Protocol

A Structured Exercise Intervention for Individuals With Psychotic Disorders Treated With Long-Acting Injectable Antipsychotics: Protocol for a Nonrandomized Controlled Study

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Abstract

Background: Individuals with psychotic disorders have high rates of physical comorbidity and considerably reduced quality of life, often aggravated by the adverse metabolic effects associated with injectable antipsychotic treatment. Physical exercise has been identified as a promising strategy for improving physical and mental health in this population. This article describes the protocol for a structured multimodal physical exercise program designed to be implemented within outpatient psychiatric services for individuals treated with long-acting injectable (LAI) antipsychotics.

Objective: This study aims to evaluate the impact of a structured exercise program on psychotic symptomatology in individuals with psychotic disorders receiving LAI antipsychotics. Secondary objectives include assessing the effects of the intervention on metabolic outcomes, particularly body composition and cardiometabolic risk factors. Exploratory analyses will be performed to investigate potential associations between exercise participation and longitudinal changes in antipsychotic treatment patterns, as well as variations in circulating biomarkers such as brain-derived neurotrophic factor, dopamine, and serotonin.

Methods: This is a prospective, controlled, longitudinal study developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations. The study will recruit a clinical population of 151 eligible participants diagnosed with psychotic disorders (mean age 46.40, SD 13.60 years) receiving LAI antipsychotics. This protocol describes the implementation and evaluation of a 24-week supervised multimodal exercise program integrated into routine psychiatric outpatient care. Participants receiving LAI antipsychotics will be allocated to either the exercise program or a treatment-as-usual control group. The intervention will include supervised circuit-based sessions combining aerobic, resistance, mobility, and balance exercises, performed twice weekly, with a progressive training load and an additional autonomous walking component introduced in the second phase of the program. Clinical, functional, psychological, and cardiometabolic outcomes will be assessed at baseline (preintervention), after 12 weeks, after 24 weeks, and at an 8-week follow-up. The study has obtained ethical approval from the Ethics Committee of the Local Health Unit of Trás-os-Montes e Alto Douro, and written informed consent will be obtained from all participants.

Results: The study was funded in January 2026. Recruitment and data collection began on January 1, 2026, and are expected to be completed by November 30, 2026. As of manuscript submission (May 2026), 25 participants had been recruited. Data analysis is projected for December 2026, with findings expected to be published in spring 2027.

Conclusions: Structured exercise interventions integrated into routine psychiatric care may represent an important strategy to improve the physical health, functional capacity, and overall well-being of individuals with psychotic disorders treated with LAI antipsychotics.

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Introduction

Mental disorders represent a major public health challenge and are among the leading causes of disability worldwide, affecting more than 970 million people in 2019 [1-4]. Among these conditions, psychotic disorders such as schizophrenia are among the most disabling psychiatric illnesses, frequently associated with cognitive impairment, social isolation, unemployment, and reduced life expectancy [5].

In Portugal, the first national epidemiological survey of mental health reported a lifetime prevalence of mental disorders of approximately 22.9% in the adult population [6]. Although more recent epidemiological estimates are not available, a projection conducted in 2013 suggested that approximately 1,557,054 adults in Portugal (16.07% of the population aged 18 to 65 years) were living with a mental disorder, and that 0.52% of the total population had a psychotic disorder [7].

The cornerstone of treatment for psychotic disorders is antipsychotic medication. Long-acting injectable (LAI) antipsychotics are widely used to improve treatment adherence and reduce the risk of relapse [8]. They are frequently prescribed for individuals with a history of poor adherence, recurrent relapses, or complex clinical trajectories. However, LAIs have been associated with adverse effects such as weight gain, metabolic syndrome, insulin resistance, and hyperprolactinemia, which may negatively affect functional prognosis and increase the risk of physical comorbidities [9-11].

Given these metabolic risks, complementary lifestyle interventions have increasingly been explored as strategies to mitigate the physical and mental health complications associated with psychotic disorders. Physical exercise has emerged as a potential complement to pharmacological treatment in individuals with psychotic disorders, highlighting the need for targeted, evidence-based interventions and emphasizing the importance of strengthening research and epidemiological monitoring in this area [7]. Systematic reviews and meta-analyses suggest that exercise interventions may be associated with changes in positive, negative, and cognitive symptoms, as well as improvements in quality of life, self-esteem, and physical health outcomes [12,13]. Nevertheless, evidence also suggests that these benefits may diminish after the completion of structured programs, highlighting the importance of sustained and supervised interventions [14].

