

Protocol

Nutritional Supplementation for Obsessive-Compulsive Disorder: Protocol for a Systematic Review of Randomized Controlled Trials

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a chronic mental health condition, and standard treatment often results in incomplete symptom relief. Growing evidence suggests that nutritional supplements, including vitamins, minerals, and amino acids, may serve as potential adjunctive treatments for OCD by influencing neurotransmitter regulation and inflammation.

Objective: Our systematic review aims to assess the comparative efficacy of nutritional supplements on relevant clinical outcomes in individuals with OCD.

Methods: A protocol was developed and registered for this systematic review. Randomized controlled trials assessing the efficacy of nutritional supplementation compared with standard treatments (pharmacological and psychological interventions) will be included. Primary outcomes are changes in cognitive performance, quality of life, and psychiatric symptoms. Secondary outcomes include the presence of comorbidities or multimorbidities (eg, metabolic syndrome). Systematic searches will be conducted in MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov from their inception onward. Two independent researchers will screen the citations and full-text studies. The risk of bias and study quality will be evaluated using validated tools, and association measures with 95% CIs will be calculated. Potential sources of heterogeneity will also be analyzed.

Results: The search commenced in January 2025. Between June and August 2025, studies were identified and the full texts reviewed. Data extraction is anticipated to be completed in September 2025. The final synthesis is scheduled for December 2025.

Conclusions: We aim to address the gaps in the current treatment paradigm for OCD by evaluating the efficacy of nutritional supplementation as an adjunctive therapy. These findings may provide insights into the potential of these supplements to improve cognitive and psychiatric outcomes. This protocol establishes a foundation for the rigorous synthesis of available evidence, which may inform future clinical practices and support the integration of nutritional strategies in OCD management.

Trial Registration: OSF Registries 10.17605/OSF.IO/NZ5MU; <https://osf.io/NZ5MU>

International Registered Report Identifier (IRRID): DERR1-10.2196/80240

KEYWORDS

obsessive-compulsive disorder; nutritional supplementation; systematic review; cognitive function; quality of life

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental health condition characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions). The lifetime prevalence of OCD is estimated to be approximately 2%-3% globally, making it a significant public health concern [1]. Despite the availability of various pharmacological and psychological treatments, a significant proportion of individuals with OCD experience persistent symptoms and impaired quality of life [2]. This underscores the urgent need for innovative therapeutic approaches to improve outcomes in this population.

Recently, interest has emerged in the potential role of nutritional supplements as adjunctive treatments for OCD. Nutritional supplements, including vitamins, minerals, and amino acids, have been hypothesized to influence brain function and mental health by modulating neurotransmitter systems and reducing oxidative stress [3,4]. For example, vitamin D regulates serotonin, a neurotransmitter implicated in OCD pathophysiology [5]. Similarly, vitamin B and glycine have been investigated for their potential to support cognitive function and reduce anxiety symptoms [6].

Existing research has examined various nutritional supplements, including vitamins D and B12 and glycine, with some studies reporting promising results in reducing obsessive-compulsive symptoms [7,8]. Marazziti et al [7] found that vitamin D supplementation significantly improved OCD symptoms in a small cohort of patients. Cleveland et al [8] demonstrated that glycine, an inhibitory neurotransmitter, reduces anxiety and improves cognitive function in individuals with OCD. However, these studies have limitations, including small sample sizes, short follow-up periods, and methodological heterogeneity. Thus, a rigorous synthesis of the available evidence is essential to draw definitive conclusions and guide clinical practice. Moreover, the existing pharmacological treatments for OCD—primarily selective serotonin reuptake inhibitors—are associated with a range of side effects and are ineffective in all patients [9]. Psychological interventions such as cognitive-behavioral therapy are effective but require substantial time and resources, which may not be accessible to all individuals. Consequently, there is growing interest in complementary and alternative therapies, including nutritional supplementation, as additional treatment options [10].

This study aims to assess the comparative efficacy of nutritional supplements on relevant clinical outcomes in individuals with OCD. Our approach involves a systematic review of randomized controlled trials (RCTs) comparing nutritional supplements alone or in combination with standard treatments, with placebo or other active treatments. Adults with OCD will be included according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

[10,11], and standard treatments are defined according to the National Institute for Health and Care Excellence clinical guideline CG31 for OCD and body dysmorphic disorders [12].

Although previous reviews have addressed nutritional supplementation for depression [3] and schizophrenia [4], no systematic review has comprehensively synthesized the evidence specific to OCD. Furthermore, findings in small clinical trials [3] are inconsistent: some report improvements in OCD symptoms, while others show no effect. This discrepancy highlights the need to clarify the role of nutritional supplements in managing OCD and to resolve uncertainties about the type of supplement, dosage, and duration of treatment.

