What Is the Recommended Dose of Physical Activity in the Treatment of Depression in Adults? A Protocol for a Systematic Review

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Abstract: The accurate measurement of physical activity (PA) in adults with depression is critical to identify important health consequences and determinants of this behavior. This study aimed to propose a protocol for a systematic review investigating the recommended dose of PA in the treatment of depression in adults aged 18 to 65 years. Additionally, we intend to examine the effect of PA interventions on the prevalence of depression. This protocol for a systematic review has been submitted in the Prospective International Register submitted in Register of Systematic Reviews of PROSPERO and is being prepared in accordance with the Declaration of Preferential Items for Systematic Reviews and Meta-Analysis Protocols. This protocol provides justification and planned methods for a systematic review to examine the respective dose of PA and how interventions have a beneficial impact on adults with depression.

Keywords: adults; depression; dose-effect; physical activity; treatment

1. Introduction

Depression is a common mental health disorder that can have a major impact on individual well-being and daily functioning [1]. Depression is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep and/or appetite, feelings of tiredness, and poor concentration [2]. In its most severe form, depression can lead to suicide [3,4]. Recently, the World Health Organization [5] indicated depression as the leading cause of disability in adults all around the world, in which nearly 300 million people suffer from this mental illness each year. Depression disorders are the third cause of global disease burden (first in developed countries) and are expected to become the first cause worldwide by 2030, with related suicide rates more likely to worsen [6].

The European Social Research [7] in a study conducted with 21 European countries, showed that women are more likely than males to experience depressive symptoms. This fact, although still with little evidence, seems to be associated with physiological and hormonal differences, low level of education, sociocultural issues, and how stressful situations are dealt with by the person [8]. According to the European Statistical Report report [7], women show more signs of depressive symptoms

(e.g., sadness, tiredness, motivation, and sleep disturbance) than men, with large discrepancies in some countries. The largest discrepancies are found in Portugal (30.9% of women compared to 15.8% of men), Poland (25.3% compared to 11.3%), Spain (24.7% compared to 12.8%), and Germany (20.2% compared to 9%). The first National Mental Health Epidemiological Study, a part of the World Mental Health Survey Initiative of the World Health Organization (WHO), and Harvard University, advanced our understanding of the measurement of depression and the application of protocols oriented to treat patients with this mental illness.

The Diagnostic and Statistical Manual of Mental Disorders–5 (DMS-5) has stipulated nine criteria for depression of which five must be present for diagnosis [9]. These symptoms include constant mood changes, extreme interest or lack in daily activities, significant weight changes, perceptions of physical and mental fatigue without any specific motive, and suicidal plans. For detailed information, see Table 1.

Table 1. DSM-5 classification of criteria for depression.

	Criteria
1	Depressed mood or irritable symptoms most of the day as indicated by either subjective report (e.g., feels sad or empty) or observation (e.g., appears tearful)
2	Decreased interest or pleasure in most activities, most of each day
3	Significant weight change (increase or decrease of 5%) or change in appetite
4	Changes in sleep habits (e.g., insomnia or hypersomnia)
5	Change in daily activities such as psychomotor agitation or retardation
6	Daily fatigue or loss of energy without any specific motive
7	Feelings of worthlessness or excessive or inappropriate guilt
8	Diminished ability to think or concentrate, or more indecisiveness
9	Thoughts of death or suicide

The treatment of depression (pharmacological or not) depends on several associated variables, namely: Severity of the depression (i.e., mild, moderate, or severe), triggering factors (i.e., severity of depressive symptoms, longer duration of episode and presensitivity of clinical and/or psychiatric comorbidities), type of symptoms displayed by the patient (i.e., depressed mood or loss of interest/pleasure), available resources in the context of care (i.e., easy-to-use support materials), patient preference, and professional familiarity with the method (i.e., maintenance posology). In the instance of mild symptoms, treatment is based on non-pharmacological measures for at least six weeks, such as: Psychoeducation, weekly outpatient follow-up, psychotherapy (if available), and if necessary, sleep and anxiety control techniques [10]. Patients who display moderate to severe symptoms, antidepressants are prescribed for the treatment of depression [10]. Treatment for depression can also involve complementary and non-invasive therapies such as PA. In fact, PA is increasingly being recognized as an effective means of treatment and/or an alternative of pharmacological therapy for depression [11–13]. PA can positively influence depressive symptoms through a variety of psychosocial and biological mechanisms, such as stimulating neuroplasticity, reducing inflammation, and increasing the level of self-esteem [14].

According to Minghelli et al. [15], PA has an effective and therapeutic action in treating depression because of its association with the reduction of anxiety and depressive symptoms. Specifically, the association between PA and depression can be explained by the increased release of hormones such as catecholamines, adrenocorticotropic hormone, vasopressin, B-endorphin, dopamine, serotonin, and by the activation of specific receptors related to the decrease in blood viscosity. Preliminary studies by Schuch and Fleck [16] have shown that PA is an effective complementary treatment also in patients with severe depression.