Beyond clinical outcomes, research attention is being increasingly directed toward the neurobiological mechanisms underlying the effects of physical exercise. Brain-derived neurotrophic factor (BDNF), a protein involved in synaptic plasticity, neuronal survival, and cognitive processes, has been proposed as a key mediator of exercise-related cognitive and functional improvements. Acute aerobic exercise has been shown to increase serum BDNF levels in both healthy populations and individuals with psychosis, whereas evidence for resistance training remains limited [15,16]. Exercise may also modulate dopaminergic and serotonergic pathways involved in mood, motivation, and behavior [17].

Physical activity offers benefits beyond physiological measures, improving mental health, quality of life, and cognitive function in the general population [18-20]. Regular exercise is associated with a lower incidence of depressive and anxiety disorders, enhanced executive function, and neuroprotective effects during aging, including a reduced risk of dementia and cognitive decline [21]. These effects are mediated both by cardiovascular and metabolic adaptations and by central nervous system changes, including the regulation of neurotrophic factors such as BDNF, angiogenesis, and neurogenesis in regions such as the hippocampus [20,22].

Aerobic exercise, including activities such as running, cycling, and swimming, is strongly linked to improved cerebral perfusion and cardiovascular adaptations [23,24]. In individuals with psychosis, aerobic training has been associated with improvements in negative and cognitive symptoms, potentially through dopaminergic modulation and enhanced neuronal connectivity [25]. The effects of resistance training, focused on increasing muscle strength and mass through exercises like weightlifting, have been less explored in populations with psychosis. Emerging studies suggest that resistance training promotes neuromuscular adaptations that support cognitive function and motor control, and it may improve metabolic and musculoskeletal health, which is particularly important for individuals at high risk of cardiometabolic diseases [26,27]. Multimodal training, combining aerobic and resistance approaches, enhances cardiovascular,

neuromuscular, and cognitive outcomes [28]. In people with psychosis, multimodal interventions appear promising for reducing psychiatric symptoms and improving quality of life, functional capacity, and cognitive performance, although heterogeneity across studies warrants further investigation [29].

International initiatives such as the Lancet Psychiatry Commission have emphasized the urgent need to integrate lifestyle interventions, including structured physical exercise, into routine mental health care to address the considerable cardiometabolic burden observed in this population [30].

However, despite this international call to action, the implementation of structured exercise programs within routine outpatient psychiatric services remains limited. This gap in care is particularly evident for individuals treated with LAI antipsychotics, a clinically relevant subgroup characterized by more complex illness trajectories and heightened cardiometabolic risk [19,31]. The regular attendance of these patients at outpatient clinics for medication administration presents a unique yet underused opportunity to deliver supervised lifestyle interventions without requiring additional travel or complex logistics [32]. Thus, individuals receiving LAIs represent a clinically relevant population for the implementation of structured lifestyle interventions.

Despite increasing evidence supporting the benefits of physical exercise in individuals with psychotic disorders [27,33-35], the absence of standardized intervention frameworks limits the reproducibility and implementation of exercise programs in psychiatric services.

This protocol addresses this need by describing a multimodal exercise program specifically adapted for individuals receiving LAIs and designed to be feasible in clinical settings with minimal equipment and space requirements.

We hypothesize that this multimodal program will lead to notable improvements in psychotic symptomatology and physical function compared with a treatment-as-usual control group. Furthermore, we anticipate that the intervention will result in positive adaptations in cardiometabolic risk factors and neurobiological markers, specifically increased serum BDNF levels, with some of these benefits persisting at the 8-week follow-up. While not a primary focus, we will also examine whether improvements in clinical and functional status correlate with greater therapeutic stability and potential optimization of LAI dosage.

Considering these aspects, the primary objective of this study is to evaluate the impact of a 24-week structured exercise program on the psychological component and physical fitness in individuals diagnosed with psychotic disorders and treated with LAIs. Secondary objectives include assessing changes in body composition and cardiometabolic risk factors. Finally, as an exploratory aim, we will investigate associations among exercise participation, circulating biomarkers (BDNF, dopamine, and serotonin), and potential optimization of antipsychotic treatment patterns.

