ÉDISON ANDRÉS PÉREZ BEDOYA

PHYSICAL EXERCISE AND DEPRESSION IN ADULTS AND OLDER ADULTS

Thesis presented in compliance with the requirements for the degree of Doctor (PhD) in Physical Education of the Department of Physical Education of the Federal University of Viçosa, Brazil.

Adviser: Osvaldo Costa Moreira

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To life itself, for showing me the path and the benefits of its trials and difficulties.

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To my family and friends, for waiting and understanding that life is about moments, I hope to live in new paths, experiences, and places...

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ABSTRACT

PÉREZ BEDOYA, Edison A, D.Sc. Universidade Federal de Viçosa, July, 2024. **Physical exercise and depression in adults and older adults**: Osvaldo Costa Moreira. Co-advisers: Claudia Eliza Patrocinio de Oliveira, Miguel Araujo Carneiro Junior and Fredy Alonso Villada Patiño.

This thesis explores the effect of different physical exercise modalities on alleviating depressive symptoms in adults with major depressive disorder (MDD) and sedentary older women. The first study is a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the benefits and risks of physical exercise in managing symptoms of MDD in adults not receiving second-generation antidepressants or cognitive behavioral therapy. The review analyzed nine RCTs involving 678 adults, revealing a small, non-statistically significant clinical effect favoring exercise (SMD = 0.27, 95% CI [-0.58, 0.04], P = 0.09). Subgroup analyses indicated potential influences of intervention duration, frequency, intensity, supervision, age, overweight/obesity status, and depression diagnosis on treatment outcomes. Sensitivity analysis showed moderate effect sizes with high heterogeneity ($I^2 = 85\%$), and overall evidence quality was low to very low.

The second study is an RCT conducted at the Federal University of Viçosa, Brazil, comparing the effects of Flywheel resistance training versus traditional methods on depressive symptoms in 29 sedentary women over 60 years old. Participants underwent eight weeks of training, performing six exercises twice a week. Results indicated no significant difference between Flywheel and traditional training in reducing depressive symptoms (p=0.193), with a small effect size ($\eta p^2 = 0.03$) and low statistical power ($1-\beta = 0.25$). Both interventions showed mild adverse events and no severe ones.

In conclusion, both studies suggest that physical exercise, including resistance training, can benefit depressive symptoms, but further research with well-designed RCTs and larger sample sizes is needed to confirm these findings. The evidence underscores the importance of cautious interpretation due to methodological limitations and variability in results.

Keywords: systematic review; meta-analysis; major depressive disorder; physical exercise; depression; elderly; exercise; resistance training; harms.

RESUMEN

PÉREZ BEDOYA, Edison A, D.Sc. Universidade Federal de Viçosa, Julio, 2024. **Ejercicio Físico y Depresión en adultos y adultos mayores**: Osvaldo Costa Moreira. Co-orientadores: Claudia Eliza Patrocinio de Oliveira, Miguel Araujo Carneiro Junior and Fredy Alonso Villada Patiño.

Esta tesis explora el efecto de diferentes modalidades de ejercicio físico en el alivio de los síntomas depresivos en adultos con trastorno depresivo mayor (TDM) y mujeres mayores sedentarias. El primer capítulo es una revisión sistemática y metaanálisis de ensayos controlados aleatorizados (ECA) que evalúan los beneficios y riesgos del ejercicio físico en el manejo de los síntomas del TDM en adultos que no reciben antidepresivos de segunda generación o terapia cognitivo-conductual. La revisión analizó nueve ECA que involucraron a 678 adultos, revelando un pequeño efecto clínico no estadísticamente significativo a favor del ejercicio (DME = 0,27, IC del 95% [-0,58, 0,04], P = 0,09). Los análisis de subgrupos indicaron posibles influencias de la duración de la intervención, la frecuencia, la intensidad, la supervisión, la edad, el estado de sobrepeso/obesidad y el diagnóstico de depresión en los resultados del tratamiento. El análisis de sensibilidad mostró tamaños de efecto moderados con alta heterogeneidad (I^2 = 85%), y la calidad general de la evidencia fue baja a muy baja.

El segundo capítulo es un ECA realizado en la Universidad Federal de Viçosa, Brasil, que comparó los efectos del entrenamiento de fuerza con dispositivo Flywheel frente a los métodos tradicionales sobre los síntomas depresivos en 29 mujeres sedentarias mayores de 60 años. Las participantes se sometieron a ocho semanas de entrenamiento, realizando seis ejercicios dos veces por semana. Los resultados no indicaron diferencias significativas entre el entrenamiento Flywheel y el tradicional en la reducción de los síntomas depresivos (p = 0,193), con un tamaño del efecto pequeño (ηp^2 = 0,03) y un poder estadístico bajo (1-β = 0,25). Ambas intervenciones mostraron efectos adversos leves y ninguno grave.

