titles, abstracts, or keywords of these records (Multimedia Appendix 1). Based on the synonyms that provided the most relevant literature, the expanded search strategies were built based on the following synonyms: "machine learning," "artificial intelligence," "algorithms," "neural networks," "deep learning," "algorithmic bias," "biased," "discrimination," "ageism," "age," and "older people." The themes of these synonyms were related to AI techniques, algorithmic bias, ageism, and age as a demographic. We revised our search strategies (Multimedia Appendix 1) and inclusion and exclusion criteria (Textbox 1) via the analyses of the key synonyms (Multimedia Appendix 1) identified in our test searches following further consultation with the research team, collaborators, and information specialist.

Textbox 1. Inclusion and exclusion criteria for the scoping review.

Inclusion criteria

- Printed in English
- Peer-reviewed publications and conference papers
- Available electronically in full text
- Meet one of the two criteria below:
  - Report "artificial intelligence" (algorithms that predict or classify data), "bias," and terms related to "age" (aging, older, demographic)
  - Report facial recognition and age or demographics

Exclusion criteria

- Theses and dissertations
- Conference abstracts and proceedings
- Perspectives and editorials
- Books and book chapters
- Letters to editors
- Manuscripts using nonhuman samples
- Manuscripts that do not use human data
- Children as the target population
- Theoretical analysis
- Mathematical formulations
- Nonhuman studies

The final search strategy was developed in Scopus and then translated to the other 5 databases (Web of Science, CINAHL, EMBASE, IEEE Xplore, and ACM digital library). As IEEE Xplore had limitations on the number of terms and wildcards used for the search, we iteratively tested one theme or combinations of themes using different subsets of the proposed synonyms. A synonym was deleted if its addition to the search did not produce relevant results. We screened the first 200 records produced in each testing and eliminated the corresponding synonyms if none of the results were relevant.

The search parameters included peer-reviewed publications and conference papers published in English and available electronically in full text. Due to the study's interdisciplinary nature, we did not limit the study design for inclusion. The search strategy was also not restricted by publication date since the term "artificial intelligence" has existed for over 50 years [18]. The following sources were excluded to balance study breadth with feasibility and timeline limitations: theses, dissertations, conference abstracts, nonpeer-reviewed conference proceedings, perspectives, editorials, books, book chapters, and letters to editors. The results of the search strategy form a base for the next steps of our scoping review of ageism in AI.

Grey Literature

Given the anticipated paucity of academic research studies directly focused on ageism in AI, grey literature will increase the breadth and relevance of our findings. With the search

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strategy established, an iterative grey literature search strategy will be used to retrieve documents in the public domain that are relevant to any of our research questions to ensure that all relevant information about age-related bias in AI is captured. Grey literature will be retrieved by searching grey literature databases (OpenGrey and Grey Literature Report). Targeted searches of websites identified by the research team (eg, Algorithm Watch, Healthcare Information and Management Systems Society, The Centre for Data Ethics and Innovation) will also be conducted to retrieve documents such as white papers, policy papers, technical papers, and government reports. These documents will be downloaded in PDF form and added to a separate Microsoft Excel table to record the website source. After a thorough full-text review of each source, a rating scale of 0 to 4 (0=no reference to AI and ageism, 1=mentioned "age" in a list of types of biases, 2=one sentence related to the age-related bias, 3=two or three sentences related to age-related bias, 4=more than three sentences relevant to AI and ageism) representing the relevancy of the document was used to identify which sources were most relevant to the study. The included sources (anything with a rating above 0) had the relevant portions of text with the corresponding page numbers highlighted and documented, which will be themed by the research team according to each research question. To date, we have completed a preliminary manual Google search using the terms "artificial intelligence" and "ageism," which identified 213 results in November 2021. A reviewer (JS) from the research team opened each web page to screen the content on the page for relevance. We found additional pages from law-related blogs that referenced employment discrimination related to age-related algorithmic bias.

Given the anticipated legal and ethical implications of ageism in AI, a review of relevant legislation, regulations, and jurisprudence (court cases) will be used to augment our academic and grey literature searches. These data sources will address research question 5 (What are the social, legal, and ethical implications of age-related bias in AI systems?). This process will be led by the team's legal scholars and focused on understanding the legal and regulatory framework to protect and prevent age-related bias and unjust discrimination in AI. The iterative legal search strategy will begin with a review of relevant secondary sources including legal dictionaries and encyclopedias, followed by a review of legal treatises, law reviews and journals, statutes, and administrative regulations, and finally an analysis of the relevant case law. The legal databases WestlawNext Canada and CanLII will be canvassed in this legal review. Given the relative novelty of AI in the legal realm, a broad keyword search will be used to capture the relevant material. The keywords include "artificial intelligence;" "A.I."; "machine learning"; "ageism"; and "discrimination." The keyword search will be periodically refined to limit search results to various legal domains, including employment law, human rights law, and health law.

Step 3: Study Selection

The search results will be exported into Covidence, a commonly used web-based literature review tool. The eligibility of the publications was determined based on a screening guideline established by 2 reviewers (JS and CHC; Textbox 1) and pilot-tested on 20 titles and abstracts. An article meets the inclusion criteria if its abstract reports "artificial intelligence" (eg, predict or classify data), "bias," and terms related to "age as a population" (eg, aging, older, demographic). Any articles about facial recognition will be included if they mention age or demographics. We consider the risks of bias as being high in facial recognition, even without the explicit reporting of "bias," because research has demonstrated an algorithmic bias of facial analysis technology among older adults with dementia [49]. Once duplicates are removed, the titles and abstracts of all remaining articles will be screened by 2 independent reviewers using the screening guideline developed. The reviewers will meet at the start of the screening process to finalize and clarify the inclusion criteria and convene shortly after the screening commences to refine the criteria. The full text of each included citation will be reviewed by 2 independent reviewers to determine the article's relevance to the primary research questions of this study. If disagreements among reviewers cannot be resolved through discussion, the principal investigator (CHC) will make the final decisions for study selection. We will hold regular biweekly meetings to discuss the results.

Step 4: Charting the Data

We will chart the data based on the primary research questions using tools such as Google sheets or Covidence. Textbox 2 represents a sample format for data charting. To test the extraction forms for both academic and grey literature, the reviewers will independently chart the data of 5 to 10 included sources. Once interrater reliability is established, the extraction forms will be distributed to all the team members. For 20% of the included academic and grey literature sources, a second reviewer will verify the extraction. As data charting is an iterative process, we expect the team may modify elements of the forms so that they reflect the relevant findings of the articles included.

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Textbox 2. Sample data that will be charted.

Article information

- Article title
- Data charted by (initials)
- Author(s)
- Year
- Country
- Aim or purpose
- Study design

Artificial intelligence (AI)

- Branch of AI
- Algorithms as described
- Type and source of data

Population

- Does the article report age as demographic information of the study population?
- Does the article report on the experience of older people with age-related bias?

Bias identification and attribution

- Data set: yes or no
- AI algorithm: yes or no
- Methods proposed to mitigate bias, if any

Implications

- Legal implications
- Societal implications
- Ethical implications

Step 5: Collating, Summarizing, and Reporting the Results

Data charting will serve as the first step to summarizing the results. We will record each study based on fundamental information including article title, author(s), publication year, country, and study aims. Based on what is commonly reported in other AI reviews, we will potentially include technology-related information such as the aim of the technology, stage of the technology development, data used, and validation methods. To synthesize the findings, we will conduct a thematic analysis and use a narrative description to describe the work according to study design (quantitative or qualitative), any emerging patterns identified, ethical implications, as well as legal considerations. Collation of the findings will inform gaps for future studies in the field of AI and ageism.

Step 6: Consultation

To allow for stakeholder involvement and additional insights beyond the literature, the preliminary summary document will be circulated to stakeholders, including our national and international research collaborators with expertise or interests in aging, subject experts from the Temerty Centre for Artificial Intelligence Research and Education in Medicine at the University of Toronto, a senior's advocate, and older adults. These stakeholders have been involved from the early stages of the research conceptualization as knowledge users on our grant application.

Results

The database searches resulted in 7595 records when the searches were piloted in November 2021. Data will be abstracted in a tabular format to support drafting of a narrative summary. A scoping review publication will serve as the main presentation of the findings. The remaining stages of the search is proposed to reach completion by December 2022.