PA and exercise have a wide range of beneficial effects [17] involving both the body and the mind. Exercise is consistently listed among the "alternative and complementary" therapies [18] for attenuating symptoms related to mental illnesses. Recent studies have begun to detect significant

associations between the intensity and duration of exercise interventions and their antidepressant effectiveness [13,19] and have found that exercise can be as effective as other first-line treatments, and is mostly free of adverse side effects.

Some meta-analyses have found that moderate PA can maintain a reduced risk of incurring depressive episodes [20,21]. In sum, the results from these studies suggest that moderate intensity of physical exercise could be an optimal treatment for the decrease in patients with depression. Other meta-analyses revealed that low CardioRespiratory Fitness (CRF), an indicator of PA fitness, was associated with 64% higher risk of depression (HR = 1.64, CI = 1.29, 2.08) compared to individuals with high CRF [22]. The evidence of these systematic reviews is crucial to conclude that PA could prevent depression or attenuate depressive symptoms.

Recent intervention studies (e.g., a German climbing study on depression: A bouldering psychotherapeutic group intervention in outpatients compared with state-of-the-art cognitive-behavioral group therapy and physical activation [23]) indicate that PA and exercise programs are associated with decreased depressive symptoms in adults. There is also evidence that PA reduces depression levels in adolescents and pre-adolescents. Past findings suggest that a monitored three times a week group-based, mild to moderate intensity PA for a period of 6 to 12 weeks could provide a decrease in depressive symptoms [24,25]. Mild PA has also consistently been associated with a reduction in depressive symptoms in adolescents [26,27].

According to DeBoer et al. [28], beyond the positive impact of PA on the reduction of depressive symptoms, PA has the additional benefit of having a positive effect on individual health in patients with depression. This is especially important because depression is associated with an increased risk of metabolic syndrome, diabetes mellitus type 2, cardiovascular disease, and associated mortality [29–31]. According to a recent Cochrane review [32], PA has a moderately beneficial effect on depression compared to no treatment or control condition and equivalent effects to usual care.

The intensity of exercise during a session can elicit different neural responses [33], which may influence how it affects depressive symptoms. For example, higher intensity exercise may produce greater changes in neuroplasticity than moderate intensity exercise [34], and moderate-to-vigorous intensity exercise is most effective for reducing depressive symptoms [35].

In a review conducted by Perraton et al. [36] on exercise interventions in the treatment of clinical depression, an attempt was made to determine the appropriate variables for successfully creating effective treatments for depression. The authors determined that a cardiovascular exercise program should be performed three times a week for least for eight weeks, with a minimum of 30 min per session of moderate intensity to have effective results in depressive symptoms. In addition, the program must accommodate any comorbidities, allow for patient activity preferences and be supervised by health professionals. The preference for PA programs is a key factor in prescribing exercise and further investigation of the most effective training determinants for reducing depression is warranted. Additionally, future systematic reviews should outline the mild-to-moderate depression state and include follow-up research to understand the impact of exercise on clinical depression in the long-term as proposed by previous studies [14,22,36].

For the treatment of moderate depression, the National Institute for Health and Clinical Excellence recommends the prescription of 10 to 14 weeks of supervised PA, three days a week, each session lasting between 45 and 60 min [37]. For the treatment of Major Depression Disorder or major depression, the recommendations are 30 min, between three and five days a week, of aerobic PA of moderate intensity. The Institute for Clinical Systems Improvement [38] recommendations are for 30 min of moderate intensity aerobic physical activity between three and five days per week.

According to Chekroud et al. [39], certain exercises, such as group exercises, cycling, and aerobic exercises with a duration of 45 min at a frequency of three to five times a week, are strongly associated with a reduction in the mental health burden, and the addition of physical and mental activities (i.e., yoga and Tai-chi) seems to be related to positive outcomes. Small decreases were also observed in individuals exercising for more than 90 min. In durations longer than three hours, worse mental health

loads were observed compared to PA performed for 45 min. However, there is still little knowledge about dose-effect relationships and the most beneficial exercise activities [40]. Hence, more studies are warranted to determine the dose-effect of PA in people diagnosed with depression.