Methods

Study Design

This study protocol was prospectively registered at ClinicalTrials.gov (NCT07360665). This study is designed as a nonrandomized, controlled, longitudinal study and follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Checklist 1) [36,37]. It involves the implementation of a 24-week multimodal exercise intervention, with 4 assessment time points: baseline (preintervention), midintervention (12 weeks), postintervention (24 weeks), and follow-up (8 weeks after the intervention). Participant allocation is not randomized but is determined by logistical and practical factors related to attendance at the exercise sessions. Consequently, this design does not constitute a randomized clinical trial. While rigorous analytical strategies, such as propensity score adjustment, will be employed to mitigate selection bias and confounding, the absence of randomization limits the strength of causal inferences. Therefore, findings will be interpreted as evidence of adjusted associations rather than definitive causal effects of the exercise intervention.

Ethical Considerations

This study will be performed in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee for Health of the Local Health Unit of Trás-os-Montes e Alto Douro (ULSTMAD), Vila Real, Portugal (CES REG 1612), which issued a favorable opinion on April 5, 2023. The clinical trial registration number is NCT07360665 (ClinicalTrials.gov). All adult participants provided written informed consent to participate in this study. Written informed consent was also obtained from the individuals for publication of the details of their medical case and any accompanying images.

Location and Implementation Period

The study will be conducted in an outpatient psychiatric clinic specializing in LAI antipsychotic treatment and integrated within a Portuguese public health care institution.

Intervention Delivery and Supervision

The intervention will be supervised and delivered by a qualified exercise professional. The exercise sessions will be supervised to ensure participant safety and adherence to the training protocol. Participants' clinical stability will be monitored throughout the intervention. The professional delivering the intervention will coordinate with the psychiatric clinical team to monitor participants' clinical status and adapt exercise intensity when necessary.

Participants

The sample will include adult patients diagnosed with psychotic disorders who are receiving outpatient psychiatric care and are prescribed LAIs.

Because of practical and logistical constraints inherent in implementing a supervised exercise program in a clinical

setting, random allocation is not feasible. These constraints include geographic accessibility of the exercise facility and participants' availability to attend exercise sessions.

Participants will therefore be allocated to either the exercise intervention or the treatment-as-usual group based on their ability and availability to attend the exercise sessions. This allocation mechanism is expected to introduce potential selection bias, particularly related to motivation, functional status, socioeconomic factors, and proximity to the clinical center. These factors may influence both the likelihood of participating in the exercise program and study outcomes.

To address this anticipated imbalance, a comprehensive set of baseline demographic, clinical, and functional variables will be collected and explicitly incorporated into the statistical analysis. Specifically, propensity score methods and multivariable adjustment will be used to mitigate selection bias.

Sample Size Calculation

An a priori power analysis was conducted using G*Power (version 3.1.9.4; Heinrich-Heine-Universität Düsseldorf). Although the primary analysis will involve mixed-effects models to account for the nonrandomized design, power was estimated using an F test for repeated-measures ANOVA (within-between interaction) as a baseline. The primary end point for this calculation is the change in the psychological component and physical fitness from baseline to 24 weeks. Assuming a medium-to-large effect size (f=0.30), justified by previous meta-analyses [12,25] of supervised multimodal exercise interventions in individuals with schizophrenia showing similar magnitudes of effect on clinical symptoms and physical capacity, with α=.05 and a power of 0.80, 35 participants are required. To maintain sufficient power after adjusting for baseline confounders (eg, age, illness duration, and baseline physical activity) and accounting for an anticipated attrition rate of 25%, the target sample size was set at 48 participants (approximately 24 per group). This sample size is considered adequate to detect meaningful changes in clinical and functional outcomes while allowing for the inclusion of covariates and exploratory analysis of biomarkers (BDNF, dopamine, and serotonin) within the mixed-effects models.

Inclusion and Exclusion Criteria

Participants eligible for inclusion in either group are aged 18 years or older, are diagnosed with a psychotic disorder, have been receiving treatment with LAI antipsychotics for at least 6 months, and are considered clinically stable and autonomous, as documented by their treating psychiatrist.

Exclusion criteria for both groups will include refusal or inability to provide informed consent, either personally or via a legal representative; medical contraindications to physical exercise; or nonaffiliation with the outpatient antipsychotic clinic.

