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Protocol

Effects of Physical Exercise on Executive Function in Adults with Depression: A Systematic Review and Meta-Analysis Protocol

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Abstract: Physical exercise is a low-cost and easy-to-implement therapeutic option proposed to reduce the negative effect of depression on the executive function cognitive dimension, including working memory, inhibition, and cognitive flexibility. Although a considerable amount of scientific literature on the topic is currently available, the effects of physical exercise interventions on the executive functions in adults with depression remain unclear. The aim of this review protocol is to synthesize the effects of physical exercise interventions on executive functions in adults with depression. Databases including Web of Science, PubMed, Scopus, and EBSCO will be searched for studies by combining keywords and different medical subject headings to identify and evaluate the relevant studies from inception up to September 2022. This study will consider longitudinal studies (duration, ≥3 weeks) with a minimum of one experimental group and pre- and post-intervention measurements involving adults with depression aged 18–65 years. Studies will be included if these reported ≥1 measures of executive function, including dimensions of working memory, inhibition, and cognitive flexibility. The Physiotherapy Evidence Database (PEDro) scale will be used to assess the methodological quality of studies. The DerSimonian and Laird random-effects model will be used for meta-analyses, with effect size (ES, i.e., Hedges' g) values reported with 95% confidence intervals (95% CIs), and $p \leq 0.05$ will indicate statistical significance. The ES values will be calculated for working memory, inhibition, and cognitive flexibility in the experimental and control groups before and after the intervention program. Our results can help professionals and stakeholders in making better evidence-based decisions regarding the implementation of physical exercise programs in adults with depression and providing relevant information to facilitate the functional performance of this population in complex daily tasks where executive functions are essential. No ethical approval is required for this study. PROSPERO registration number: CRD42022358339.

Keywords: working memory; inhibition; cognitive flexibility; executive function; mental processes; depressive disorder; neurocognitive disorders; exercise

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1. Background

Depressive disorders, including major depressive disorder and dysthymia, are the most frequent mental health conditions reported among the general population according to the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, which provides a systematic scientific analysis of published data on the incidence, prevalence, and mortality of 369 diseases and injuries for 204 countries and territories. In 2019, it was estimated that 3440 persons per 100,000 (both women and men combined) had depressive disorders, the incidence being higher among women (4158 per 100,000) than men (2713 per 100,000) [1]. Moreover, depression increases the risk of other diseases compared to the general population (e.g., diabetes, metabolic syndrome, and cardiovascular diseases) [2–5], increasing the burden for both families and society [6–9]. The Global Burden of Disease Project estimated that depression will be among the top three causes of the burden of disease in 2030, based on global projections of economic and social development [10]. People with depression usually experience altered mood or loss of interest and pleasure, as well as low self-esteem, guilt, tiredness, sleep disturbances, and altered cognitive symptoms (e.g., processing speed, visual selective attention, verbal learning, long-term memory, and executive functioning) [11–14]. Depression is often chronic, and in these cases it is associated with higher levels of depressive symptoms, somatic symptoms, and cognitive dysfunction [12,15].

Several cognitive functions are compromised in the clinical course of depression, and cognitive deficits are a central characteristic in this pathology [12–14]. Rock et al. [13] demonstrated that approximately two thirds of patients with depression have cognitive deficits and that this persists in at least one third of subjects in whom mood-related symptoms have already ceased. Similarly, after remission from a depressive episode, deficits in selective attention, working memory, and long-term memory remain, with patients even experiencing detrimental effects with repeated episodes [12]. Therefore, the cognitive deficits in depression could manifest independently of other symptoms, even though it interacts with relevant emotional and social factors in order to contribute to individuals' social functioning [16–19]. The executive function is among the most affected cognitive dimensions and stands out owing to its significant contribution to the psychosocial adaptation of individuals with depression. Even after remission, it influences occupational and relational performance, regardless of the clinical improvement of other types of symptoms [13,19,20].