The specific research problem addressed in this study is the need to determine the efficacy of nutritional supplements in improving primary outcomes such as cognition, quality of life, and psychiatric symptoms, as well as secondary outcomes such as comorbidity rates [13,14]. We hypothesized that nutritional supplementation when combined with validated pharmacological and psychological interventions would offer additional benefits in managing OCD symptoms compared with standard treatment alone.

Although this protocol aims to maximize internal validity, particular attention has also been given to ensuring its relevance to real-world populations with OCD by addressing comorbidities, sample heterogeneity, and implementation challenges.

Methods

Study Design and Ethical Considerations

This protocol has been registered in the Open Science Framework (OSF; registration: osf.io/NZ5MU). This study will be conducted according to the guidelines of the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement [15,16] (see [Multimedia Appendix 1](#)). Ethics approval is not required for the conduct of this study.

Criteria for Considering Studies for This Systematic Review

Types of Studies

We will include RCTs that have compared a nutritional supplement alone or in combination with a standard treatment with a placebo or another alternative active treatment. Standard treatment is defined as treatment validated by the National Institute for Health and Care Excellence clinical guidelines, whether pharmacological and/or psychological.

We will exclude crossover trials because obsessive ideation and compulsions may evolve over time, and washout periods themselves may induce detrimental effects in the second period of the trial. We will also exclude cluster RCTs because of the

potential for identification/recruitment bias and overestimation of the precision of the results.

Types of Participants

We will include adults aged ≥ 18 years with OCD. Participants will be defined as having OCD by using the DSM-5 criteria. We will exclude studies in which participants have organic causes of OCD. Additionally, we will exclude participants with comorbid psychiatric disorders such as schizophrenia, bipolar disorder, depressive disorder, eating disorders, and suicidal behavior. Participants presenting with subthreshold symptoms of depression or anxiety will not be excluded, provided that the diagnostic thresholds for another psychiatric disorder are not met.

Participants with organic causes of OCD, including temporal lobe epilepsy, will be excluded to prevent confusion with neurobiological mechanisms. Individuals with subthreshold depressive or anxiety symptoms will be eligible, provided they do not meet all the diagnostic criteria for another psychiatric disorder. This approach ensures that we retain internal validity while keeping our findings relevant to the diverse OCD population encountered in clinical practice.

Types of Interventions

We will include nutritional supplementation (eg, vitamin D, vitamin B12, glycine) combined with pharmacological and psychological interventions that have been clinically validated to reduce obsessive-compulsive symptoms.

Comparator

The comparator will include other nutritional supplements, placebos, or an alternative active drug. Co-interventions will be acceptable in both the intervention and comparison groups provided that they are administered equally across all groups in the trial. If a trial included multiple arms, any arm that met the inclusion criteria will be included.

We will consider intervention durations of 12 weeks or longer because nutritional supplementation is more likely to affect the relevant primary outcomes during this timeframe. We do not impose a limit on the maximum duration of intervention. Studies reporting one or more of our outcomes at least 6 months after the start of the intervention will be included. Therefore, the minimum follow-up duration of the studies will be set at 6 months.

Trials should include a minimum intervention duration of 12 weeks and at least 6 months of follow-up to assess the sustained effects. A sensitivity analysis will also incorporate trials with shorter follow-up periods to assess the robustness of the findings.

Types of Outcome Measures

The primary and secondary outcomes are defined as outlined below. Trials will not be excluded solely because one or several of our primary or secondary outcome measures are not reported in the publication. However, if none of our primary or secondary outcomes are reported, we will include the trial only for information purposes.

Primary Outcomes

We consider the following primary outcomes.

1. Cognition: measured using validated instruments (eg, Stroop Color and Word Test, Complutense Verbal Learning Test, Trail-Making Test).
2. Quality of life: measured using validated instruments (eg, Functional Assessment Short Test and Short Form-36 item Health Survey questionnaire).
3. Psychiatric symptoms: measured using validated instruments that include one or more of the following domains (eg, depression, anxiety, stress, obsessions, compulsions, psychotic symptoms).

Secondary Outcomes

We consider the following secondary outcome: morbidity or comorbidity, which is the occurrence of physical illnesses (eg, diabetes, metabolic syndrome, cardiovascular events) at any time before or after the initiation of the intervention with nutritional supplementation (eg, Kaplan-Feinstein Scale, Charlson Comorbidity Index).