En conclusión, ambos estudios sugieren que el ejercicio físico, incluido el entrenamiento de fuerza, puede beneficiar los síntomas depresivos, pero se necesita más investigación con ECA bien diseñados y tamaños de muestra más grandes para confirmar estos hallazgos. La evidencia subraya la importancia de una interpretación cautelosa debido a las limitaciones metodológicas y la variabilidad de los resultados.

Palabras clave: revisión sistemática; metaanálisis; trastorno depresivo mayor; ejercicio físico; depresión; ancianas; ejercicio; entrenamiento de fuerza; daños.

SUMMARY

GENERAL INTRODUCTION

Depression is globally the second leading cause of disability, affecting almost 5% of the population, with women being disproportionately affected. Annually, there are 800,000 deaths by suicide. Reports from the Pan American Health Organization (PAHO) and the World Health Organization (WHO) highlight that men are at a higher risk of dying by suicide. Recent studies indicate that nearly 20% of suicide deaths occur in individuals without a clinical diagnosis of depression, emphasizing the need to expand the focus beyond diagnosed populations.

The American Psychiatric Association commonly recommends pharmacological therapy and cognitive-behavioral therapy (a strong recommendation with moderate certainty). However, patient preferences often lean towards alternative strategies with fewer adverse effects, such as physical exercise. Exercise, a viable and safe approach, has shown promising effects in alleviating depressive symptoms in both clinical and non-clinical populations.

In the initial chapter of this doctoral thesis, entitled "Physical Exercise and Major Depressive Disorder in Adults: A Systematic Review and Meta-analysis" (https://doi.org/10.1038/s41598-023-39783-2), an examination was conducted to assess the effect of various physical exercise modalities on depressive symptoms in a clinical population not subjected to conventional treatment before the interventions. The utilization of checklists to ascertain the clarity, reproducibility, and thoroughness of clinical trial reports revealed that aerobic exercise may yield a minor reduction in symptoms; however, no statistically significant variances were noted when compared to control conditions. Furthermore, it was determined that physical exercise yielded fewer adverse effects than standard treatment. These conclusions were subjected to evaluation utilizing the GRADE approach, which indicated a low methodological quality.

In the second chapter of this thesis, a randomized controlled trial (RCT) was conducted, involving 29 elderly women residing in the community of Viçosa. The participants underwent two types of resistance training: the first comprising eccentric overload using the Flywheel device, and the second involving traditional resistance training with gym machines and free weights. Following 16 sessions, it was observed that both supervised training protocols were safe and led to a significant reduction in depressive symptoms within the groups. Notably, none of the participants had a clinical diagnosis of major depression or were undergoing pharmacological treatment prior to the interventions. It is significant to note that comparisons between the groups revealed no statistically significant differences. However, both

interventions displayed small effect sizes and low statistical power, potentially indicating a Type II error.

1 CHAPTER 01: PHYSICAL EXERCISE AND MAJOR DEPRESSIVE DISORDER IN ADULTS: SYSTEMATIC REVIEW AND META-ANALYSIS.

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Abstract

The objective of this study was to assess the benefits and potential risks associated with different physical exercise modalities for managing symptoms in adults with major depressive disorder who were not receiving second-generation antidepressants or cognitive behavioral therapy. A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted. The search included multiple databases: Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PsycINFO, Web of Science, Clinical Trials repository, gray literature, and manual search. No language restrictions were applied. Eligible studies involved RCTs of adults with major depressive disorder who were not on antidepressants or receiving psychological therapy, comparing various exercise modalities with second-generation antidepressants or cognitive behavioral therapy, body-mind exercise, or no exercise interventions. Nine RCTs involving 678 adults were analyzed. The pooled results indicated a small clinical effect favoring exercise in reducing depressive symptoms, although the difference was not statistically significant (SMD = 0.27, 95% CI [-0.58, 0.04], P = 0.09). Subgroup analyses suggested that intervention duration, frequency, intensity, supervision, age, overweight/obesity status, and diagnosis of depression could influence treatment outcomes. A sensitivity analysis was conducted for studies with controls without exercise interventions and a low risk of bias in the domains related to the randomization process and deviations from the intended interventions. The results showed that there are no statistically significant differences when interventions are compared with medication and body-mind exercise ($p = 0.12$, $I^2 = 78\%$). Furthermore, the analysis showed a moderate effect size favoring exercise, but no statistically significant difference between groups ($p = 0.05$), with high heterogeneity ($I^2 = 85\%$). The evidence quality was generally low to very low, and methodological limitations compromised the certainty of the findings. Adverse events associated with exercise were manageable. The study emphasizes the need for well-designed RCTs to provide clearer insights into the potential benefits of exercise in managing major depressive disorder symptoms. Caution is warranted in interpreting these results due to the limitations of the included studies.