Discussion

The findings of this review will provide foundational information to advance our understanding of the concept and extent of digital ageism, which occurs when technologies deliberately or inadvertently exclude older adults, prioritize younger adults, or fail to recognize the diverse needs of the older adult demographic through various means [9]. The results

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from this study will provide interdisciplinary insights about digital ageism and the ways in which it is perpetuated in AI systems, such as from a lack of representative data sets (ie, data disparity). Overlooking older people prevents them from enjoying the full benefits of AI-based technologies and innovations, which can reinforce societal biases and inequity in our increasingly digital society.

A strength of our review is that our study is interdisciplinary and will shed light on AI and age-related bias regarding older adults from societal, legal, ethical, and technical perspectives. We have a rigorous methodology based on a scoping review framework and a comprehensive search strategy that includes interdisciplinary and discipline-specific databases. A team of researchers from different fields will interpret and generate findings that will foster further discussions and provide a direction for future work related to AI and older adults. One of the potential limitations of this study is the exclusion of publications in non-English languages as well as studies that do not discuss bias or age-related bias explicitly, potentially excluding research that unknowingly uses skewed data due to age-related bias embedded in specific AI algorithms. The inclusion of literature that explicitly discusses or recognizes the potential for age-related bias allows us to answer our current research questions. Our future work will explore the presence of implicit age-related bias in AI, as well as how ageism is reflected in a subset of AI algorithms.

To our best knowledge, this is the first scoping review to explore how age-related bias is encoded or amplified in AI systems and consider the societal, legal, and ethical implications. This scoping review protocol documents the search strategy and outlines the in-depth process for our rigorous synthesis of the literature on AI and ageism. Once the review is complete, we will connect with organizations at provincial, national, and international levels to discuss the findings and build the corresponding interview guides for in-depth semistructured interviews. Our review has the potential to establish the intersection of AI and ageism, advance knowledge about digital ageism, and inform future regulation and policy in this currently uncharted territory.

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Authors' Contributions

All authors have made substantial intellectual contribution to conceptualize the protocol development. CHC, KL, JS, and AL developed the manuscript. All authors have edited, reviewed, and approved the manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies and synonyms.
[DOCX File , 2097 KB - resprot_v11i6e33211_app1.docx]

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Abbreviations

AI: artificial intelligence
OSF: Open Science Framework
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Use of and Experiences With Online Access to Electronic Health Records for Parents, Children, and Adolescents: Protocol for a Scoping Review

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Abstract

Background: As patient online access to electronic health records becomes the standard, implementation of access for adolescents and parents varies across providers, regions, and countries. There is currently no international compilation of evidence to guide policy decisions in matters such as age limit for access and the extent of parent proxy access.

Objective: This paper presents the protocol for a scoping review of different stakeholders' (including but not limited to end users) perspectives on use, opinions, and experiences pertaining to online access to electronic health records by parents, children, and adolescents.

Methods: This scoping review will be conducted according to the Arksey and O'Malley framework. Several databases will be used to conduct a literature search (PubMed, CINAHL, and PsycInfo), in addition to literature found outside of these databases. All authors will participate in screening identified papers, following the research question: How do different stakeholders experience parents', children's, and adolescents' online access to the electronic health records of children and adolescents? Data abstraction will include but will not be limited to publication type, publication year, country, sample characteristics, setting, study aim, research question, and conclusions. The data to be analyzed are from publicly available secondary sources, so this study does not require an ethics review.

Results: The results from this scoping review will be presented in a narrative form, and additional data on study characteristics will be presented in diagrams or tabular format. This scoping review protocol was first initiated by Uppsala University in June 2021 as part of the NordForsk-funded research project NORDeHEALTH. The results are expected to be presented in a scoping review in June 2022. The results will be disseminated through stakeholder meetings, scientific conference presentations, oral presentations to the public, and publication in a peer-reviewed journal.

Conclusions: This is, to our knowledge, the first study to map the literature on the use and experiences of parents' and adolescents' online access to the electronic health records of children and adolescents. The findings will describe what benefits and risks have been experienced by different stakeholders so far in different countries. A mapping of studies could inform the design and implementation of future regulations around access to patient-accessible electronic health records.

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KEYWORDS

electronic health record; patient-accessible electronic health record; adolescents; parents; children; patient experience; patient portal; electronic portal; review; scoping review; youth; patient perspective; user experience; patient access

Introduction

Background

Digitalized health records, also called electronic health records (EHRs), contain clinical information (eg, doctor visit notes, lists of medications, and diagnostic information) and are used by health care professionals. Technological advancements have enabled patients to read their EHRs via online patient portals, often called patient-accessible EHRs (PAEHRs), quickly and easily, which promotes patient empowerment. It appears that PAEHRs are becoming the standard [1-5], as an increasing number of patients worldwide gain access to their records [6]. Today, health institutions in over 15 countries are providing patients with online access to their medical records via secure online portals [4]. Furthermore, a recent US policy of "open notes" mandates health care providers by law to share the records with patients [7]. In response to this rapid development, legal frameworks are continuously being adapted to improve use and ensure privacy of such PAEHR systems [4,8].

As PAEHRs continue to be implemented worldwide, vast uncertainty remains in the area of access by parents, children, and adolescents [9]. This is evident from the variation in the age of a child at which parents gain and lose access as well as the age at which young patients can access their records on their own [4]. On a national level, some countries (eg, Sweden and Finland) hold nationally regulated systems while others use a case-by-case approach (eg, the United States and New Zealand) [4]. In some countries, parents and guardians (herein, referred to as parents) are offered access while in other countries, parents are blocked from accessing records by law when their children reach a certain age threshold. In Sweden, for example, a parent has default access to their child's PAEHR until the child turns 13 years old, and the age limit for accessing one's own data is 16 years. Thus, no one has access to the child's EHR when the child is between 13 and 15 years of age. At this point, adolescents in Sweden can decide to provide their parent(s) with continued access to their records through an administrative process requiring approval by a health care professional. In Australia, on the other hand, adolescents can make similar decisions with a click on their computer. In France, adolescents receive access at 18 years of age when, in turn, the parent loses access. Decisions about earlier access in France may also depend on the perceived maturity of the minor. In many countries and regions, a lack of user continuity of access is apparent [4]. Currently, there is no international consensus on PAEHR regulations for parents, children, and adolescents.

For the most part, PAEHRs have been investigated for the general adult population. Effects of PAEHRs are not conclusive, yet indicate benefits including improved medication adherence and self-care, as well as improved relationships between patients and their physicians [3,10,11]. However, a growing body of literature is exploring access to PAEHRs for parents, children, and adolescents in particular. Patient online access to EHRs during the transition from child to adult is complex; parental access, while often appreciated by parents [12], may lead to ethical challenges. For example, some health information may be considered sensitive by adolescents, such as health care data pertaining to the disclosure of alcohol or drug abuse, sexual activity, or stigmatized illnesses such as anxiety or depression. Adolescents have also been observed to withhold information from health care professionals if they are uncertain about who may access it [13,14]. Furthermore, it has been suggested that adolescents' acceptability of parental PAEHR access will vary depending on the relationship with their parent(s) [15]. With regard to adolescents' own access, a strong desire for control has been expressed [16] while health care professionals have expressed concerns [17]. Therefore, while it appears that PAEHR access offers information transparency that might contribute to patient empowerment and enhanced health care [3,18], evidence suggests the adolescent population requires targeted analysis.

Study Objectives

The objective of the proposed scoping review is to identify, categorize, and summarize knowledge about different stakeholders' (eg, children and adolescents, parents, health care professionals, policy-makers, and designers of patient portals or PAEHRs) use and experiences of PAEHR access for parents, children, and adolescents. Countries are currently at different stages of development and implementation of PAEHRs; therefore, compiling the literature is timely and has, to our knowledge, not yet been undertaken. This scoping review is anticipated to aid policy-makers in designing future regulations around PAEHR access for parents and adolescents, and to potentially improve the design and implementation of PAEHRs to meet the needs of end users.

Methods

Approach

A scoping review will be conducted using the Arksey and O'Malley [19] framework. The framework includes 6 stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results, and (6) consulting with relevant stakeholders. Methodological comments on the framework will be consulted during the process to enhance the method [20-22].