Attendance below the predefined adherence threshold (75%) and incomplete assessments will be recorded as study outcomes rather than used as exclusion criteria.

Recruitment

Overview

Recruitment will be carried out by the hospital medical team based on predefined eligibility criteria. Eligible patients will be provided with detailed verbal and written information regarding the study objectives and procedures and will be invited to participate by providing written informed consent. The number of eligible patients approached, the number who decline participation, and the reasons for refusal, where available, will be documented. These indicators will be used to evaluate feasibility and potential selection bias.

Intervention: Physical Exercise for Psychosis

The Physical Exercise for Psychosis (PEP) program is a 24-week multimodal intervention followed by an 8-week independent follow-up phase. The intervention is structured into 3 distinct stages. Phase 1 (weeks 1-12) consists of 2 supervised 60-minute sessions per week; phase 2 (weeks 13-24) maintains these supervised sessions while introducing a 30-minute autonomous walking component to promote long-term engagement. Phase 3 (weeks 25-32) serves as a follow-up period in which participants are encouraged to independently maintain their exercise regimen.

Each training session is designed to be progressive and adaptable. A session begins with a 5-minute warm-up consisting of low-intensity cardiovascular activities, such as step-based exercises. This is followed by the core circuit training component, which integrates aerobic activities (eg, cycling or stepping) with functional strength exercises targeting the upper and lower limbs, trunk, and multijoint movements like kettlebell swings. To ensure clinical relevance and participant safety, sessions conclude with a 5- to 10-minute cooldown focused on mobility, balance, and flexibility.

The training plan is dynamic, with exercise intensity and complexity adjusted weekly based on individualized progression. Figure 1 presents a sample circuit layout representative of the initial training period (weeks 1-3). Details of load progression, including adjustments to the number of sets, rest intervals, and execution time, are summarized in Table 1. A formal intermediate assessment will be conducted at week 12 to guide subsequent intensity adjustments.

Figure 1. Example of a multimodal circuit training session implemented in the first 3 weeks of the Physical Exercise for Psychosis program.

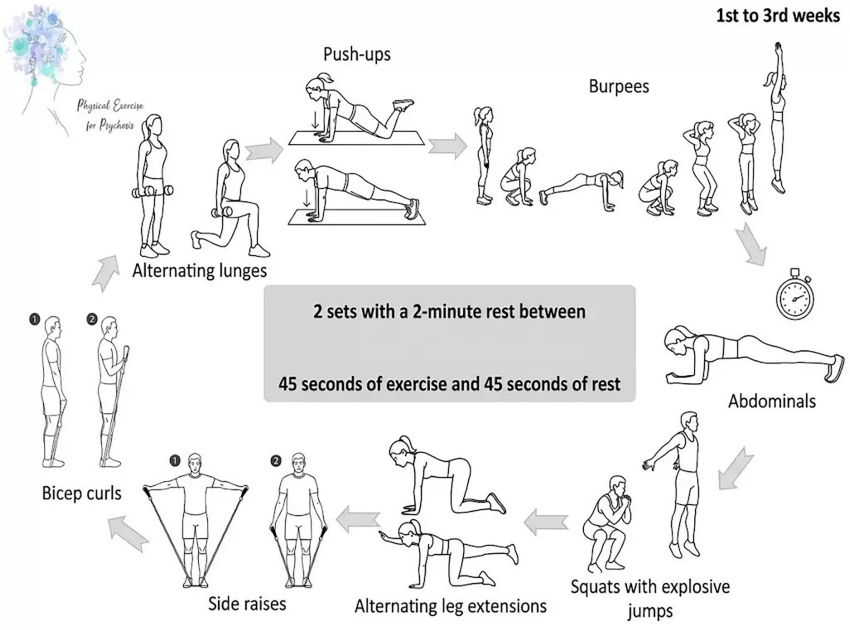

Table 1. Load progression across the 24-week exercise program.

Weeks	Sets	Interval between sets (minutes)	Execution time (seconds)[a]	Rest between exercises (seconds)	Walking (minutes)[b]
1-3	2	2	45	45	N/A[c]
4-6	2	2	45	45	N/A
7-10	2	2	45	30	N/A
11-14	3	2	45	30	30
15-18	3	2	45	30	30
19-21	3	2	45	30	30
22-24	2	2	60	20	30

[a]Active exercise duration.
[b]The walking component is introduced from week 13 onward.
[c]N/A: not applicable.