Keywords: systematic review; meta-analysis; major depressive disorder; physical exercise.

STATEMENTS AND DECLARATIONS

Competing Interests: The authors report that they have no conflict of interest.

Systematic review registration: PROSPERO CRD42022356741

Key Points

This meta-analysis represents an important investigation assessing various exercise modalities' effects on major depressive disorder in untreated individuals. By focusing on non-treatment-seeking individuals, the meta-analysis aims to provide valuable insights into exercise as an alternative or adjunctive therapy for managing depressive symptoms.

The findings suggest that there are limitations in the description of physical exercise interventions, specifically aerobic exercise, which hinders reproducibility. The quality of evidence supporting the effects of these interventions on depressive symptoms is low to very low, emphasizing the need for additional research. No significant differences were observed between physical exercise interventions and control conditions, highlighting the complex nature of the relationship between exercise and major depressive disorder.

2 Background

Major depressive disorder (MDD) is indeed more prevalent in women than in men, with a prevalence rate of 14.4% in women and 11.5% in men (Nieuwenhuijsen et al., 2020). It is characterized by persistent symptoms such as a depressed mood, loss of interest, and a reduced ability to experience pleasure in daily activities for a minimum duration of two weeks (Cooney et al., 2013; Javier I. Escobar, 2014; Nieuwenhuijsen et al., 2020; Sanhueza Pastén & Caneo, 2022; Seshadri et al., 2020). It typically emerges in early adulthood, with an average onset age of around 20-25 years (Malhi & Mann, 2018). The prevalence tends to be higher in developed countries among individuals aged 16 years and above (Iemmi, 2022; Santomauro et al., 2021). In 2020, it was estimated that 264 million people worldwide were affected by MDD (Sanhueza Pastén & Caneo, 2022). Individuals with this disorder are at an increased risk of developing various comorbidities, including diabetes mellitus, cardiovascular morbidity and mortality, lower back pain, and a decline in overall quality of life (Amiri, 2022; Orsolini et al., 2022). It has profound implications for both individual and public health. It is the leading cause of suicide deaths worldwide, with an estimated incidence of up to 800,000 suicides annually (Arias et al., 2022). Additionally, it has emerged as an independent risk factor for all-cause mortality, further underscoring its impact on overall health (Fernandes et al., 2022). Before the COVID-19 pandemic, it was already the second leading cause of disability globally, and since 2020, there has been a noticeable increase in its incidence, affecting approximately 53.2 million individuals (Iemmi, 2022; Santomauro et al., 2021). The economic burden associated with it is substantial; in the United States, the economic losses were around $210.5 billion in 2010, and by 2020, they had escalated to nearly $390 billion per year (Nieuwenhuijsen et al., 2020). Interestingly, effective treatment could potentially yield a net global economic benefit of $230 billion by 2030 (Dishman et al., 2021). Despite the high burden and economic impact, mental health expenditures receive only a small fraction of government health budgets, with approximately 2% allocated to mental health worldwide, as reported by UNICEF (Santomauro et al., 2021).

Clinical practice guidelines recommend the use of psychotherapy and/or pharmacotherapy for MDD treatment (Qaseem et al., 2016). However, these approaches may face barriers to adherence: stigma surrounding mental health and concerns about medication-related adverse effects (such as constipation, diarrhea, dizziness, headache, insomnia, nausea, decreased sexual desire, and somnolence) can significantly impact treatment acceptance and adherence (Qaseem et al., 2016; Ravindran et al., 2016). Therefore, there is an urgent need to explore non-

pharmacological and patient-centered strategies that are safe, feasible, and easily integrated into the daily routines of adults.

Physical exercise (PE) interventions have been shown to effectively alleviate depressive symptoms in adults and are recommended by international guidelines, including the Canadian Network for Mood and Anxiety Treatments and the American College of Physicians (Morres et al., 2019; Qaseem et al., 2016; Ravindran et al., 2016).

The evaluation of non-pharmacological therapies, including exercise, has been the focus of various guidelines, systematic reviews, and meta-analyses (Cooney et al., 2013; Fernandes et al., 2022; Miller et al., 2020; Morres et al., 2019; Qaseem et al., 2016; Ravindran et al., 2016; Sanhueza Pastén & Caneo, 2022; Seshadri et al., 2020). However, it is worth noting that not all these reports have specifically considered PE in their recommendations. Some guidelines have primarily focused on cognitive-behavioral therapy or second-generation pharmacological therapy as the primary treatment options, potentially overlooking the potential benefits of exercise (Qaseem et al., 2016). These guidelines strongly recommend these therapies with moderate certainty.