Traditional antidepressant therapy focuses on the remission of mood-related symptoms without necessarily focusing on cognitive deficits [21]. This could provide insufficient tools for patients to achieve optimal functioning in highly demanding daily tasks occurring in a fluctuating environment, where it is important to make decisions or manage a large amount of information efficiently in order to meet objectives (e.g., academic or work environments) [20,22,23]. In this sense, physical exercise has been proposed as a low-cost and easy-to-implement therapeutic option for adults with depression to lower the functional impact of cognitive symptoms, and it can be applied as a single, adjuvant, or combined therapy [20,24,25]. The physiological mechanisms that have been described as those involved in such an effect include the expression of neurotransmitters, neurotrophic factors (e.g., Brain-Derived Neurotrophic Factor), synaptic plasticity, the modification of inflammatory pathways, the activation of hormonal mechanisms, and cerebrovascular function [26–30].

Exercise is a physical activity performed systematically according to a planned program to improve fitness and physical or health-related outcomes [31]. Clinical research on the effects of chronic exercise on the cognition of adults with depression has mainly used aerobic exercise training programs [32–35], but has also included strength training [36] or multicomponent training (coordination, endurance, and strength) [30]. The results of these studies show improvements in short-term memory [34,35], inhibitory control [33], processing speed [35,37], attention, verbal fluency, and cognitive flexibility [37] after implementing chronic exercise programs. However, other studies did not find improvements in cognitive measures when comparing physical exercise with a control condition in this

population [36,38]. Hoffman et al. [38] explain that the lack of effect of their intervention program on the cognitive functioning of adults with depression could be explained by the lack of baseline cognitive impairment among participants, the diagnostic characteristics of depression (mild to moderate severity, non-recurring, early onset, and with good response to treatment), the relatively short duration of treatment (4 months in both studies), and a small percentage of improvement in the aerobic capacity of participants (6%). This may not have been enough to cause effects on cognitive functioning near the end of the intervention. However, Krogh et al. [36] suggest that the lack of significant effects of their 4-month training programs (strength training versus relaxation and aerobic training versus relaxation) on the cognitive abilities of adults with depression could be due to the following factors: possible antidepressant effect of the control condition, lack of patient and therapist blinding when allocating treatment, inclusion of participants who had received prior pharmacological treatment for more than 6 weeks, low participation in training programs (approximately 50%), low scheduled weekly frequency (twice a week), and possible initial absence of cognitive deficit among patients.

Previous systematic reviews assessed the effect of exercise on mood-related symptoms in participants with depression [39–41]. Additionally, previous studies included memory and attention as primary or secondary outcomes in their analyses [24,42]. However, only two meta-analyses reported the effects of physical exercise on cognitive function in adults with depression, including global cognition and different cognitive domains such as processing speed, attention/vigilance, verbal learning and memory, and visual learning and memory [22,43]. The cognitive domains chosen in both studies were categorized in accordance with the structure of the MATRICS Consensus Cognitive Battery (MCCB) [44]. This allows for comparing the results obtained from both reviews; however, it does not show results associated with the three main dimensions of executive function (that is, inhibition, working memory, and cognitive flexibility), which are especially relevant in the symptomatology and functional performance of this population [45–48]. The reviews mentioned above [22,43] also included interventional studies with a meditation component [49] in their meta-analyses, thus limiting the interpretation of their results in terms of the independent effect of physical exercise. Moreover, the increasing number of publications in this field will likely render any systematic review quickly outdated. Indeed, in rapidly emerging research fields, 25% of systematic reviews are obsolete within 2 years and 50% within 5 years [50]. Considering that the aforementioned reviews [22,43] were conducted in 2017, an update on the topic would be advisable.

Therefore, we aim to synthesize the currently available scientific literature related to the effects of physical exercise programs on executive functions in adults with depression, compared to a control condition, through a systematic review with meta-analysis protocol.

2. Methods

2.1. Research Question

Does physical exercise improve executive functions in adults with depression when compared to controls?