Stage 1: Identifying the Research Question

Through discussion among research team members, the main research question is: How do different stakeholders experience parents', children's, and adolescents' online access to the electronic health records of children and adolescents? We do not limit the question only to children's and adolescents' or parents' experiences but also include other relevant stakeholders including health care professionals and policy-makers. For this review, PAEHR access is defined as access provided via an

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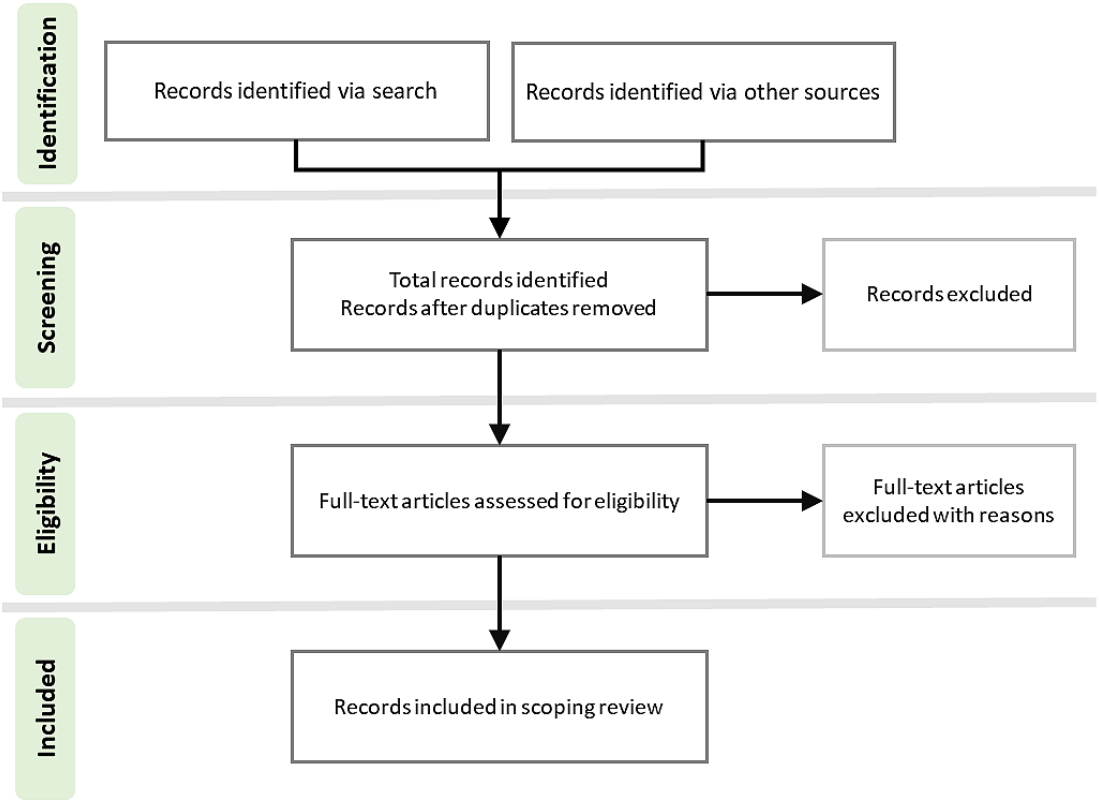
online patient portal that can encompass the entire electronic record or parts of it (eg, access to test results, clinical notes, or medications). The practice of "open notes" is included in the concept of EHR access [1,23], referring specifically to health care professionals sharing the visit note summaries they write with patients.

Stage 2: Identifying Relevant Studies

The literature search will be carried out by an experienced research librarian at Uppsala University. The search strategy, presented in Figure 1, is designed to include formally published peer-reviewed articles and selected gray literature (eg, dissertations, conference abstracts, editorials, and letters). Published works will be identified using the following electronic literature databases: PubMed, CINAHL, and PsycInfo. The time frame for the search will be 2005 onwards. Search terms will be identified with input from the research team and the literature. The search term is based on 3 key concepts: (1) EHR, (2) sharing EHRs with service users, and (3) pediatric or adolescent access, which will be combined with the Boolean operator "AND." The following search string will be used and adapted for the different databases: ("open notes" OR "opennotes" OR (("health record" OR "patient record" OR "pediatric record" OR "clinical record" OR "health notes" OR "clinical notes" OR "pediatric notes") AND (access OR show OR open OR share OR read OR participant*)) AND (pediatric OR adolescent* OR parent*)). Subsequently, references in the retrieved articles will be scanned backward to identify prior work that should be considered for the research topic. The key concept "PAEHR" is considered redundant, as it is covered in the "AND access" search term. Furthermore, the authors will be able to include records found but not identified in the search.

Figure 1. The search strategy for the scoping review.



Stage 3: Selection of Eligible Studies

The scientific literature will be systematically compiled and the selection will be inclusive, striving to encompass publications and reports that employ a variety of methodologies. Inclusion and exclusion criteria are informed by the review process and will be applied at the study selection stage.

Inclusion Criteria

Studies will be included if they meet the following criteria:

- Patient user population: parents, children, and adolescents
- Population studied: parents, children, adolescents, and health care professionals
- Outcomes: use, implementation, and experiences of access or proxy access to PAEHRs
- Study design: all study types

Exclusion Criteria

Studies will be excluded if they:

- Are not written in English
- Were published outside the study period
- Do not focus on PAEHRs

Search Strategy

The research team will identify eligibility criteria and search terms. A software program, Rayyan [24], will be used during the screening process after which included articles will be

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extracted into an Excel spreadsheet (Microsoft Corp) to facilitate analysis. The first author will set up the Excel spreadsheet and have the main responsibility of verifying the accuracy of its data. Study titles and abstracts will be independently screened by 5 investigators. Next, full-text articles will be divided among the 5 investigators so that each article is screened by at least 2 people. Where disagreements arise, these will be resolved by a third reader, and, if necessary, by group discussion.

Stage 4: Data Collection

Study characteristics will be identified by the research team and extracted into the Excel spreadsheet created in stage 3. Characteristics will include but will not be limited to publication type, publication year, country, sample characteristics, setting, study aim, research question, and conclusions. All researchers will be able to contribute to the spreadsheet. Ideas emerging during the process will be discussed among the authors in regular meetings set up by the main author.

Stage 5: Data Summary and Synthesis of Results

Results reported in the included studies will be compiled and read multiple times. Results will then be analyzed independently by 2 researchers (JH and MH) using thematic analysis [25]. In this process, the analytical material will be further summarized, and key themes will be identified to organize the study results. The results of this synthesis process will be discussed and approved by the entire research team. Tentative themes include but are not limited to positive and negative experiences, concerns, and benefits, as informed by a previous scoping study in a similar area [26].

Stage 6: Consultation

Because consultation can provide additional information and insights [21], the results of the literature review will be presented to and discussed with important stakeholder representatives from pediatric care, including a pediatric oncologist, a young patient council at a public hospital in Sweden, and the Ombudsman for Children in Sweden. These stakeholder representatives will be provided with material via email. The youth panel will discuss these results in a meeting, and all 3 stakeholder representatives will be able to choose whether to provide their thoughts in text via email or verbally in a Zoom (Zoom Video Communications, Inc) meeting.

Ethical Considerations

As the scoping review methodology consists of reviewing publicly available materials only, this study is not subject to ethical approval.

Results

The main results of our analysis will be presented in a narrative form focusing on research results to date regarding different stakeholders' experiences of providing children and adolescents and their parents with online access to their EHRs. Additional data on year, country, study design, study population, and setting will be presented in diagrams or tabular format. This scoping review protocol was first initiated by Uppsala University in June 2021 as part of the NordForsk-funded research project NORDeHEALTH. We expect the results to be presented in a scoping review in June 2022.

Discussion

The results from this scoping review will aim to inform a variety of stakeholders, including policy- and decision-makers, vendors, designers of patient portals and PAEHRs, and perhaps most importantly, end-user representatives. We aim to describe the benefits and risks experienced by different stakeholders so far in different countries. This knowledge may improve both the design and implementation of future PAEHRs to become more useful to the population, and also guide policy-makers and other decision-makers to provide the right preconditions for future implementations. In both Sweden and Estonia, the current patient portals are being redesigned, and there may be opportunities to influence both portal design and policy development. Therefore, results will be communicated outside the traditional scientific publications, through, for example, seminars and reports focusing specifically on the context in Sweden and Estonia. Results that are of interest to parents, adolescents, and health care professionals (eg, reports on the benefits or risks of record access) will be shared in more easily accessible formats like social media communications, popular science publications, and presentations for practitioners. We hope that this may have a direct impact on how record access is used by health care professionals, parents, and adolescents to increase potential benefits and minimize any risks.

To date, several literature reviews have been performed regarding PAEHRs or open notes in general [10,27,28], but to our knowledge, this will be the first review focusing specifically on the unique challenges in this particular subgroup. We also aim to identify current knowledge gaps in parents' and children's access to EHRs to guide future research in this area.