However, there is evidence suggesting that certain forms of exercise could serve as monotherapy for individuals with mild to moderate MDD or as adjunctive treatment for those in the moderate to severe stages of the disorder (Ravindran et al., 2016). It is important to acknowledge that the effect of exercise on symptomatology may vary from moderate to small, and some studies included in these reports have a high risk of bias (Ravindran et al., 2016).

For example, a Cochrane review and a systematic review included a diverse population, encompassing individuals with a range of characteristics, including some who were receiving drug therapy in combination with exercise interventions. These reviews also included healthy individuals who exhibited depressive symptoms, in addition to those specifically diagnosed with MDD (Cooney et al., 2013; Heissel et al., 2023). Similarly, network meta-analyses have incorporated older adults with dementia, some of whom were prescribed antidepressant medication, in their analyses (Miller et al., 2020).

It is worth noting that while systematic reviews have reported a moderate and mild effect of exercise on this disorder, there remains uncertainty regarding the optimal type, intensity, duration, and frequency of exercise that may be most effective (Fernandes et al., 2022; Morres et al., 2019; Seshadri et al., 2020). The lack of evaluation of the strength and certainty of results in previous systematic reviews and meta-analyses is indeed a significant concern. Only the

Cochrane review and network meta-analysis assessed the level of certainty in the results, and the network meta-analysis found varying levels of certainty for different exercise interventions (Cooney et al., 2013; Miller et al., 2020). This highlights the need for a comprehensive evaluation of the evidence using robust methodologies.

It is essential to determine the level of confidence we can have in the potential mild to moderate effect of exercise. None of the reviews published in the last five years have assessed the strength and certainty of the results using the GRADE approach, which is a rigorous framework for evaluating the quality of evidence (J. Andrews et al., 2013; J. C. Andrews et al., 2013). As a result, our understanding of the harms associated with physical exercise practice for this population is limited since previous reviews have not adequately assessed adverse events.

Therefore, this meta-analysis aims to investigate the effect of physical exercise in reducing depressive symptoms in adults diagnosed with MDD who are not receiving treatment. Additionally, we will assess the effect of exercise on quality of life and examine any adverse events associated with the interventions.

3 Methods

3.1 Protocol and Registration

The study was registered in PROSPERO with the registration number CRD42022356741. The protocol adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol (PRISMA-P) (Shamseer et al., 2015), and the final report was prepared following the recommendations of the PRISMA Statement (Page et al., 2021).

3.2 Study Eligibility Criteria

Two reviewers, EAPB and LFPL, independently extracted and analyzed the references from Rayyan QCRI (Ouzzani et al., 2016). They conducted their analysis in a blinded manner and assessed the trials based on the predetermined eligibility criteria. Any discrepancies that arose between the reviewers were resolved by a third reviewer, DALG.

The PICOTS acronym was used to define the inclusion criteria for this systematic review and meta-analysis (Samson & Schoelles, 2012). The following criteria were applied:

Participants: Adults of both sexes aged 18 years or older diagnosed with MDD according to the DSM-5™ Diagnostic Criteria reference guide (Uher et al., 2014). Participants should not have been using antidepressant medication or undergoing psychological therapy before the exercise

interventions. They may or may not have had chronic communicable or non-communicable diseases.

Interventions: randomized controlled trials (RCTs) examining different modalities of PE, including aerobic training (AT), resistance exercise (RE), combined exercise (CE), and multi-component exercise (MCE).

Comparators or control conditions: The interventions were compared to treatment recommended by the American College of Physicians (Qaseem et al., 2016) (second-generation antidepressants or cognitive behavioral therapy), body-mind exercise (Yoga, Tai chi, Qi gong, stretching exercise), and no exercise interventions.

Outcomes: the primary outcome of interest was depressive symptoms (Hamilton, 1960; Hubley, 2020; Kroenke et al., 2001). Secondary outcomes included adverse events or damage (such as dizziness, headache, blurred vision, and chronic muscle pain), quality of life, and mortality.

Studies were excluded from the meta-analysis if they met any of the following criteria:

1. RCTs in progress or those that conducted PE interventions with pregnant or breastfeeding women.
2. RCTs with comparators involving nutritional proposals.
3. Studies that included adults with clinical diagnosis of anxiety or bipolar disorder.
4. Studies with a population experiencing posttraumatic stress disorder.
5. Studies that did not provide sufficient information on the components of frequency, intensity, time, volume, and progression (FITVP).