Implementation Environment

Exercise sessions will take place in a supervised clinical or adapted functional space within the health care facility to ensure safety, confidentiality, and accessibility. Remote walking sessions will be executed using participants' personal mobile devices, when available.

Adherence and Safety Monitoring

Attendance will be monitored, physical and psychological symptoms will be recorded during each session, and clinical monitoring will be conducted by the multidisciplinary team. Any adverse events will be reported to the clinical team and documented according to institutional procedures.

Assessments Throughout the Program

Sociodemographic and Clinical Characterization

Sociodemographic characterization of participants will be performed using a structured questionnaire designed to collect information on variables such as age, gender, marital status, educational level, employment status, and family context. This instrument provides a comprehensive description of the sample characteristics and enables the analysis of potential sociodemographic factors associated with the clinical and functional variables under study. Baseline clinical data will include diagnosis, duration of illness, psychiatric medication, dosage of LAI antipsychotics, and relevant medical comorbidities (eg, diabetes, hypertension, cardiovascular disease, and chronic respiratory disease).

Anthropometric Measurements

Anthropometric assessment will include body composition analysis using electrical bioimpedance with the Tanita BC-418 Body Composition Analyzer [38]. This method allows for the rapid estimation of variables such as body weight, BMI, fat mass percentage, lean mass, and segmental body composition. It is widely used in clinical and research contexts because of its reliability, practicality, and applicability to different populations, including people with severe mental disorders [39,40]. Waist circumference will be measured using a flexible, nonelastic tape measure, following the recommendations of the World Health Organization [41]. Measurements will be taken with the participant standing upright, at the midpoint between the last palpable rib and iliac crest, after normal exhalation. This anthropometric indicator

is widely used as a marker of cardiometabolic risk and is associated with abdominal fat accumulation and an increased risk of metabolic and cardiovascular diseases [42].

Functional Assessment

Functional assessment will include the sit-to-stand test [43], which will be used to measure lower limb strength based on the number of repetitions performed in a specific period. This is a simple, reliable test widely used in clinical and research contexts. The handgrip test [44] will be used to assess upper limb muscle strength, as it is considered a robust predictor of overall strength, functionality, and health status. Both tests have demonstrated adequate validity and sensitivity in clinical populations, including people with severe mental disorders [45,46].

Psychological and Quality of Life Measures

EUROHIS-QOL-8 (European Health Interview Survey–Quality of Life 8-item index) [47] was developed as a shortened and easy-to-apply version of WHOQOL-BREF (World Health Organization Quality of Life Instrument-Abbreviated Version) to provide a comprehensive but brief assessment of quality of life. The scale consists of 8 items covering physical, psychological, social, and environmental dimensions and has exhibited good psychometric properties for use in clinical and research settings. The EUROHIS-QOL-8 version has been translated and validated for the Portuguese population [48].

The 9-item Patient Health Questionnaire (PHQ-9) [49] was developed as a brief, valid, and reliable instrument for assessing the severity of depressive symptoms. It consists of 9 items that directly reflect the diagnostic criteria for major depressive episodes according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) [50]. The PHQ-9 is a self-administered scale that is easy to use in clinical practice and research. It was translated and validated for the Portuguese population in 2013 [51].

The Positive and Negative Affect Schedule (PANAS) [52] was developed to address the need for reliable and valid scales for assessing affect. To facilitate administration, 2 shorter 10-item mood scales were developed [52]. The PANAS has been translated and validated for the Portuguese population [53].