Authors' Contributions

JH wrote the manuscript and designed Figure 1. MH contributed to drafting the protocol and was responsible for the conception of the study. All authors read, provided feedback, and approved the paper for submission.

Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record
PAEHR: patient-accessible electronic health record

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Protocol

Examining the Relationships Between Sleep Physiology and the Gut Microbiome in Preclinical and Translational Research: Protocol for a Scoping Review

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Abstract

Background: Sleep is an instrumental behavioral state with evidence supporting its active role in brain function, metabolism, immune function, and cardiovascular systems. Research supports that there are pathways underlying the bidirectional communication between the brain and gastrointestinal system, also known as the "gut-brain axis." Primary research examining sleep and gut microbiome relationships continues to increase. Although current data include both preclinical and clinical research, gut microbiome results are reported through a wide range of metrics (alpha diversity, beta diversity, and bacterial compositional changes), which makes cross-study comparison challenging. Therefore, a synthesis of the research examining sleep and gut microbiome relationships is necessary to understand the state of the science and address gaps in the literature for future research.

Objective: In this paper, we outline a scoping review protocol to evaluate and synthesize preclinical and clinical primary research focused on the associations between sleep and the gut microbiome.

Methods: The search strategy was facilitated through a medical research librarian and involved electronic databases including PubMed/MEDLINE, Embase, Scopus, Web of Science, CENTRAL trials database, BIOSIS Citation Index, and the Zoological Record. Gray literature sources including medRxiv and bioRxiv preprint servers were also searched. Studies were screened according to the aims and exclusion and inclusion criteria of the protocol. After screening, data will be extracted and synthesized from the included studies according to predefined sleep and microbiome methodology metrics.

Results: The search strategy yielded 4622 references that were imported for study screening, and source screening was completed in May 2022 by 2 independent investigators, resulting in a total of 93 sources for data extraction and synthesis. The data synthesis table is expected to be completed by August 2022, and the results will be disseminated through paper submission by December 2022 and presented at conferences related to neuroscience, sleep physiology, bioinformatics, and the microbiome.

Conclusions: A scoping review of preclinical and clinical research is needed to synthesize the growing data focused on the relationships between sleep and the gut microbiome. We expect the results of this synthesis will identify gaps in the literature and highlight pathways linking the gut-brain axis and sleep physiology to stimulate future research questions.

Trial Registration: Open Science Framework 69TBR; https://osf.io/69tbr

International Registered Report Identifier (IRRID): PRR1-10.2196/38605

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KEYWORDS

microbiome; microbiota; bioinformatics; scoping review; genomics; sleep quality; sleep time; disrupted sleep; sleep; review; microbe; microbiology; search strategy; information science; library science; gut-brain; gastrointestinal; medical librarian; health science librarian

Introduction

Definition and Importance of Sleep

Sleep is defined as a reversible behavioral state associated with unresponsiveness to the external environment and involves a complex orchestration of physiological processes for its initiation and maintenance [1]. The importance of sleep is elucidated through evidence supporting its active role in several different physiological functions necessary for survival, namely immune health [2], physical growth [3], metabolism [4], tissue repair [5], and the maintenance of cognitive performance [6,7]. Sleep also contributes to the maintenance of major biological processes; in particular, it can aid in the peripheral and neurologic clearance of metabolic end products, consolidation of long-term memories, learning through long-term potentiation, and restoration of biological systems [8-10].The onset of sleep is partly controlled by circadian factors as well as homeostatic factors (ie, sleep pressure), and the interplay between circadian and sleep pressure is often referred to as the two-process system of sleep regulation [11]. In addition, intrinsic and extrinsic variables influence sleep, including the environment, work schedules, food and drink consumption, and health behaviors.

Sleep Physiology and Pathophysiology

Reduction in sleep duration or quality (ie, sleep fragmentation) is associated with sleep disorders such as insomnia and obstructive sleep apnea [12,13] and may result from occupational factors that alter sleep patterns or habits [14]. Reduced sleep duration or quality can also be a consequence of other chronic diseases such as congestive heart failure or chronic obstructive pulmonary disease [15,16]. The reduction in substantial sleep duration or sleep quality can further contribute to increased risk of human diseases and disorders, including cardiovascular disease [17], obesity [18], and diabetes [19]. More recently, the role of the glymphatic system in waste byproduct clearance and metabolite distribution within brain tissue has been uncovered [20]. As the glymphatic system is most active during slow wave sleep [8,21], the neurologic clearance of toxins and potentially harmful byproducts is also dependent on healthy sleep patterns [22]. The association of the proper function of the glymphatic system with the prevention of cerebral amyloid angiopathy and Alzheimer disease highlights the importance of the role that adequate sleep also plays in neurologic disease prevention [23]. Molecular clocks have evolved in most living organisms to synchronize vital physiologic activities with the external environment and rotation of the Earth's axis around the sun. The superchiasmatic nucleus is responsible for the central maintenance of the rhythm of approximately 24-hour cycles (or the circadian rhythm), is located in the hypothalamus [24,25], and responds primarily to light and darkness cues [26]. Conversely, peripheral oscillators located in many organ systems respond to other cues such as food intake, exercise, and temperature [27,28].

In mammals including humans and rodents, the oscillatory central and peripheral rhythms synchronize important functions ranging from intracellular signaling to food metabolism and immune system activity [29]. These carefully orchestrated processes are disrupted when there is a misalignment between the activities of the central and peripheral oscillators and the external environment, which may happen when traveling across time zones, alternating sleep patterns related to occupational factors such as shift work, or when sleep is disrupted due to sleep pathology (ie, insomnia or obstructive sleep apnea) [30,31]. Although altered sleep quality and duration have been linked to chronic disease risk and mortality in numerous epidemiological studies and systematic reviews [32-34], current treatment options for inadequate sleep or sleep disorders are limited. Therefore, we are also including preclinical studies in this scoping review to understand the mechanisms associated with disrupted sleep that can be expanded on and confirmed in future translational clinical research. Continued research aimed at uncovering these mechanisms of healthy and pathologic sleep has the potential to elucidate specific biomarkers and signaling mechanisms that act as mediators between sleep impairment and broader physiological changes. An initiative toward understanding and mitigating the effects of chronic sleep loss is imperative to reducing the prevalence of comorbidities and the need for health care services and its accompanying costs that otherwise may not be needed in a time of limited health care delivery resources and access.

Gut Microbiome

The gut microbiota, or the community of bacteria in the gastrointestinal system, has been shown to display diurnal fluctuations in composition and function, which are both coordinated with host feeding time, the anticipation of nutrient digestion, and energy metabolism [35]. The human gut microbiome is characterized by the bacteria that occupy the digestive tracts of humans in combination with their collective genetic information [36]. Gut microbiome bacteria perform vital physiological functions related to nutrient intake, such as the production of metabolites and synthesizing compounds that have the potential to influence human health and pathophysiology (ie, short-chain fatty acids and trimethylamine N-oxide) [37,38]. The bacteria of the gut microbiome communicate with the brain via metabolites, immune cells, and the vagus nerve [39]. This communication, or gut-brain axis signaling, is associated with the modulation of systemic and gastrointestinal motor, sensory, and secretory functions [40]. Different physiologic and pathophysiologic states have been found to shape the gut microbiome's bacterial content, diversity, and activity. For example, changes in the bacterial composition of the gut microbiome have been associated with diet [41], stress [39], and the external environment [42]. Due to the fact that gut microbes are associated with health maintenance through their metabolic activity and gut-brain communication, a substantial

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increase or decrease in specific taxa may have functional and physiologic implications for the host [43].

Pathologic gut microbiome bacterial community alterations have been linked to similar disorders associated with inadequate sleep in preclinical and translational research models, including cardiovascular disease [44], obesity [45], diabetes mellitus [46], and hypertension [47]. Furthermore, established signaling mechanisms between the gut microbiome and brain through the gut-brain axis provide the mechanistic rationale that sleep and microbiome alterations may be linked [39]. Reduced sleep duration–associated gut microbiome changes have also been associated with putative inflammatory metabolite implications such as reduced short-chain fatty acid and increased secondary bile acid levels [47,48]. Recent studies modeling sleep fragmentation and deprivation in mice have shown significant changes in the diversity of and specific bacterial taxa [47,49,50], whereas other studies found no major effects on bacterial composition [51]. Studies examining the relationship between sleep and the gut microbiome have used various models of pathologic sleep, including circadian disruption [35], sleep fragmentation [47,52,53], and reduction in sleep quantity [54] and quality [49] (Table 1).