The quality of the included RCTs in this systematic review and meta-analysis was assessed using the Study Quality Assessment Tool and Exercise Reporting Tool (TESTEX) (Neil A. Smart et al., 2015). The TESTEX scale is a quality assessment tool specifically designed for exercise training studies. It focuses on evaluating the quality and reporting of exercise training trials, with a particular emphasis on criteria relevant to exercise specialists. The scale includes criteria that may not be mentioned in other quality assessment tools, such as the transition from a sedentary control group to an exercise group, the periodic adjustment of exercise training intensity based on physical training adaptation, and the detailed reporting of exercise program characteristics. By using the TESTEX scale, researchers and exercise specialists can assess the quality and reporting of exercise training studies in a comprehensive and specific manner.

The reviewers, LFPL and DALG, independently assessed the quality of the studies based on predetermined criteria. Only RCTs with high methodological quality, scoring between 12 and 15 points on the TESTEX, were included in the metanalysis.

3.3 Search procedures and study inclusion

The systematic search for eligible studies was conducted independently and in a blinded manner by two reviewers, EAPB and LFPL. The search included international electronic databases such as Medline (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, PsycInfo, Web of Science, and the Clinical Trials repository (clinicaltrials.gov). Additionally, gray literature repositories including OpenSIGLE, PsycEXTRA, Healthcare Management Information Consortium (HMIC), and the National Technical Information Service (NTIS) were searched following the guidelines outlined in the Cochrane Handbook (T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), 2022).

To ensure thoroughness, a manual search of the reference lists of selected articles, previous systematic reviews, and meta-analytic studies was conducted to identify any potentially relevant studies that may have been missed in the electronic searches.

Any discrepancies or disagreements regarding the inclusion of a study were resolved through consensus discussions involving a third author, DARJ. There were no language or publication year restrictions, allowing for a comprehensive range of studies to be considered.

The specific search terms used in the systematic search can be found in *Supplement 1* of the review, providing transparency, and allowing for replication of the search strategy.

Two authors, EAPB and LFPL, performed the study selection and data extraction, as well as assessed the risk of bias among the included studies. Disagreements between the two authors were resolved by another author, OCM. Additionally, two independent reviewers, EAPB and DALG, who were blinded to each other's assessments, utilized the Consensus on Exercise Reporting Template (CERT) (Susan C. Slade et al., 2016) to evaluate the included RCTs.

The risk of bias assessment was performed independently and in a blinded manner by the review group consisting of EAPB and LFPL. The Cochrane Revised Risk of Bias Tool for Randomized Trials (RoB2) (Minozzi et al., 2020) was employed for this assessment. The severity of adverse events was assessed and graded using version 5.0 of the "Common Terminology Criteria for Adverse Events" (CTCAEv5.0) (Health & Human, 2020). Adverse events were categorized into different grades based on their severity. Grade one adverse events may include muscle events, chest pain, and muscle/joint pain. Grade two adverse events may involve mood disturbances such as worsening of MDD or antidepressant-related follow-up. Grade three adverse events may encompass unspecified medical reasons, medication-related adverse events such as dizziness, drowsiness, agitation, or diarrhea, medical contraindications, new medical conditions, psychiatric emergencies related to mood disturbances, or admission to psychiatry.

Grade four adverse events may refer to mood disturbances specifically related to suicidal ideation. Finally, grade five adverse events will be recorded in case of death by suicide.
To evaluate the certainty and strength of evidence in the findings provided by the included RCTs, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (J. Andrews et al., 2013; J. C. Andrews et al., 2013) was utilized. EAPB and LFPL, as independent and blinded reviewers, employed this approach to evaluate the quality of evidence and assign it to one of four levels: high certainty, moderate certainty, low certainty, or very low certainty. The A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) (Shea et al., 2017) was used to evaluate the quality of this review.

3.4 Statistical analysis

For continuous outcomes, the study included group sizes, mean values, and standard deviations (SD) were compared. Pooled effects were calculated using an inverse variance model. Since some studies reported data from different instruments, the effects were evaluated based on the standardized mean differences (SMD) of PE interventions on the results obtained from questionnaires that measure symptoms related to MDD and the perception of quality of life. The corresponding 95% confidence intervals (CI) were established, with statistical significance set at $p < 0.05$. SMD was calculated to determine Cohen's d for each study, and Hedges' g was used to account for potential bias in small sample sizes. The interpretation of SMD followed Cohen's guidelines, where SMD values < 0.2 were considered trivial, 0.2-0.3 as small, 0.5 as moderate, and > 0.8 as large (Cohen, 2013).