While there is considerable research demonstrating links between PA and depression, comparatively less research has focused on the role fo dose that PA has on patients with depression. Specifically, little is know about the dose-response effect between intensity and volume in this specific mental illness. While some systematic reviews have been conducted in the past [20–22], there are still under-researched associations between the dose of PA and how interventions could be based on the intensity and volume for reducing depressive symptoms or by reducing the risk of experiencing depression. Additionally, research on the differences between groups with different characteristics seems to be virtually nonexistent. Specifically, little is know how PA can actively impact depression in individuals from different age groups, sex, and depressive symptomatology. Considering previous limitations and agenda for future research, this protocol aimed to propose a systematic review investigating what dose of PA is recommended in the treatment of depression in female and male adults aged 18 to 65 years. Additionally, we intend to examine the effect of PA interventions on the prevalence incidence of depression. Specifically, this protocol intends to determine: (1) The recommended dose of PA (frequencies, intensity, duration, and type of activity), (2) the effects of different doses of PA interventions on depression and depressive symptoms, and (3) whether the effects were equivalent across groups with different characteristics (e.g., age, sex, depressive symptomatology).

2. Methods

This protocol for a systematic review was prepared in accordance with the declaration of Preferential Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) 2015. The final revision will be described using the Preferred Items for Systematic Reviews and Statement of Target Analysis as guidance. Relevant alterations to the protocol will be documented and published within the results of the final review.

3. Eligibility Criteria

The proposed systematic review will include randomized control trials (parallel group or cluster-randomized) as well as quasi-experimental trials examining the dose-effect response of PA interventions on people with depression. For eligibility, studies should include adults between the ages of 18 and 65, patients with diagnosed depressive symptoms or depression by medical doctors, and no other associated health condition. Only studies published in English and in peer-reviewed journals will be included. Articles that evaluate the effect of PA in adults with clinical diseases (i.e., diabetes mellitus, hypertension, among others) will be excluded, such as studies targeting individuals aged less than 18 and/or over 65 years old.

4. Data of Interest

The main results of interest include the dose of PA, namely: Levels and type of activity, frequency, and duration. The secondary results of interest refer to the effect of PA on psychosocial and psychological well-being, quality of life, and functional fitness. For research purpose, studies that include quantitive data collected using questionnaires such as: The Beck Inventory (BDI-II), psychological well-being and life satisfaction questionnaires, the PA questionnaire (PHQ-9), the Hamilton evaluation questionnaire for depression (HRSD-17), and health-related quality of life (SF36) will be considered. Studies that have used pedometers and accelerometers to evaluate PA in patients with depression and obtained quantitive results will also be considered. In order to allow an analysis of the impact of PA intervention on people with depression, results should be collected in pre-test and post-test (or follow-up) using central tendency means (e.g., mean and/or median) as well as deviation measures (e.g., standard deviation and/or interquartile range). The effect sizes will be calculated according to the criteria proposed by Cohen [41].

5. Research Strategy

The main source of literature will be a structured search in the following electronic databases: Web of Science, PubMed, Cochrane Library, SciELO, Physical and SportDiscus (EBSCO) using several combinations of MeSH keywords, namely: 201Cdepress*", "adult*", "intervention*" and "physical activity". The combination of keywords is shown in the Appendix A (Table A1). The PICOS (Patient, Intervention, Comparison, Outcome, and Study design) will be considered to assist in the organization of the data focusing on the foreground question in the electronic databases (see Table 2).

Table 2. Categories and keywords used to identify the study based on the PICOS protocol.

Categories	Keyword
Population	Adults, women, men, depressive, depression
Intervention	Intervention, program, treatment, physical activity, protocol
Comparison	Effect of PA programs, control group and experimental group, duration, frequency, and type of exercise
Outcome	Subjective well-being, psychological well-being, well-being, quality of life, and physical fitness
Study design	Experimental and/or quasi-experimental

6. Study Selection

All identified studies from the literature search will be selected by at least two of the authors from this protocol (DM, EC, AV, FR, DST, TB, or LC). First, the titles and abstracts of the articles returned from the initial search will be selected based on the above-identified eligibility criteria. Second, full articles will be analyzed in detail and selected for eligibility. Third, the bibliographic references of all articles considered will be manually searched to identify relevant articles lost in the initial search strategy. If necessary, disagreements between the authors will be resolved by discussion to reach a consensus. Records will be managed with EndNote x9 (Clarivate Analytics, Philadelphia, PA, USA).

7. Data Extraction

Two authors from the protocol (DM, EC, AV, FR, DST, TB, and LC) will systematically and individually extract the study details of interest using a pilot data extraction form with the EPPI-Reviewer, RevMan, or TrialStat SRS software. The study selection process as well as the retrieval of publication information, study design, study population (i.e., characteristics of participants), intervention methods (i.e., the content of the intervention for the control and intervention group including duration, frequency, intensity, and content of the PA), associated theoretical frameworks, evaluation tools, and intervention results (i.e., results on the effectiveness of the intervention on depressive symptoms) will be synthesized and included in a flowchart for transparency. The PRISMA will be used as a reference [42]. If information is missing or data clarifications are needed, the authors of the original studies will be contacted. In these instances, a maximum of two attempts of contact will be made.