Despite the growing research on this topic, studies focused on sleep and microbiome associations include varying sleep intervention models and intervention durations. Furthermore, a wide range of global, taxonomic, and functional microbiome analysis techniques and a lack of reporting standardization across studies create challenges in comparing the global and specific gut microbiome community responses to healthy and disordered sleep. Although the associations between sleep and gut microbiome community changes have been established, it is unknown if altered sleep influences the microbiome, the microbiome influences sleep, or sleep and the microbiome mutually modulate each other and are altered by a disruption in either system. It is also unclear if the risk for health conditions with shared associations to sleep and microbiome changes are primarily driven by pathologic changes in one or both systems, and several studies on this topic are exploratory and observational. A concern that preclinical research results may not always be replicable in human studies necessitates our synthesis of both preclinical and translational studies to evaluate congruence and disagreement across sleep and microbiome associations. Therefore, a scoping review with rigorous data abstraction, charting, and outcome measure synthesis is essential to understand gut microbiome responses across various sleep conditions in preclinical and translational clinical research.

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Table 1. Operational definitions.

Term	Definition
Preclinical sleep disruption grouping	
Mechanical sleep disruption	A form of sleep disruption that uses a machine to wake the subjects. Example: • Mechanical sweeping bars across the bottom of rodent cages programmed to disrupt sleep for a specified duration [47,53]
Paradoxical (REM[a]) sleep disruption	A form of sleep disruption that takes advantage of muscle atonia during REM sleep to wake the subjects. Example: • Platform water bath [49]
Circadian light alteration intervention	A form of sleep disruption that changes the light and dark cycle in the recording room (typical conditions are lights on for 12 hours/day and lights off for 12 hours/day). Examples: • Constant light conditions [55] • Constant dark conditions [56] • Light-dark cycle inversion/switch in the recording room throughout the study protocol [57,58]
Biological circadian disruption	A form of sleep disruption that changes the host circadian clock through the knockout of a related gene. Examples: • BMAL[b] knockout [59] • Per1/2[c] knockout [60] • Gcg-Arntl[d] knockout [61] • NPAS2[e] (also called MOP4[f]) knockout [62]
Translational clinical sleep disruption grouping	
Sleep disruption	An experimental procedure used with individuals (and experimental animals) to induce partial sleep loss during their usual sleep period. Examples: • Sleep deprivation [63] • Sleep restriction [51]
Sleep pathology (with subjective and objective sleep measures)	Disorder based on poor sleep quality and sleep complaints. Examples: • Insomnia [64,65] • Narcolepsy [66] • Obstructive sleep apnea [67] See examples of subjective and objective sleep measures below.
Subjective and objective sleep measures	
Subjective sleep measures	Pittsburg sleep quality index, subjective sleep time (hours), or time in bed or awake
Objective sleep measures	Actigraphy: time in bed, sleep duration, and wake after sleep onset
Microbiome sequencing methodology	
16S rRNA[g] gene amplicon sequencing	A sequencing method that uses a variable region of the 16S rRNA gene to identify the bacteria or fungi in a given sample.
Shotgun metagenomics sequencing	A sequencing method that sequences all given genomic DNA from a sample. Usually has a higher taxonomic resolution than 16S rRNA sequencing and can be used for functional profiling.
Microbiome and microbiome-associated data items (synthesis table columns)	
Microbiome sample	Sample material and site (ie, proximal colon, distal ileum, fecal pellet, whole stool sample, and rectal swab)
DNA extraction and sequencing methodology	DNA extraction kit and protocol, the sequencing platform (ie, Illumina or Ion Torrent) and methodology used to generate microbiome sequencing reads (ie, 16S rRNA or shotgun metagenomics sequencing), and the hypervariable region of the 16S rRNA gene (if applicable)
Microbiome analysis considerations	Bioinformatic pipeline used to analyze microbiome data, reference database used for taxonomy identification, and statistical methods used for microbiome analysis.

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Term	Definition
Alpha diversity [68]	An estimate of a bacterial sample's richness, evenness, or both. Estimators include: • Shannon index • Chao1 • Simpson index • Phylogenetic diversity
Beta diversity	An estimate for how much a bacterial sample differs from another. Estimators include: • UniFrac metrics • Bray-Curtis dissimilarity • Visualization through PCoA[h] plots in a 2D or 3D manner
Global phylum changes	Broad changes at the phylum level happening within a bacterial community. Generally described through the Firmicutes/Bacteroidetes ratio.
Differential abundance [69]	A measure of differences in the relative abundance of an individual bacteria for the purposes of comparing across conditions (ie, intervention vs control group or within group across time). Analysis methods include: • ANCOM[i] • ALDEx2[j] • DESeq2[k] • EdgeR[l] • LEfSe[m]
Functional gene prediction	The use of bacterial genetic data (16S rRNA amplicon sequencing or shotgun metagenomics sequencing output) to gain insight on the functional potential of a bacterial community. One method is using PICRUSt2[n] software to compare against the KEGG[o] database.
Metabolomics	The study of the type and concentration of metabolites present within a given sample, which can give insight into the biochemical processes happening. Differential abundance analyses can be used to compare metabolite differences across groups, similar to microbial differential abundance.
Cytokine and immune markers	Types of cells that can be associated with sleep physiology changes. For example, individuals with poorer sleep may have increased levels of systemic inflammation markers, such as CRP[p], IL-6[q], and fibrinogen [70,71].

[a]REM: rapid eye movement.

[b]BMAL: brain and muscle aryl hydrocarbon receptor nuclear translocator-like.

[c]Per: period.

[d]Gcg-Arntl: Gcg-Aryl hydrocarbon receptor nuclear translocator-like protein.

[e]NPAS2: neuronal PAS domain protein 2

[f]MOP4: member of PAS protein 4.

[g]16S rRNA: 16S ribosomal ribonucleic acid.

[h]PCoA: principal coordinates analysis.

[i]ANCOM: Analysis of Compositions of Microbiomes.

[j]ALDEx2: Analysis of Variance-Like Differential Expression version 2.

[k]DESeq2: Differential Expression Sequence Count Data 2

[l]EdgeR: Empirical Analysis of Digital Gene Expression in R.

[m]LefSe: Linear Discriminant Analysis Effect Size.

[n]PICRUSt2: Phylogenetic Investigation of Communities by Reconstruction of Unobserved States.

[o]KEGG: Kyoto Encyclopedia of Genes and Genomes.

[p]CRP: c-reactive protein.

[q]IL-6: interleukin-6.

Objectives

Our objective is to explore the influence of sleep and sleep pathology on the gut microbiome in preclinical and translational clinical studies to determine the extent sleep and gut microbiome–focused research has been undertaken, what sleep disorders have been studied, the methodologies used, and whether these studies are sufficient in characterizing the global and specific bacterial gut microbiome changes (and their byproducts) associated with healthy sleep and alterations in sleep physiology. Subresearch objectives with relevant examples

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are presented in Textbox 1, and the operational definitions used to formulate these research questions are listed in Table 1.

Textbox 1. Research objectives.

Overarching objective

- Explore the influence of sleep and sleep pathology on the bacterial gut microbiome in preclinical and translational research studies to determine the extent sleep and gut microbiome–focused research has been undertaken, what sleep disorders have been studied, the methodologies used, and whether they are sufficient in characterizing the global and specific bacterial gut microbiome changes (and their byproducts) associated with healthy sleep and alterations in sleep physiology.

Subresearch objectives

- Evaluate the extent sleep and gut microbiome–focused research has been undertaken
  - Proposed action: Identify and compile all references and source material focused on the associations between sleep and the gut microbiome.
- Present which sleep disorders have been studied in the context of the microbiome
  - Proposed action: Group sleep disorder, sleep disruption interventions, and the metrics of sleep into the operational definitions (see Table 1). For each group, evaluate which instruments and metrics have been reported.
- Analyze the research methodologies used and whether they are sufficient in characterizing sleep and gut microbiome community changes
  - Proposed action: Evaluate which instruments and metrics are used to quantify sleep quality, quantity, and characteristics. Similarly, organize and compare the analysis strategies and measures used in the characterization of the bacterial and functional (metabolic genes and metabolites) gut microbiome community structure.
- Present the global and specific bacterial gut microbiome changes (and their byproducts) associated with healthy sleep and alterations in sleep physiology
  - Proposed action: Synthesize the preclinical and translational research evaluating the associations between sleep and the gut microbiome, and systematically present the results to facilitate comparison and interpretation across studies.