Biochemical and Neurobiological Markers

The assessment of biochemical parameters will include metabolic markers, namely, lipid profile (total cholesterol, high-density lipoprotein cholesterol, direct low-density lipoprotein cholesterol, and triglycerides) and blood glucose. These parameters will be measured immediately before LAI antipsychotic administration. These parameters were selected as key indicators of metabolic status to enable the analysis of potential effects of the physical exercise intervention on participants' physical health. Additionally, exploratory assessments will include serum levels of BDNF and peripheral markers related to dopaminergic (serum dopamine) and serotonergic (serum serotonin) pathways. These markers will be measured using enzyme-linked immunosorbent assay kits: the Human BDNF ELISA Kit (catalog number RAB0026; Sigma-Aldrich) for BDNF; Dopamine ELISA Kit (catalog number ab285238; Abcam) for dopamine; and Human 5-HT ELISA (catalog number KitELK8524; ELK Biotechnology) for serotonin (5-hydroxytryptamine). Serum levels of BDNF, dopamine, and serotonin will be treated as secondary outcomes. Additionally, genomic DNA will be extracted from peripheral blood samples to analyze selected genetic polymorphisms as exploratory variables. Given the multiplicity of biomarkers and assessment time points, procedures to control the type I error will be applied. To reduce preanalytical variability, blood samples will be collected before the training session and at least 48 hours after the previous session. This timing is intended to minimize the influence of acute exercise-induced fluctuations and circadian variation, thereby reflecting chronic neurobiological adaptations to the exercise program rather than transient responses. All samples will be processed using the same assay kits and laboratory procedures. Analyses will be performed in duplicate, and samples from both groups will be analyzed within the same batches whenever possible to reduce interassay variability.

Assessment sessions will be scheduled on nontraining days or, when conducted on training days, before the training session to avoid acute exercise-related effects on physiological or functional measurements. Each evaluation will begin with blood collection for biochemical analyses, followed by psychological and functional assessments. Four assessment time points have been selected: preintervention (baseline), midintervention (12 weeks), postintervention (24 weeks), and follow-up (8 weeks after program completion) (Table 2). Hospital admissions and psychiatric relapses occurring during the study period will be recorded as exploratory clinical outcomes.

Table 2. Assessment schedule at baseline, 12 weeks, 24 weeks, and 8-week follow-up for the 24-week Physical Exercise Program[a], including anthropometric, functional, psychological, and biochemical measures.

Assessment methods	Assessment time points			
	Baseline	12 weeks	24 weeks	8-week follow-up
Sample characterization				
Sociodemographic questionnaire	✓	N/A[b]	N/A	N/A
Anthropometric assessment				

Assessment methods	Assessment time points			
	Baseline	12 weeks	24 weeks	8-week follow-up
Body composition (bioimpedance)	✓	✓	✓	✓
Waist circumference	✓	✓	✓	✓
Functional assessment				
Sit-to-stand test	✓	✓	✓	✓
Handgrip test	✓	✓	✓	✓
Psychological assessment				
EUROHIS-QOL-8[c]	✓	✓	✓	✓
PHQ-9[d]	✓	✓	✓	✓
PANAS[e]	✓	✓	✓	✓
Assessment of biochemical parameters				
Brain-derived neurotrophic factor (BDNF)	✓	✓	✓	✓
Genetic polymorphism	✓	✓	✓	✓
Dopamine	✓	✓	✓	✓
Serotonin	✓	✓	✓	✓
Lipid profile[f]	✓	✓	✓	✓
Blood glucose	✓	✓	✓	✓

[a]First 12 weeks: twice per week, 60-minute sessions. Last 12 weeks: twice per week, 60-minute sessions + 1 walk session.
[b]N/A: not applicable.
[c]EUROHIS-QOL-8: European Health Interview Survey–Quality of Life 8-item index.
[d]PHQ-9: 9-item Patient Health Questionnaire.
[e]PANAS: Positive and Negative Affect Schedule.
[f]Total cholesterol, high-density lipoprotein cholesterol, direct low-density lipoprotein cholesterol, and triglycerides.

Statistical Analysis

Statistical analyses will be performed using SPSS Statistics for Windows (version 29.0; IBM Corp). Descriptive statistics will be calculated for all variables. Data distribution will be assessed, and parametric or nonparametric tests will be selected accordingly.

Control of Selection Bias

Given the nonrandomized design, rigorous analytical strategies will be implemented to minimize the impact of selection bias and confounding. A propensity score representing the probability of allocation to the exercise program conditional on baseline characteristics will be estimated using logistic regression, with participation in the exercise intervention as the dependent variable. The following covariates will be included in the propensity score model: sociodemographic variables (eg, age and sex), clinical features relevant to psychotic disorders (eg, duration of illness and medication use), functional status, lifestyle-related factors (eg, baseline physical activity levels and smoking status), socioeconomic indicators, and distance from the clinic. These factors have been selected based on their potential influence on both group allocation and study outcomes.