8. Quality Assessment

For the assessment of the risk of bias in randomized trials, the Cochrane Collaboration tool will be used. The Cochrane Collaboration tool makes separate critical evaluations for sequence generation (selection bias), allocation sequence hiding (selection bias), participant and staff hiding (performance bias), results hiding (detection bias), incomplete results data (friction bias), selective results reporting (reporting bias), and other potential sources of bias. The judgment for each entry will involve assessing the risk of bias as "low risk", "high risk", or "unclear risk", with the latter category indicating either lack of information or uncertainty about the potential bias. Bias risk judgments will be graphically represented within and through studies in each domain. Two authors of the protocol (DM, EC, AV, FR, DST, TB, and LC) will independently assess the methodological quality of the studies. Uncertainties or disagreements will be discussed with a third author.

9. Data Synthesis

It is expected that the studies included in this systematic review will have a diverse range of research methods (e.g., study design, characteristics of the intervention, site of intervention, evaluation methods, characteristics of participants, and results). Thus, a narrative synthesis of the results will be performed. Summary tables describing the studies will be performed, their results and methodological quality will be provided, and additional information will be presented (e.g., journal title and respective impact factor). The results of the included studies are planned to be grouped according to age and measured physical and psychological outcomes (i.e., subjective well-being, depressive symptoms, and quality of life). The results will be evaluated considering the proposed theoretical framework, intervention strategies, and methodological quality to determine the effectiveness of PA interventions in patients with depression.

Additionally, the results of the interventions on PA behavior will be grouped according to the PA variables, such as duration and frequency. Similar to the analysis of physical and psychological results, results will be analyzed considering the theoretical framework, intervention strategies, age of participants, and methodological quality. In this respect, the objective is to determine the recommended dose of PA in the treatment of depression in adults.

10. Discussion and Conclusions

Although previous systematic reviews have shown some associations between PA and depression, little is known about the dose-effect responses of PA on patients with depression. Furthermore, the effects of PA on patients with depression and its association with psychological outcomes have not been explored in detail. Thus, this protocol provides a description of the future systematic review to be carried out, exploring these unanswered limitations in previous studies. Specifically, the systematic review will investigate the association between dose-effect of PA, depression, and psychological outcomes, aiming to provide detailed guidance for professionals and scholars to adequately promote and prescribe PA in patients with depression.

Strengths of this study protocol are that it will guide the authors to conduct a valid and reliable systematic review considering all factors related to the risk of bias, study eligibility, comprehensive search strategy, and the inclusion of psychological outcomes such as quality of life. Performing an inclusive search in major databases as those reported previously also will also some major strengths to the systematic review to be conducted. Results of the present study are expected to provide a deeper understanding of the relationship between depression and the effective dose of PA to decrease symptoms of depression and increase psychological outcomes such as quality of life.

This protocol provides the justification and planning methods for a systematic review, aiming to analyze the impact of PA-based interventions in adults with depression. We will consider the strengths and limitations of the studies identified in the search procedure, as well as those of our proposed systematic review, and discuss the results in the context under analysis. The potential limitations of this revision could include the restriction to a synthesis of narrative data, which could result in a bias in the interpretations of the interventions related to the treatment of depression. The restriction on published English written studies could also limit our interpretations and generalizations of the proposed results. If changes are made to the protocol, these will be described in the systematic review to be considered for publication.

The systematic review to be carried out in the near future can provide information on the recommended dose of PA in the treatment of depression in adults, as well as describe the impact of PA on psychological outcomes in patients with depression. The results of this review should help professionals and scholars involved in health promotion and health education to develop and implement interventions that effectively promote PA behavior in people with depression. As a consequence, it is theoretically expected that people with depression could foster positive outcomes related to the increase in PA, such as increased quality of life and subjective well-being. In order to

disseminate the proposed systematic review, the results will be published across academic publications, conferences, peer-reviewed presentations, and formal meetings.

Abbreviations

PA	Physical Activity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P	Preferred reporting items for systematic review and meta-analysis Protocols
RCT	Randomized Control Trial

Appendix A

Table A1. Search Strategy.

	Search Terms
1.	(adult *)
2.	(Men *)
3.	(Women *)
4.	(depression *)
5.	(depressi *)
6.	(depressed *)
7.	(disturbance *)
8.	(antidepressiv *)
9.	(physical activit *)
10.	(exercis *)
11.	(train *)
12.	(program *)
13.	(treatment *)
14.	(intervention *)
15.	(experience *)
16.	(assessment *)
17.	(quality)
18.	(skills)
19.	(well-being)
20.	(satisfaction)
21.	1 OR 2 OR 3
22	4 OR 5 OR 6 OR 7 OR 8
23.	9 OR 10 11 OR 12 OR 13 OR 14
24.	15 OR 16 OR 17 OR 18 OR 19 OR 20

Note. * = wildcard symbol that broadens search.

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