The adverse events were analyzed as dichotomous outcomes, and a Mantel-Haenszel random effects model was used to pool and compare the total number of events in the AT, RE, CE, and MCE groups versus second-generation antidepressants or cognitive behavioral therapy, BME, or no exercise interventions. The risk difference (RD) was calculated with a 95% confidence interval (CI), and a positive value for RD indicated a favorable safety profile for PE. RD was chosen as the effect measure to ensure that RCTs reporting zero adverse events (indicating no difference between exercise and usual care) were not excluded from the meta-analysis. Statistical heterogeneity was assessed using the Higgins test (I^2) and classified according to the Cochrane Manual: negligible heterogeneity (0% to 40%), moderate heterogeneity (30% to 60%), substantial heterogeneity (50% to 90%), and considerable heterogeneity (75% to 100%) (T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), 2022).

A random effects model (Tantry et al., 2021), was employed, assuming potential differences between the included studies and aiming to examine discrepancies among them. Subgroup analyses (Cuijpers et al., 2021) were conducted to explore the effects of PE, age, sex, health and training status, body composition, frequency, intensity, duration, and modes of PE. Additionally, a sensitivity analysis was performed for studies that had control conditions without PE interventions and demonstrated a low risk of bias in the domains related to the randomization process and deviations from the intended interventions. These two domains were selected based on their significance in assessing the quality of RCTs. The domain related to the randomization process evaluates whether the allocation sequence was randomized, adequately concealed, and if any initial differences between the intervention groups suggest a problem with the randomization process. Randomization helps to ensure that known and unknown prognostic factors, such as disease severity or comorbidities, are balanced between the intervention groups. This reduces the potential for bias in the assignment of individual participants to interventions. The most important elements assessed in RCTs for randomization include the generation of the allocation sequence (randomization elements) and the concealment of the allocation sequence (preventing participants or trial staff from knowing about upcoming assignments). The other domain selected for the sensitivity analysis is related to deviations from the intended interventions, which assesses performance bias. This domain considers whether there were any deviations from the trial protocol, such as administering additional interventions that are inconsistent with the protocol or not implementing the protocol interventions as intended. It also evaluates the participants' compliance with the assigned intervention. One way to minimize this bias is through blinding or masking, where the participants or trial staff are unaware of the assigned interventions. By conducting a sensitivity analysis focusing on these domains, we aimed to evaluate the robustness and reliability of the findings, ensuring that studies with high methodological quality and adherence to the intended interventions were given additional consideration (S. J. Higgins JPT, Page MJ, Elbers RG, Sterne JAC. , 2022). Publication bias was not assessed due to the insufficient number of studies (less than 10) required for such analysis. All meta-analyses were performed by two reviewers (EAPB and OCM) using RevMan 5.4 (T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), 2022), and an author (LFPL) reviewed the extracted data for verification.

4 Results

4.1 Literature Identification

The initial search identified a total of 2,429 studies. After removing duplicates, 558 studies were left. Following the screening of titles and abstracts, 1,871 studies were excluded. Subsequently, 53 RCTs were assessed in full text by reviewers EAPB and LFPL. Among them, 50 trials did not meet the PICOTS criteria outlined in this review, and the reasons for (Neil A. Smart et al., 2015), two studies (Krogh, 2014 and Sadeghi, 2016) (Krogh et al., 2014; Sadeghi et al., 2016) were their exclusion are provided in *Supplement 1*. After applying the TESTEX tool excluded from the quantitative synthesis *(Supplement 1).* Finally, nine trials were included for qualitative synthesis. A visual representation of the search results can be found in the PRISMA flow chart in *Figure 1.*

4.2 Demographic and Study Characteristics

The review included a total of nine RCTs with a combined sample size of 678 adults. Of these, 211 participants (31.12%) were men and 467 (68.88%) were women. The age range of the participants varied from 20 to 72 years old. The earliest publication included in the review was from 1996, and the most recent was from 2016 (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016; Singh et al., 1997). It is worth noting that Blumenthal (1999) (Blumenthal et al., 1999) and Herman (2002) (Herman et al., 2002) used the same sample in their studies. Most of the research was conducted in the United States of America, with six trials (66.66%) taking place in this country (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Singh et al., 1997). Denmark contributed two studies (22.22%) (Krogh et al., 2014; Krogh et al., 2012), and Iran contributed one study (11.11%) (Sadeghi et al., 2016). In terms of body composition, some studies reported that the participants were overweight (three studies, 33.33%) (Krogh et al., 2014; Krogh et al., 2012; Singh et al., 1997), obese (one study, 11.11%) (Blumenthal et al., 2007), or a combination of overweight and obesity (one trial, 11.11%) (Dunn et al., 2005). Four RCTs (44.44%) did not provide detailed information about the physical characteristics of the participants (Blumenthal et al., 1999; Herman et al., 2002; Khatri et al., 2001; Sadeghi et al., 2016).