Following estimation, inverse probability of treatment weighting (IPTW) will be applied to create a weighted pseudopopulation in which baseline covariates are balanced across groups. Covariate balance after weighting will be assessed using standardized mean differences, with values <0.1 considered indicative of adequate balance.

Primary outcome analyses will be conducted in the IPTW-weighted sample using multivariable regression models adjusted for clinically relevant baseline covariates identified a priori based on the existing literature.

As a sensitivity analysis, propensity score matching will also be performed using a nearest-neighbor algorithm with a predefined caliper to ensure comparability between individuals in the exercise and control groups. Analyses conducted in the matched sample will be used to evaluate the robustness of the findings. These combined procedures aim to approximate the balance typically achieved through randomization and strengthen causal inference in this quasi-experimental study of individuals with psychotic disorders.

Inferential Statistics

To examine changes over time, repeated-measures analyses are planned. Mixed-effects models will be used to evaluate group×time interactions while accounting for within-subject correlations and missing data. Effect sizes (partial η^2 or Cohen *d*) will be reported alongside 95% CIs. Statistical significance will be set at $P<.05$.

Biomarker changes over time will be analyzed using the same mixed-effects modeling framework described above. Models will be adjusted for relevant baseline covariates identified a priori based on clinical relevance and existing literature.

Results

The study was funded in January 2026 by the Universidade de Trás-os-Montes et Alto Douro (protocol ID 2024.04489.BDANA).

Data collection commenced on January 1, 2026, and is anticipated to conclude by October 31, 2026, for the primary outcome, with full study completion by November 30, 2026. At the time of manuscript submission in May 2026, 25 participants had been recruited toward the target sample of 48. Data analysis is scheduled for late 2026, and the final results are expected to be submitted for publication in spring 2027.

Discussion

Principal Findings

This study protocol describes a structured multimodal exercise intervention integrated into routine outpatient psychiatric care for individuals receiving LAI antipsychotics. The principal anticipated findings are that the intervention will lead to significant improvements in psychological symptomatology, functional capacity, and cardiometabolic health while also promoting favorable adaptations in neurobiological markers such as BDNF. If confirmed, these findings may support the integration of supervised exercise programs as adjunctive strategies within public mental health services.

The present protocol provides a structured framework for implementing a multimodal exercise intervention within outpatient psychiatric services for individuals treated with LAI antipsychotics. By detailing the components of the intervention, including exercise type, progression, supervision, and monitoring procedures, the protocol aims to facilitate replication of the program in similar clinical contexts. Despite increasing evidence supporting the benefits of physical exercise for individuals with psychosis, the integration of such interventions into standard clinical practice remains limited, particularly among populations receiving LAI treatments.

The research design reflects clinical conditions frequently encountered in outpatient psychiatric services. The adoption of a multimodal exercise program combining aerobic, strength, mobility, and flexibility components aligns with current evidence-based recommendations for physical activity in individuals with severe mental disorders. In addition, the inclusion of multiple assessment domains, including functional performance, metabolic parameters, psychological outcomes, and neurobiological markers, provides a multidimensional perspective on the potential mechanisms through which exercise may influence both mental and physical health outcomes in this population. The integration of feasibility indicators, such as adherence and acceptability, also allows evaluation of the practical implementation of the intervention within a routine health care setting.

Special consideration has been given to safety aspects related to the combination of physical exercise and LAI antipsychotic treatment. Reports have suggested that intense physical exercise may influence the pharmacokinetics of depot antipsychotics, potentially through increased blood flow at the injection site, which could affect drug absorption and contribute to the emergence or worsening of extrapyramidal symptoms [54]. However, current evidence remains limited and is largely based on case reports [55]. To mitigate potential risks, the present intervention adopts a moderate-intensity multimodal exercise approach, with continuous monitoring of participants' clinical status and close collaboration with the treating psychiatric team. Any worsening of extrapyramidal symptoms or other adverse events will be systematically recorded as part of the safety monitoring procedures.

If the intervention proves feasible and acceptable, this protocol may contribute to the development of structured exercise programs as adjunctive strategies within public mental health services. Given the high prevalence of cardiometabolic comorbidities among individuals with psychotic disorders, particularly those receiving long-term antipsychotic treatment, lifestyle interventions such as supervised exercise programs may represent an important component of comprehensive care. By integrating clinical outcomes with biological and functional indicators, the present study may provide preliminary evidence supporting the role of exercise as a complementary approach for improving both physical and mental health outcomes in this vulnerable population.