2.2. Review Strategy

Following international standards [51], a systematic search was performed in electronic databases (PubMed, Web of Science, EBSCO, and Scopus) without filters (e.g., sex) or date restriction up to September 2022. Medical subject headings (MeSH) and free-text terms were used to identify and evaluate relevant studies (Appendix A, Table A1). Additionally, the reference lists of included studies and identified reviews, will be manually searched for other potentially eligible trials. In the same databases, systematic reviews will be searched with the filters "systematic review" or "review" after the usual search strategy. Independent experts (n = 2) in executive functions will be consulted to review the list of included items and propose possible items for inclusion. The experts will be selected

from the Expertscape rank for "Executive+function" that can be found in the link: https://www.expertscape.com/ex/executive+function (accessed on 21 September 2022).

2.3. Eligibility Criteria

Table 1 presents details regarding inclusion–exclusion criteria. Of note, to be included, studies should incorporate valid tools, such as the N-back task [52], the Stroop task [53] and the Trail Making Test-Part B [54].

Table 1. Eligibility Criteria.

	Inclusion	Exclusion
Population	Participants aged 18–65 years diagnosed with major depression or unipolar depression according to the criteria of a validated instrument, such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or the International Classification of Diseases 10th Revision (ICD-10).	Children, adolescents, or older adults. Presence of another primary neurological or psychiatric diagnosis (e.g., dysthymia, bipolar disorder, dementia, or schizophrenia). Medical comorbidities limiting participation in physical exercise activities (e.g., significant musculoskeletal difficulties, or cardiorespiratory disorders). Active alcohol or drug abuse or dependence. Pregnant or lactating women. Intellectual disability.
Intervention	Physical exercise (≥3 weeks) applied as independent therapy or therapy complementary to pharmacological treatment. Interventions should include aerobic training or strength training or programs that combine different types of exercises (e.g., endurance, coordination, or strength training).	Acute exercise (i.e., a single bout of exercise). Chronic exercise intervention programs combined with meditation. Interventions not related to physical exercise.
Comparator	A group made up of adults diagnosed with depression not exposed to physical exercise intervention. The control condition may be active (e.g., relaxation techniques) or passive (e.g., placebo).	No comparator.
Outcome	Working memory, inhibition, or cognitive flexibility, assessed with valid direct techniques before and after intervention.	Executive functions measured indirectly (e.g., questionary).
Study design	Controlled studies.	Cross-sectional studies.

According to previous studies, a minimum effective duration of 3 weeks was determined for the intervention programs [30,35]. The definition of exercise used corresponds to "a type of physical activity consisting of planned, structured, and repetitive bodily movement, aimed to improve and/or maintain one or multiple components of physical fitness" [55].

2.4. Data Management

Documents will be incorporated into a reference management software, with automatic deletion of repeated documents. Document's titles and abstracts will be independently assessed for inclusion by two authors (F.C.-O. and C.C.-J.), and any interauthor discrepancies will be resolved by consensus with a third author (R.R.-C.).

Reference lists of included articles and reviews (those retrieved from original database search) will also be examined. A PRISMA flowchart [51] will be used to document the selection process and the reasons for exclusion where appropriate.

2.5. Data Extraction

One author (F.C.-O.) will complete the data extraction, which will then be verified by a second author (C.C.-J.). The data to be extracted from included studies are: year of publication, author, sample size, characteristics of the participants (sex, age, fitness level, psychiatric diagnosis, severity, comorbidities, and pharmacological treatment), description

of the exercise training program, weekly frequency, intervention length (i.e., weeks), session length (i.e., minutes) and intensity, dimensions of the executive function assessed (i.e., working memory, inhibition, or cognitive flexibility), tasks used (for example, the Stroop test to assess inhibition), and control condition.

From the included studies, the means and standard deviation values from relevant outcomes will be extracted, considering pre- and post-intervention periods. The extracted data will be saved in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). If the required data were not communicated in the includable study, contact protocols previously described will be followed [56,57] Two authors (F.C.-O. and C.C.-J.) will perform the data extraction independently, and a third author (R.R.-C.) will participate in case of conflicts between F.C.-O. and C.C.-J.