Methods

Protocol

A scoping review of the currently published literature was chosen due to the variability of the microbiome and sleep measures reported to synthesize human and preclinical data on the associations between sleep and the gut microbiome. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews) and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines will be used to guide the search strategy, study selection, and synthesis of results [72,73]. Briefly, PRISMA-ScR and PRISMA-P involve identifying research questions and objectives, identifying relevant studies through an electronic search strategy, study selection, and data charting and synthesis of results. The protocol for this scoping review is registered on Open Science Framework (69TBR).

Eligibility Criteria

Inclusion Criteria

Primary research papers published in peer-reviewed journals will be included. Additionally, papers housed on preprint servers and conference proceedings or abstracts that adequately address the overarching research question will be included in this study. If a preprint paper or conference abstract is included in the final scoping review, a notation will be made in the summary of the included evidence table that the paper has not been peer reviewed. All study designs will be included in this scoping review, including studies with adults aged ≥18 years (human studies) and rodents (preclinical research). No date limits will be set in the search strategy, and studies will be restricted to papers and abstracts published in the English language. For preclinical research studies, analyses must examine the associations between the bacterial gut microbiome and objective sleep measures or sleep disruption, restriction intervention, or circadian disruption intervention groups. For translational research protocols, analyses must contain the associations between the bacterial gut microbiome and objective or subjective sleep measures to compare across sleep pathology or intervention groups with the confirmation of sleep disruption (sleep inclusion groups defined in Table 1).

Exclusion Criteria

Review articles and studies that include the following are excluded: outcomes not related to the microbiome, analyses of the microbiome and sleep not performed, outcomes related to other gut microbiome organisms (virus, protozoa, and archaea, etc.), intervention used a symptom of sleep pathology but not alteration of sleep (ie, intermittent hypoxia), additional intervention not associated with the gut microbiome simultaneously used, other model organisms in preclinical research, and English language version not available.

Search Strategy

Our research team met and developed relevant search terms to capture data sources covering the full scope of the intended aims, including the different iterations of sleep or sleep disruption, the gut microbiome, and human or rodent studies

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(for a full list of search terms and individual database search strategies, see Multimedia Appendix 1).

Sources of Knowledge

We worked closely with our institutional medical research librarian to develop and refine our search strategy and Medical Subject Headings terms and identify pertinent databases to be searched. The search strategy and methods were peer reviewed by a medical librarian independent of the scoping review team to improve validity and reproducibility. The databases listed previously will be used to identify the primary sources of evidence. Secondary searches will be performed within Web of Science using snowballing technique conducting backward and forward citation analysis of the reference lists as well as the cited studies of the included studies for additional relevant articles.

The following databases will be searched:

- PubMed/MEDLINE (National Library of Medicine)
- Embase (Elsevier)
- Scopus (Elsevier)
- Web of Science: Core Collection (Clarivate Analytics)
- CENTRAL trials database (Wiley)
- BIOSIS Citation Index
- Zoological Record

No limitations will be placed on year of publication. Gray literature sources will also be searched, such as medRxiv and bioRxiv preprint servers.

Study Records

Data Management

All information sources retrieved by the medical research librarian will be imported into Covidence systematic review screening software (Veritas Health Innovation), and duplicates will be removed. The data sources that pass initial screening for the full-text review will have PDF versions of the data source uploaded into Covidence by the medical research librarian. Naming conventions will be structured by the medical research librarian for the uploaded PDF files with an abbreviated title and year of publication. Excel spreadsheets will be used for the data collection of the included studies, with different tabs for preclinical and translational clinical studies. Naming and version control conventions using the date of last edit will be used for the data collection (synthesis table) Excel spreadsheet (eg, Sleep_Microbiome_Synthesis_Table_2022_04_24.xlsx). Synthesis tables will be stored in Box cloud-based storage system, and copies will be downloaded for backup regularly (at least weekly) on an institutional server. KAM will be responsible for managing the data resulting from this search and scoping review and after the project is completed.

Selection of Relevant Scientific Literature

The study screening and eligibility methods will be illustrated in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram in the scoping review where the final number of included sources will be listed. Initially, 2 researchers (KAM and JA) will screen all the sources selected independently using the predefined inclusion and exclusion criteria in Covidence, and any discrepancies will be reviewed by a third researcher (GRW), where full agreement will be reached by all reviewers before a final decision is made to include a source. Prior to initiating, screening, and importing all sources into Covidence, a "pilot" of the protocol was performed by the 2 primary reviewing researchers where 15 randomly selected records were uploaded to ensure both reviewers had a shared understanding of the inclusion and exclusion criteria. The reviewers met regularly to discuss the consistency of their screening and data extraction form, revising the form if needed as additional microbiome outcome categories were identified and resolving disagreements through discussion.

Data Collection Process

After the final sources of evidence that will be included in the review are selected, data will be systematically collected using the synthesis table. Data charting will initially be performed by one team member (JA) and regularly audited by KAM (weekly) to ensure data abstracted from the included sources are consistent with the overarching research objectives and research questions. Data charting will be audited by other members of the research team as needed or if questions arise.

Data Items and Outcomes

Synthesis Table

Key pieces of information from each study (author, year, aim of manuscript, and population) will be collected in a standard format on a separate tab on the synthesis table and presented in table format in the scoping review. Based on a research group discussion, we developed a priori preclinical sleep disruption categories (Table 1) and translational sleep disruption, subjective sleep metric, and objective sleep metric categories (Table 1). The included studies will be organized according to the type of sleep disruption model or the subjective or objective sleep assessment being studied, and preclinical and translational studies will be reported separately. The type of microbiome sequencing (ie, 16S ribosome ribonucleic acid amplicon sequencing or shotgun metagenomics sequencing) will be collected in the synthesis table. Microbiome, functional and metabolic gene, and metabolomics data will be collected, if reported, and annotated according to the synthesis table data columns outlined in Table 1. Cytokine and immune markers will also be extracted as both variables have known associations with sleep and the gut microbiome [74]. As we cannot assume directionality between sleep and microbiome metrics, we will focus on the associations between sleep pathology groups or measures and the gut microbiome instead of identifying specific outcome measures. Synthesis table data columns will be iteratively reviewed, and if it is determined by the study team that a key piece of information is not captured with the currently available extraction groups, an additional column will be added. If additional columns are added, previously reviewed studies will be re-examined to identify if new data need to be added to the synthesis table. Synthesis table data columns will be identical in the preclinical and translational clinical data collection tabs.

Risk of Bias in Individual Studies

One anticipated bias is the selective reporting of microbiome metrics across research studies reporting microbiome data. In

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an attempt to overcome this bias, we will collect all diversity (alpha and beta) metrics and other microbiome/metabolomics data related to our predefined data columns that are reported in the information source and supplemental data. We also will include data on the sample size, study population, and intervention used, if applicable, so that the synthesis of data can be examined in light of the populations or groups studied.

Synthesis of Results

The purpose of this scoping review will be to aggregate overarching findings and relationships with sleep quality and quantity with the gut microbiome, supplemented by functional gene, metabolite, and biologic marker associations, if available. Global microbiome, bacterial differential relative abundance, the predictive functional profiling of the gut microbiome community, and metabolomics results will be compiled in a standard format in both preclinical and translational studies. Individual bacterial taxa differential abundance between sleep disruption and sleep metric groups, along with bacterial relative abundance associations with sleep metrics, will be reported so agreement and disagreement across studies can be quantitatively analyzed. All data items and metrics aligning to the synthesis table data columns will be recorded in the synthesis table, but we will focus on metrics that have been reported across several studies to evaluate agreement or disagreement across the currently available data. The main results will be summarized, and the limitations of the scoping review process will be discussed. The collated data will be appraised for patterns and themes to identify possible pathways connecting sleep physiology and pathophysiology to gut microbiome functional and bacterial community characteristics. Possible physiologic pathways, the areas of study disagreement, and gaps in the literature will be presented to identify future areas of research and whether study replication is needed. We plan to use the PRISMA-ScR reporting guidelines to ensure all essential reporting items are included in the final scoping review [72].