Limitations

Several limitations should be considered when interpreting the results of this study. First, the nonrandomized quasi-experimental design was adopted owing to practical constraints such as unequal access to supervised exercise sessions and transportation barriers, which may limit participation and are likely to occur in multiple clinical settings. These factors may introduce selection bias and reduce comparability between groups. Although this design reflects pragmatic clinical conditions, it may compromise the internal validity of causal inferences. To address these concerns, rigorous analytical strategies have been incorporated to mitigate selection bias, including propensity score adjustment and sensitivity analyses. These methods are expected to strengthen the internal validity of the study and align the design with recommended approaches for pragmatic, real-world clinical research where random allocation is impractical. Second, maintaining long-term adherence to structured exercise interventions among individuals with severe mental disorders remains a recognized challenge. To address this issue, the intervention incorporates supervised sessions and a gradual transition toward partially autonomous physical activity during the later phase of the program.

An additional limitation relates to the clinical heterogeneity associated with LAI antipsychotics, as different compounds and dosages may influence metabolic profiles and clinical outcomes. Although medication type and dosage will

be documented throughout the study, the modest sample size may limit the ability to fully control for these factors in statistical analyses. Furthermore, the inclusion of neurobiological markers, such as BDNF, together with peripheral indicators related to dopaminergic and serotonergic pathways, should be considered exploratory. Peripheral measurements of these biomarkers do not directly reflect central nervous system activity; therefore, findings related to these variables will be interpreted cautiously and primarily as hypothesis-generating observations.

The findings of this study will be disseminated through peer-reviewed publications and presentations at national and international conferences to reach the broader scientific community. Furthermore, a local dissemination plan includes sharing the results with clinical stakeholders and the administrative board of ULSTMAD to facilitate the potential translation of this protocol into routine clinical care.

Overall, this protocol provides a structured methodological framework for evaluating the feasibility and safety of implementing a multimodal exercise intervention for outpatients with psychotic disorders who are treated with LAI antipsychotics. By focusing on both implementation processes and multidimensional health outcomes, the study may contribute to the development of integrated lifestyle interventions within routine psychiatric care and support future research aimed at improving the physical and mental health of individuals living with psychotic disorders.

Conclusion

This protocol establishes a rigorous framework for integrating supervised exercise into the psychiatric treatment of individuals receiving LAI antipsychotics. Beyond its methodological structure, this study addresses a critical gap in clinical practice by evaluating a pragmatic lifestyle intervention within a health care setting. If the anticipated improvements in functional capacity and neurobiological markers are observed, this work could provide the necessary evidence to transform standard psychiatric care, positioning structured exercise as an essential, rather than optional, adjunctive therapy. Ultimately, this research aims to promote a more holistic recovery model that targets both the physical and mental health of a population that has traditionally been underserved.

Generative AI Use

The authors declare that generative AI was used in the creation of this manuscript. Generative AI (Gemini 3 Flash) was used for proofreading and editing, adapting and adjusting emotional tone, and reformatting. The authors verified all outputs of the tool used in the preparation of this manuscript and take full responsibility for the final content of the manuscript.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author, SS.

Authors' Contributions

Conceptualization: SS
Data curation: SS
Formal analysis: SS, EC
Intervention delivery: SS
Methodology: SS
Project administration: SS
Supervision: DM, MPM
Writing – original draft: SS
Writing – review & editing: SS, DM, EC, MPM

Conflicts of Interest

None declared.

Checklist 1

SPIRIT checklist.
[PDF File (Adobe File), 248 KB-Checklist 1]

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Abbreviations

BDNF: brain-derived neurotrophic factor
EUROHIS-QOL-8: European Health Interview Survey – Quality of Life 8-item index
IPTW: inverse probability of treatment weighting
LAI: long-acting injectable
PANAS: Positive and Negative Affect Schedule
PHQ-9: 9-item Patient Health Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
ULSTMAD: Unidade Local de Saúde de Trás-os-Montes e Alto Douro
WHOQOL-BREF: World Health Organization Quality of Life Instrument-Abbreviated Version

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