In two trials (22.22%), participants with endocrine, cardiac, pulmonary, and orthopedic disorders were included (Blumenthal et al., 1999; Herman et al., 2002). Additionally, one RCT (11.11%) included adults diagnosed with chronic noncommunicable diseases (Blumenthal et

al., 2007). In several studies, the intervention was conducted with sedentary individuals (five studies, 55.55%) (Blumenthal et al., 2007; Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012; Singh et al., 1997). Furthermore, one study (11.11%) reported a population without employment (Krogh et al., 2012), while three RCTs (33.33%) included both unemployed and full-time workers (Blumenthal et al., 1999; Herman et al., 2002; Khatri et al., 2001). The assessment of MDD symptomatology was conducted using the Hamilton Depression Scale (HAM-D) in four studies (44.44%) (Blumenthal et al., 2007; Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012), the Beck Depression Inventory (BDI) in four studies (44.44%) (Blumenthal et al., 1999; Herman et al., 2002; Sadeghi et al., 2016; Singh et al., 1997), and both HAM-D and BDI scales in one study (11.11%) (Khatri et al., 2001). For more details on the characteristics of the participants, please refer to *Table 1.*

Fig. 1 *Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the study selection*

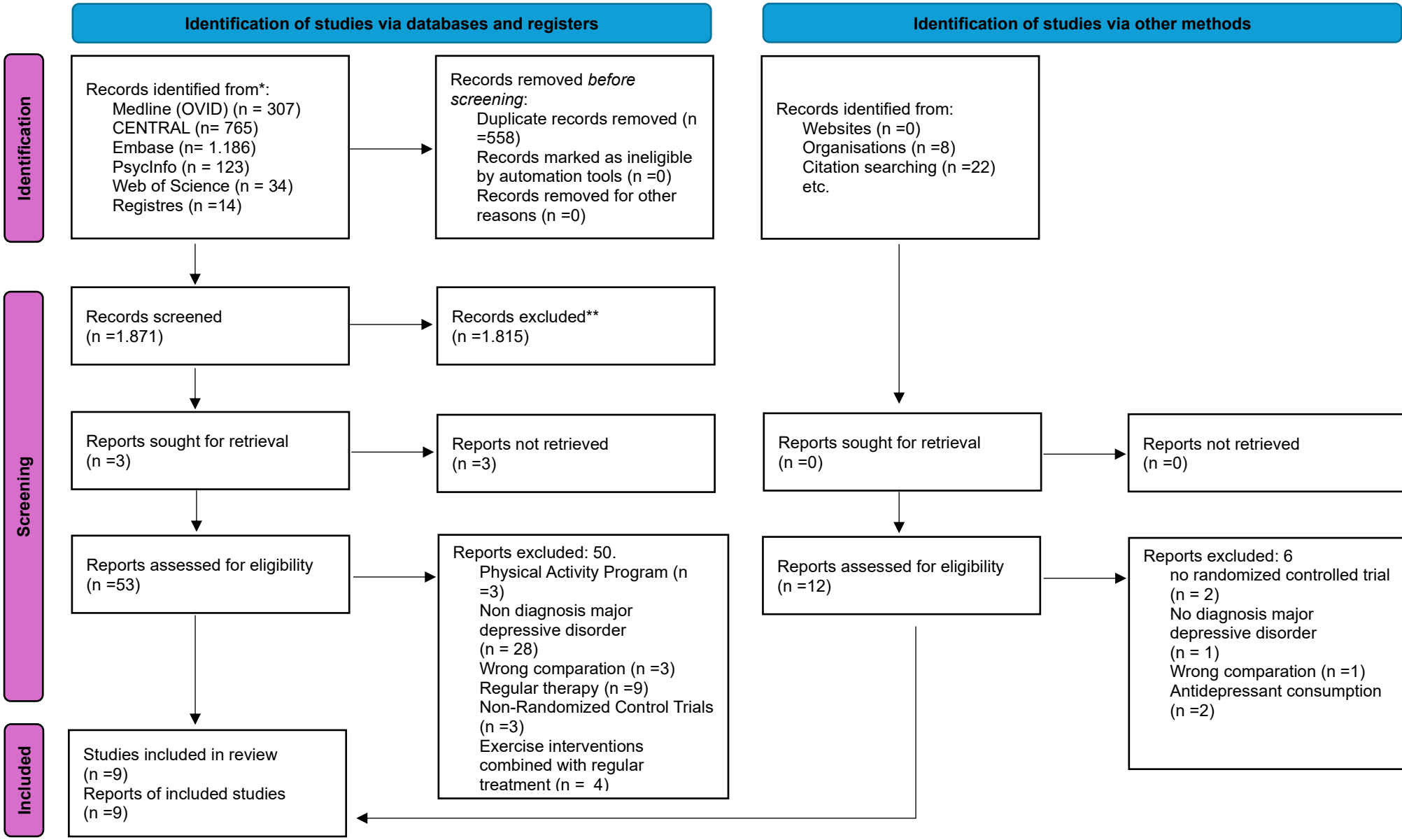

Table 1 *Characteristics of the studies included*

Study, year, country	Characteristics of the participants									Depressive symptoms instrument	Results of the interventions.[24] Std. Mean Difference, 95% CI	TESTEX SCORE
	Age (Years)	Participants, n	Male, n	Female, n	Sex (%)	Body composition	Health condition	Physical Exercise and Physical Activity Status	Occupational status (%)			
Krogh, 2012 Denmark	**INT:**39,7 ± 11,3 **CON:** 43,4 ± 11,2	115 **INT:** 56 **CON:** 59	**INT:** 16 **CON:** 22	**INT:** 40 **CON:** 37	**Men** (33) and **Women** (67)	Overweight	No chronic disease diagnosis	Sedentary behavior	Unemployed **INT:** 35,7 **CON:** 45,7	HAM-D	At the end of the interventions, no significant differences were found between the groups in terms of depressive symptoms. 0.12, [-0.24, 0.49]	14

Krogh, 2014 Denmark	**INT:**39,8 ± 11,7 **CON:** 43,8 ± 112,2	79 **INT:** 41 **CON:** 38	**INT:** 11 **CON:** 15	**INT:** 30 **CON:** 23	**Men** (32,9) and **Women** (67,1)	Overweight	No chronic disease diagnosis	Sedentary behavior	Not reported	HAM-D	They found an association between an increase in hippocampal volume, improved depression, and verbal memory independent of exercise. **Not included in the meta-analysis**	11