Results

The search strategy yielded 4622 references that were imported into Covidence systematic review screening software for study screening, and 87 duplicates were automatically identified and removed. Title and abstract screening of the 4535 remaining studies occurred, and full-text screening of the 154 full-text studies that passed title and abstract screening was completed in May 2022 by the 2 independent investigators identified in the methods section. A total of 93 sources were included for data extraction and synthesis. Data extraction of the identified sources will occur using the sleep and microbiome measures outlined in Textbox 1, and the synthesis table is expected to be completed by August 2022. The results of this scoping review will be disseminated through paper submission by December 2022 with the study findings and interpretation, along with presentation of the results to conferences related to neuroscience, sleep physiology, bioinformatics, and the microbiome.

Discussion

Unreliable translation of preclinical studies to human populations and replication across human microbiome research studies has slowed progress in understanding the mechanisms and pathways underlying the connection of the microbiome to pathology and disease. Multiple factors contribute to bias in microbiome results, ranging from gut microbiome sample collection to sequence analysis [68,75,76], and the variability and heterogeneity in microbiome analysis metrics and statistical methods make standard cross-study comparison challenging. Therefore, we present our scoping review protocol in which we aim to extract, compile, and synthesize the primary sources of preclinical and translational clinical research focused on the relationships between sleep and sleep pathology with the gut microbiome. Our initial aim will be to survey which sleep disruption models have been used in preclinical research including mechanical sleep disruption [47], paradoxical sleep disruption [49], circadian light alteration sleep disruption [58], and biological sleep disruption [60] in gut microbiome research. We will also identify the extent that sleep disruption interventions have been used in human gut microbiome studies including sleep deprivation [63] and sleep restriction [51], and what pathological sleep conditions have been explored in the context of the microbiome. We hypothesize that sleep disruption will be associated with disruptions in global diversity measures and changes in specific bacterial taxa and metabolic genes, but these results will vary based on the microbiome analysis metric and sleep disruption model. Although several associations between sleep and gut microbiome community changes have been established in the currently available research, to our knowledge, this is the first systematic synthesis compiling specific bacterial and functional gut microbiome associations with sleep that takes the multiple sources of microbiome reporting bias into account. We hope this synthesis and presentation of results will inspire future microbiome researchers to comprehensively report and account for factors that potentially bias microbiome results [77]. Furthermore, we are working with other experts in the field to develop reporting standards and prioritize a consensus in base microbiome metrics to report across all research, regardless of statistical significance, to facilitate cross-study comparison and replication [78]. Our overarching aim of the proposed scoping review is to advance the current understanding of the mechanisms connecting the gut microbiome to sleep through gut-brain communication and the associated pathways. Therefore, we will initially synthesize and present the microbiome and related functional findings specific to each sleep measure or pathology, but we will also evaluate this data in relation to previously established pathways in the literature to provide researchers with opportunities to test the hypothesized mechanisms in future research. We will submit the findings of this scoping review for future publication to disseminate the results to the greater research community.

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Acknowledgments

In memory of Christine Caufield-Noll: we want to express our deepest gratitude to Christine, who both spearheaded the development of this scoping review protocol and search strategy and left an indelible legacy on our interdisciplinary research team, reflecting the importance of reproducible and rigorous literature reviews to inform future research and promote data dissemination.

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Authors' Contributions

Study concept: KAM and GRW; protocol design: KAM, JA, GB, and GRW; initial draft: KAM and JA; critical revisions: GB and GRW; approved final manuscript: KAM, JA, GB, and GRW. KAM serves as the guarantor of the review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Base and database-specific search strategy.
[DOCX File , 13 KB - resprot_v11i6e38605_app1.docx]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Familiarity in Rural Life: Protocol for a Scoping Review and Concept Analysis

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Abstract

Background: Familiarity is a concept often used in literature but is not well defined or understood. As a key concept in rural nursing theory, the conceptual understanding of familiarity is currently incomplete. The findings from this scoping review will inform a concept analysis using Walker and Avant's method and to identify and define the missing key components of familiarity.

Objective: The objective of this scoping review is to examine and analyze what is known in the existing literature about the concept of familiarity.

Methods: The Joanna Briggs Institute scoping review framework guided the identification of literature published from 2016 to 2022 on familiarity. Following the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) reporting standard, the familiarity scoping review is registered on Open Science Framework (registration digital object identifier: 10.17605/OSF.IO/ZB8VF). A total of 8 databases, including PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus with full text, APA PsychInfo, Communication Source, EBSCO MegaFILE, Medline, Nursing & Allied Health Database, and ScienceDirect, will be searched for 22 search terms. Covidence software will be used to manage the scoping review with each citation independently reviewed by 2 research team members for eligibility. Eligibility will be determined using a 2-level process. Each title and abstract will be screened for eligibility; for citations deemed eligible, a full-text article review will be conducted. The scoping review is expected to locate a large body of literature, and eligibility criteria will be refined during the title and abstract screening process. In addition, reference list scanning will be performed to locate relevant literature.

Results: Familiarity data will be collected beginning October 2021 with anticipated completion in March 2022. Dissemination of findings will occur through scholarly presentations and in rural-focused and nursing publications in 2022 or 2023. The findings from this review will further the understanding of familiarity and how it affects rural life and nursing practice.

Conclusions: This review will support a full understanding and add clarity to the concept of familiarity as a component of rural life. These new insights will advance the understanding of how familiarity influences rural health care practice. The concept analysis will provide theoretical support for rural nursing theory and promote an understanding of the interrelationships of rural concepts.

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KEYWORDS

familiarity; scoping review; rural; nursing; nurse; healthcare professional; health care professional; healthcare worker; health care worker

Introduction

Familiarity is a common word used in everyday communication and in all settings. Most often, familiarity denotes knowledge of a person, place, or thing, or is indicative of informal behavior [1]. As people go about life, familiar interactions with or exposures to objects, people, and locations are stored as memories in the brain [2]. Thus, people become accustomed to what is repeatedly experienced. This is particularly true for people who live in rural or small locations. Rural dwellers often report having a strong experience with familiarity, particularly with people and places [3,4]. Small locations, with limited numbers of individuals, promote increased knowledge and greater familiarity [5]. As such, it makes sense that early rural nurse researchers identified familiarity as a concept present in rural locations [4,6]. More specifically, familiarity is identified as a core concept in rural nursing theory [7,8].

Williams et al [9] identified that rural nursing research is hampered by a lack of understanding of rural concepts. Many rural concept analyses are dated, completed in 1998 or before, and lack rigorous literature reviews using current guidelines and methods. There is a need to develop rural concepts so a strong theoretical foundation is established, which will guide future research, particularly on rural topics [9].

Within the rural nursing literature, the concept of familiarity is not well defined or understood. The original concept analysis was incomplete; a definition of familiarity was presented and defining attributes, or characteristics, were identified [7]. As specified in Walker and Avant's [10] concept analysis process, antecedents, consequences, and empirical referents were not identified [8]. In addition, an unknown number of articles were reviewed, and limited disciplines were included in the analysis [7].

Our interest in familiarity grew from a completed concept analysis on the rural concept *lack of anonymity* [11]. In that analysis, familiarity was identified as a consequence of lack of anonymity [11]. As our theoretical work developed, we recognize that familiarity requires further exploration. The process was arduous, as familiarity is commonly used as a word to replace descriptive words such as knowledge, experience, awareness, and others. Thus, literature searches for familiarity yielded extensive amounts of literature, from multiple disciplines, without a thorough understanding of the concept. After two limited attempts to examine familiarity as a concept [12,13], it became apparent that a scoping review was necessary to fully explore the concept.

Understanding familiarity as a concept is foundational to rural nursing theory and to the influence of familiarity on everyday life. A scoping review of literature will be conducted on familiarity. Findings from this scoping review will inform a concept analysis using Walker and Avant's [10] process to understand key components of familiarity and how familiarity relates to rural nursing theory and practice. The aim of this review is to examine and analyze what is known in the existing literature about the concept of familiarity.

Methods

Scoping Review

A scoping review supports clarification of the concept and the exploratory nature of the review [14]. Walker and Avant [10] support a broad, multidisciplinary review of the literature to gain a full understanding of a concept. The Joanna Briggs Institute scoping review methodology, as outlined by Aromataris and Munn [15], builds on the seminal work of Arksey and O'Malley [16] and will be the framework for this review. In accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) reporting standard [17], the familiarity scoping review is registered on Open Science Framework (registration digital object identifier: 10.17605/OSF.IO/ZB8VF).

Step 1: Identify the Purpose

The research question guides the review, and for a concept analysis, it must be broad and comprehensive [10,15]. The research question developed by the research team is "What is known from the existing literature about the concept of familiarity?"