Search Methods for the Identification of Studies

We will attempt to identify all the relevant trials, regardless of their language, publication status (published, in press, or in progress), or publication date. To minimize bias in the search results, we will develop a search strategy following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions [17].

Electronic Searches

We will search the following electronic databases: MEDLINE through PubMed (National Library of Medicine), Embase through the Elsevier platform, CENTRAL via the Cochrane Library, and ClinicalTrials.gov. We will search these databases since their inception. The research team will design and execute a detailed search strategy by using the same strategy with appropriate adjustments for each database. Search terms will include keywords related to names/clusters of nutritional supplements, cognition, quality of life, psychiatric symptoms, comorbidity, and randomized studies. No restrictions will be imposed on the dates. The initial literature searches of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews began in January 2025. The draft strategies for MEDLINE and Embase are provided in [Multimedia Appendix 2](#).

Searching Other Resources

We will search the reference lists of all identified trials, relevant review studies, and current treatment guidelines to identify additional potentially eligible studies. We will contact the authors of the identified studies and research groups known to be active in pharmacological interventions for OCD to request unpublished material or further information on ongoing studies. The search will be conducted and updated as necessary before publication. We will provide the actual dates of the electronic search during the review stage.

Data Collection and Analysis

Selection of Studies

First, 2 researchers will independently screen the titles and abstracts of the studies obtained from the initial searches, masked to each other's decisions and based on the eligibility criteria. We will obtain the full texts of all potentially relevant reports. Second, these full texts will be examined in detail and screened for eligibility, with the reasons for exclusion recorded. Third, the references of all the considered studies will be manually searched to identify any relevant reports missed by the search strategy. We will examine the full studies and supplementary materials containing data and analyze their general and methodological characteristics and study results. The final versions of the studies available online will also be reviewed.

The authors will be contacted in the case of ambiguity or missing data. Duplicate records will be identified and excluded, and multiple reports from the same study will be collated such that the analysis, rather than individual reports, will serve as the unit of interest in the review. Disagreements will be resolved by consensus or consultation with a third reviewer. If disagreements cannot be resolved, we will categorize the study as "awaiting classification" and contact the authors for clarification. Studies for which relevant data cannot be obtained will also be classified as "awaiting classification."

Data Collection and Management

Once the searches have been performed, items identified in the databases will be imported into Rayyan software (Rayyan Systems) [18]. Following the recommendations of the PRISMA 2020 declaration [19], a flowchart showing details of the studies included and excluded at each stage of the selection process will be provided.

Data from each report will be used to build evidence tables describing the included studies. A standardized data extraction form will include the following information of interest: first author's name, year of publication, type of nutritional supplementation (eg, vitamin B12), outcomes (eg, memory, depression), comparison, participant details (eg, diagnostic criteria, age, sex, years of education, comorbidity, risk factors), and maximally adjusted effect sizes, including corresponding 95% CIs, hazard ratios, odds ratios, and relative risks.

When sufficient data are available, random-effects meta-analyses will be performed. Continuous outcomes will be synthesized as standardized mean differences (Hedges g) and dichotomous outcomes as risk ratios with 95% CIs. Heterogeneity will be assessed using the I^2 statistic, and subgroup analyses will be conducted based on supplement class, dose, and duration. Sensitivity analyses will examine the influence of study quality and follow-up duration. If quantitative synthesis proves unfeasible, results will be summarized narratively by supplement type and clinical outcome.

Subgroup analyses will be performed by supplement class (eg, amino acids, vitamins, fatty acids), dose, and duration of treatment. Implementation in practice may be influenced by variability in supplement quality, dosing guidelines, patient

adherence, and placebo effect. These factors will be considered when interpreting the results.

If meta-analysis is not feasible, a structured narrative synthesis will be performed, organized by supplement type, outcome measure (symptom severity, cognition, quality of life), and study quality. Findings will be contextualized in relation to methodological rigor and clinical applicability.

Risk of Bias and Quality Assessment in the Included Reviews

At least 2 researchers will independently assess the risk of bias and the quality of each study, and any disagreements will be resolved by discussion. For the RCTs, we will evaluate the risk of bias in each included study by using the Cochrane Risk of Bias 2.0 tool [20]. This tool considers random sequence generation, allocation concealment, blinding of the participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. We will judge the risk of bias for each study based on these criteria and classify the studies as having a low, high, or unclear risk of bias. The quality of the RCTs will also be assessed using the Cochrane Collaboration tool to assess the risk of bias [21]. This scale evaluates 7 items as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases [22]. Each item will be scored as high risk, low risk, or unclear risk based on the available evidence. Published trial results will be systematically checked against trial registry entries (eg, ClinicalTrials.gov) to assess for selective reporting of results and potential publication bias.