2.6. Risk of Bias (Quality) Assessment

Included studies will be assessed for their methodological quality with the Physiotherapy Evidence Database (PEDro) scale, as previously [58–60]. The methodological quality of studies shall be interpreted using the following convention [57,61–63]: ≤3 points—"poor" quality, 4–5 points— "moderate" quality, and 6–10 points— "high" quality. The methodological quality of included studies will be independently screened by two reviewers—F.C.-O. and C.C.-J.—and any disagreements between them will be resolved by consensus with a third reviewer (R.R.-C.).

Independently of their methodological quality, all studies that meet the inclusion criteria will be included in the review. Nevertheless, this aspect will be considered when interpreting and discussing the results.

2.7. Meta-Analyses

Following previous instructions [57], meta-analysis will be performed with ≥3 studies for each outcome [64,65]. Hedges' g effect size (ES), with 95% confidence intervals [95% CIs] will be calculated for the main outcomes, according to the DerSimonian and Laird random-effects model, and categorized as trivial, small, moderate, large, very large, or extremely large (ES < 0.2, 0.2–0.6, >0.6–1.2, >1.2–2.0, >2.0–4.0, and >4.0, respectively) [66]. The I^2 statistic will be used to categorize heterogeneity as low, moderate or high (<25%, 25–75%, and >75%, respectively) [67]. The risk of publication bias will be assessed only if ≥10 studies are available per outcome [68,69] using the extended Egger's test [68], with adjustments according to the trim and fill method [70], with L0 as the default estimator for the number of missing studies [71]. All analyses will be performed using the Comprehensive Meta-Analysis software (version 2, Biostat, Englewood, NJ, USA). Statistical significance will be set at $p \leq 0.05$.

Moderator Analyses

As the responses to exercise programs may be affected by intensity of exercise [22,32] and exercise duration per week [72], these factors will be considered as potential moderator variables between physical exercise and working memory, inhibition, and cognitive flexibility. Additionally, participants gender will be analysed as a potential moderator [73]. Further, baseline depression severity according to the criteria of a validated instrument (e.g., the Hamilton Depression Rating Scale) will be explored as a potential moderator [74]. When appropriate, analyses will be divided using the median split technique. The median will be calculated if at least three studies provide data for a given moderator. Of note, if two experimental groups with the same information for a given moderator are included in a study, only one of the groups will be considered in order to avoid an undue influence on the median calculation. In addition, to minimize heterogeneity, instead of using a global median value for a given moderator, median values will be calculated using only those studies that provide data for the outcome being analyzed.

3. Discussion

Our systematic review is aimed at clarifying the effects of chronic exercise programs on the executive function of adults with depression considering the potential of physical exercise interventions on the executive function of these patients and the considerable literature currently available on the subject. The results can aid professionals and stakeholders in making better evidence-based decisions regarding the implementation of physical exercise programs in adults with depression and providing relevant information to facilitate the functional performance of this population in complex daily tasks where executive functions are essential (e.g., workforce performance), even after the remission of other types of symptoms [75].

Furthermore, participating in activities that involve physical exercise promotes the maintenance and/or improvement of physical condition. It also influences quality of life and the reduction of health risks related to sedentary behaviors and low levels of physical activity [76,77]. In turn, it enhances executive functions, emotional health, and the capacity to respond to daily situations of high cognitive demand, such as university life or work [24,78,79].

Maintaining an active lifestyle and performing activities that favor social contact are excellent ways to develop the executive functions, since the person must manipulate new information, thus responding effectively to the contextual demands. Undoubtedly, motivating people with depression to break their routines and start new activities is challenging; however, it can be an opportunity for many of them to interact with others and to commit to new challenges.