Step 2: Search Strategy

For the review, 8 databases will be searched for relevant literature, including PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus with full text, APA PsychInfo, Communication Source, EBSCO MegaFILE, Medline, Nursing & Allied Health Database, and ScienceDirect. Gray literature is not included in the review; however, reference list scanning will be completed during the literature screening procedure. Thus, literature outside of the search dates may be included if deemed relevant.

A challenge for this review is the pervasive use of the word and quantity of literature that may be located during the search. As suggested by Aromataris and Munn [15], the search terms must be both specific and broad to access relevant literature for full conceptualization while balancing the need for a manageable amount of literature for a review. The search parameters include the word "familiarity" in the abstract or title and from a peer-reviewed source from January 1, 2016, to 2022 (Textbox 1). The review was conducted late in 2021, and 2022 literature may be released and will be included in the scoping review. The search terms include "empathy and familiarity" OR "memory and familiarity" OR "recognition and familiarity" OR cognit* and familiarity" OR "spatial familiarity" OR "contextual familiarity" OR "personal familiarity" OR "belonging familiarity" OR "relationship and familiarity" OR "lack of anonymity and familiarity" OR "privacy and familiarity" OR "confidentiality and familiarity" OR "nurs* and familiarity" OR "medicine and familiarity" OR "social work and familiarity" OR "healthcare and familiarity" OR "rural and familiarity" OR

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"gaming and familiarity" OR "social media and familiarity" OR "culture and familiarity" OR "religion and familiarity" OR "spirit* and familiarity." The search terms will be run in each of the selected databases using the asterisk symbol as an end-of-root-word-truncation mark. The identified literature will be imported to the Covidence software program with duplicate records removed.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Define or directly discuss familiarity as a concept
- Apply to humanity or human beings
- Indicate a study result or finding on familiarity
- English language literature including international sources

Exclusion criteria:

- Studies or articles referring to animals or nonhumans
- Studies on genetics (human and nonhuman)

Step 3: Selection Process

The literature screening is composed of 2 separate reviews. Covidence software will be used to manage the scoping review with each citation independently reviewed by 2 research team members for eligibility. Eligibility will be determined using a 2-level process. Each title and abstract will be screened for eligibility; for citations deemed eligible, a full-text article review will be conducted. The scoping review is expected to locate a large body of literature, and eligibility criteria will be refined during the title and abstract screening process. In addition, reference list scanning will be used to locate relevant literature. The literature screening process is consistent with the screening strategy described by Aromataris and Munn [15].

The research team will have regular meetings (every 1-2 weeks) to discuss the project, refine eligibility criteria, and resolve conflicts on article eligibility. Resolution of disagreement on the eligibility of an article will occur during the full team meeting. The majority will decide eligibility. If the team is unable to establish consensus, the project leader will resolve the disagreement.

Title and Abstract Screening

Prior to the start of literature screening, research team members will receive education from the project leader followed by a pilot test. The purpose of the education and pilot study is to promote consistency in evaluating literature among the team members. At a team meeting, each team member will receive detailed instructions on how to use the Covidence software. Additionally, the inclusion and exclusion criteria will be discussed in detail and questions answered. Following the instruction, a pilot test will be conducted. For the pilot test, each pair of researchers will have 25 randomly selected abstracts to review based on the inclusion and exclusion criteria, followed by an interrater reliability (IRR) calculation between each pair of team members. The expected IRR achievement between each pair of team members is >0.75 [15]. Upon conclusion of the pilot study, the team will meet to discuss discrepancies and will consider modifications to the inclusion and exclusion criteria. Consistent with Arksey and O'Malley [16], modifications to the inclusion and exclusion criteria can be made as the team understands the scope of the literature being reviewed.

Full Text Screening for Eligibility

Prior to the start of the full text screening, the full-text articles will be uploaded in the Covidence software, and the research team will meet to discuss the screening process, including the use of the Covidence software at this phase of the review. Once completed, each team member will begin to review articles, with an IRR calculated when each team pair reviews at least 25 articles. The expected IRR achievement between each pair of team members is >0.75; if not met, the research team will meet for additional instruction and discussion.

Reference list scanning will be carried out during the full text screening process. Research team members will send citations to the project leader. Upon conclusion of the full text screening, the project leader will present the reference list articles for consideration to the research team. The majority will decide eligibility. If the team is unable to establish consensus, the project leader will resolve the disagreement.

Step 4: Charting the Data

The research team has developed a draft charting table for data extraction (Textbox 2). Data will be charted using a descriptive method that aligns to the scoping review's research question and extract descriptions, definitions, and other relevant findings on familiarity. Key to this review is to identify all the ways familiarity is used, both implicit and explicit, in the identified literature.

Aromataris and Munn [15] suggest that the draft charting table be piloted by each team member. For this review, each team member will trial the charting table by extracting data from 3 articles [15]. At the end of the trial, the research team will meet to determine the adequacy of the charting table and make modifications, if needed. Owing to the broad nature of the concept, the data charting process is considered iterative [15]. Thus, the charting table may be continually updated by the team, if deemed necessary, to fully understand the concept.

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Similar to the literature screening process, selected articles will have data charted by 2 team members. Team members will independently extract data from the selected literature. In the event of disagreement on the data extracted, the research team will discuss at a full team meeting. The majority will decide data disagreements. If the team is unable to come to an agreement, the project leader will resolve the disagreement.

Textbox 2. The data and details for extraction.

- Article information:
  - Authors
  - Year of publication
  - Title
  - Type of study
  - Discipline
  - Country of origin
- Study setting
- Study population
- Types of data sources
- Was familiarity measured or described? (Yes or no)
- Familiarity definition or description
- Relevant findings

Step 5: Data Analysis

The data analysis will be guided by Walker and Avant's [10] 8-step concept analysis process, starting with step 4:

1. Select a concept.
2. Determine the aims or purpose of analysis.
3. Identify all uses of the concept that you can discover.
4. Determine the defining attributes.
5. Identify a model case.
6. Identify borderline, related, contrary, invented, and illegitimate cases.
7. Identify antecedents and consequences.
8. Define empirical referents.

Central to the process is to identify the defining attributes of familiarity, which reveal the characteristics of the concept [10]. For the analysis, each team member will independently review the data tables and begin to cluster data that offer broad insight into the concept of familiarity. The process is iterative as the team identifies phenomena and occurrences in the data. The defining attributes will be considered complete when each attribute can "stand alone" and fully capture the essence of the concept [10].

Identification of *cases* demonstrates what the concept is and what it is not in situational life examples. A model case will demonstrate familiarity using the defining attributes identified [10]. To delineate related concepts that may be close to familiarity, additional cases will be developed, including borderline, related, contrary, invented, and illegitimate cases [10].

Once clarity on the defining attributes is achieved, the antecedents and consequences will be identified. Antecedents are "those events or incidents that must occur or be in place prior to the occurrence of the concept" [10]; consequences are "those events or incidents that occur as a result of the occurrence of the concept—in other words, the outcomes of the concept" [10]. This portion of the analysis supports a theoretical understanding of how the concepts fit together.

The final part of the analysis is to identify the empirical referents or how familiarity is revealed in everyday life [10]. The empirical referents represent categories that will support the development of a measure [10].

Results

The scoping review will begin in October 2021 and is expected to be completed in March 2022. A flow diagram will be developed to demonstrate how literature screening will be managed during the selection process [17]. Dissemination of the results of the scoping review and concept analysis will be carried out through peer-reviewed scholarly presentation at a research conference in March 2022 and in a rural nursing publication in 2022 or 2023. Additional manuscripts are planned for publications with a rural focus and readership.

The findings from the review and analysis are foundational to support a common understanding of the concept of familiarity that supports future research, theory development, and health care initiatives [10].

Discussion

In rural practice settings, familiarity is a recognized concern for nurses and health care professionals. Nurses in rural practice experience familiarity with patients, families, and the environment without recognizing it as a factor in rural settings. Research into rural issues is complicated by a general lack of

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understanding of basic concepts such as familiarity, which exist in rural life.

The outcomes of this scoping review and concept analysis will fully conceptualize familiarity as a component of rural life and may support the development of a guide on how familiarity may affect nurses and health care professionals in rural practice locations. In addition, the concept analysis will provide theoretical support for rural nursing theory and extend the model of lack of anonymity by understanding the interrelationship among rural concepts [13].

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Conflicts of Interest

None declared.

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Abbreviations

APA: American Psychological Association
CINAHL: cumulative index to nursing and allied health literature
DOI: digital object identifier
IRR: interrater reliability
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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