Results

The search commenced in January 2025. Between June and August 2025, studies were identified and the full texts reviewed. Data extraction is anticipated to be completed in September 2025. The final synthesis is scheduled for December 2025.

Discussion

We anticipate that our systematic review will synthesize current evidence from RCTs, offering insights into the efficacy of vitamins, minerals, and amino acids in improving cognitive performance, psychiatric symptoms, and overall quality of life in individuals with OCD.

This protocol describes a systematic review of RCTs that evaluates the efficacy of nutritional supplements as adjunctive treatments for OCD. The systematic review will establish the extent of clinical evidence supporting the association between nutritional supplementation and improvements in cognition and psychiatric symptomatology in a rigorous and reproducible manner.

Emerging evidence suggests potential benefits of nutritional supplementation as an adjunctive treatment to enhance cognitive performance, quality of life, and psychiatric symptoms in individuals diagnosed with OCD. Understanding the complex relationship between nutritional supplementation and clinical

outcomes in OCD could serve as a foundation for integrating these interventions into clinical practice as complementary approaches to standard treatments. This perspective may be particularly valuable for individuals who are resistant to treatment, experience adverse effects of current pharmacotherapies, or have comorbidities. Although reviews on depression [3] and schizophrenia [4] have highlighted the beneficial effects of nutritional supplements, evidence of their effects in patients with OCD remains scarce and heterogeneous. Our systematic review will address this deficiency by applying standardized risk of bias tools and synthesizing the different classes of supplements.

The proposed systematic review will adhere to the reporting standards outlined in the PRISMA 2020 statement [15,16]. Any amendments made to this protocol will be documented and outlined in the final manuscript. The results will be disseminated

through presentations at scientific conferences and through publications in peer-reviewed journals. All data underlying the findings reported in the final manuscript will be deposited in OSF [23], a cross-disciplinary public repository.

The strengths of this protocol include prospective registration, comprehensive search strategies, and adherence to PRISMA-P. Limitations include anticipated heterogeneity among interventions and trial quality, as well as potential publication bias. These challenges will be mitigated by sensitivity analyses and comparison with trial registries.

Finally, we aim to identify the knowledge gaps that future research can address. The implications for future studies will be discussed in the final manuscript. The findings of this review will determine whether specific supplements warrant further large-scale trials for OCD and will guide the refinement of treatment protocols.

Acknowledgments

The authors would like to thank all colleagues and institutions that indirectly supported the development of this work. Artificial intelligence tools were not used in the design, data collection, analysis, or interpretation of results. Artificial intelligence assistance was limited to language editing and formatting of the manuscript.

Funding

This study was supported by the Ministry of Education of the Valencian Regional Government (PROMETEO/CIPROM/2022/58) and Spanish Ministry of Science, Innovation and Universities (PID2021-129099OB-I00). RTS receives funding from CIBERSAM/Institute of Health Carlos III. The funder was not involved in the protocol design or decision to submit it for publication, nor will be involved in any aspect of the study.

Authors' Contributions

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The study protocol was conceived by PSM and JVSO, with critical inputs from PCG, VBM, DMSG, IFD, and RTS. JVSO registered the protocol in the Open Science Framework. All the authors provided input for the study design, edited the draft protocol, and commented on the manuscript for important intellectual content. RTS accepts full responsibility for the finished paper and organizes the decision to publish it. RTS and VBM also contributed equally to this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-P checklist.

[\[DOCX File , 34 KB-Multimedia Appendix 1\]](#)

Multimedia Appendix 2

Detailed search strategies.

[\[DOCX File , 29 KB-Multimedia Appendix 2\]](#)

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition

OCD: obsessive-compulsive disorder

OSF: Open Science Framework

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

RCT: randomized controlled trial

Edited by A Schwartz; submitted 14.Jul.2025; peer-reviewed by B Najand; comments to author 28.Aug.2025; revised version received 13.Sep.2025; accepted 23.Sep.2025; published 18.Nov.2025

Please cite as:

Soldevila-Matías P, Sánchez-Ortí JV, Correa-Ghisays P, Balanzá-Martínez V, Macías Saint-Gerons D, Fuentes-Durá I, Tabarés-Seisdedos R

Nutritional Supplementation for Obsessive-Compulsive Disorder: Protocol for a Systematic Review of Randomized Controlled Trials
JMIR Res Protoc 2025;14:e80240

URL: <https://www.researchprotocols.org/2025/1/e80240>

doi: [10.2196/80240](https://doi.org/10.2196/80240)

PMID: [41252714](https://pubmed.ncbi.nlm.nih.gov/41252714/)

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