The effects of chronic exercise interventions on working memory, inhibition, and cognitive flexibility will be analyzed. We will also discuss the limitations of this study and those found in the literature in detail in order to analyze the possible lines of research on this topic. Our systematic review will be focused on adults, excluding older adults (age $\geq$ 65 years), as the later may exhibit greater symptoms severity, time until remission, and risk of chronic symptoms [80]. The aforementioned differences usually are in line with differences in physiological markers [81], greater functional deterioration, and greater risk of cognitive deficit [82].

This review is expected to provide further clarification regarding the effects of physical exercise on the executive function of adults with depression through the moderator analyses of gender, baseline depression severity, exercise intensity and weekly exercise duration. Such clarification might help to improve the dose of exercise. The methodological assessment of included studies (and the reasons of exclusion from those not included) may provide an overview of quality aspects that researchers must consider to develop in future intervention projects. Finally, the results will be published in a peer-reviewed scientific journal and will be broadcast to various audiences so that adult patients with depression may benefit from this information, thus helping to improve their functional performance and quality of life.

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Conflicts of Interest: The authors deny any conflict of interest.

Appendix A

Table A1. Specific Search Strategy for Each Database.

Database	Search Strategy
EBSCO	TX (“executive functions” OR “cognitive function” OR cognition OR “inhibitory control” OR inhibition OR “working memory” OR “executive functioning” OR “cognitive flexibility”) AND TX (sport OR “modified sport” OR fitness OR exercise OR “physical activity” OR athletics OR “sport practice”) AND TX (depression OR “depressive disorder” OR “mood disorders” OR “major depressive disorder”)
PubMed	((((((((“executive function”[Title/Abstract]) OR (“cognitive function”[Title/Abstract])) OR (cognition)) OR (“inhibitory control”[Title/Abstract])) OR (inhibition[Title/Abstract])) OR (“working memory”[Title/Abstract])) OR (“executive functioning”[Title/Abstract])) OR (“cognitive flexibility”[Title/Abstract])) AND (((((((sport[Title/Abstract]) OR (“modified sport”[Title/Abstract])) OR (fitness[Title/Abstract])) OR (exercise[Title/Abstract])) OR (“physical activity”[Title/Abstract])) OR (athletics[Title/Abstract])) OR (“sport practice”[Title/Abstract]))) AND ((((depression[Title/Abstract]) OR (“depressive disorder”[Title/Abstract])) OR (“mood disorders”[Title/Abstract])) OR (“major depressive disorder”[Title/Abstract]))
Scopus	((TITLE-ABS-KEY (depression)) OR (TITLE-ABS-KEY (“depressive disorder”)) OR (TITLE-ABS-KEY (“mood disorders”)) OR (TITLE-ABS-KEY (“major depressive disorder”))) AND ((TITLE-ABS-KEY (sport)) OR (TITLE-ABS-KEY (“modified sport”)) OR (TITLE-ABS-KEY (fitness)) OR (TITLE-ABS-KEY (exercise)) OR (TITLE-ABS-KEY (“physical activity”)) OR (TITLE-ABS-KEY (athletics)) OR (TITLE-ABS-KEY (“sport practice”))) AND ((TITLE-ABS-KEY (“executive function”)) OR (TITLE-ABS-KEY (“cognitive function”)) OR (TITLE-ABS-KEY (cognition)) OR (TITLE-ABS-KEY (“inhibitory control”)) OR (TITLE-ABS-KEY (inhibition)) OR (TITLE-ABS-KEY (“working memory”)) OR (TITLE-ABS-KEY (“executive functioning”)) OR (TITLE-ABS-KEY (“cognitive flexibility”)))
Web of Science	((TS = (“executive function” OR “cognitive function” OR cognition OR “inhibitory control” OR inhibition OR “working memory” OR “executive functioning” OR “cognitive flexibility”)) AND TS = (sport OR “modified sport” OR fitness OR exercise OR “physical activity” OR athletics OR “sport practice”)) AND TS = (depression OR “depressive disorder” OR “mood disorders” OR “major depressive disorder”)

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