Singh, 1996 USA	**INT:** 70,0 ± 1,6 **CON:** 72,0 ± 1,9	28 **INT:** 15 **CON:** 13	**INT:** 5 **CON:** 6	**INT:** 10 **CON:** 7	**Men** (39,29) and **Women** (60,71)	Overweight	No chronic disease diagnosis	Sedentary behavior	Not reported	BDI	Progressive resistance exercise significantly reduced all measures of depression compared to control. -0.43,	12

											[-1.18, 0.32]	
Herman, 2002 USA	**INT:**57 ± 5,8 **CON:** 57 ± 7,0	101 **INT:** 53 **CON:** 48	**INT:** 14 **CON:** 10	**INT:** 39 **CON:** 43	**Men** (23.76) **Women** (76,23)	Not reported	Endocrine, Cardiac, Pulmonary, and Orthopedic disorders	Not reported	Unemployed 35 employed 65	BDI	No treatment group differences in remission rate were found. -0.26, [-0.65, 0.13]	13
Blumenthal, 1999 USA	**INT:**57 ± 5,8 **CON:** 57 ± 7,0	101 **INT:** 53 **CON:** 48	**INT:** 14 **CON:** 10	**INT:** 39 **CON:** 38	**Men** (23.76) **Women** (76,23)	Not reported	Endocrine, Cardiac, Pulmonary, and Orthopedic disorders	Not reported	Unemployed 35 employed 65	BDI	After 16 weeks of treatment, there were no statistically significant differences between the groups in terms of scores on BDI. 0.13,	12

											[-0.26, 0.52]	
Khatri, 2001 USA	**56,73 ± 6,45**	84 **INT:** 42 **CON:** 42	20	64	**Men** (23,80) **Women** (76,19)	Not reported	Not reported	Not reported	Unemployed 32 employed 68	HAM-D BDI	Both groups demonstrated significant improvements in depressive symptoms as HAM-D and BDI. 0.28, [-0.15, 0.71]	12
Blumenthal, 2007 USA	**INT:**52 ± 7 **INT:** 53 ± 8 **CON:** 52 ± 8	153 **INT:**51 **INT:** 53 **CON:** 49	**INT:**12 **INT:** 14 **CON:** 12	**INT:**39 **INT:** 39 **CON:** 37	**Men** (24.83) **Women** (75.17)	Obesity	chronic disease diagnosis	Sedentary behavior	Not reported	HAM-D	All treatment groups had lower HAM-D scores after treatment; scores for the active treatment groups were not	13

											significantly different from the placebo group. -0.16, [-0.55, 0.23]	
Sadeghi, 2016 Iran	**INT:** 20.93± 1.06 **CON:** 21.12± 1.25 **CON:** 20.92 ± 1.20	46 **INT:** 16 **CON:** 16 **CON:** 14	**INT:** 13 **CON:** 12 **CON:** 11	**INT:** 3 **CON:** 4 **CON:** 3	**Men** (78,26) **Women** (21,73)	Not reported	Not reported	Not reported	Not reported	BDI-II	Aerobics, compared to the control group, causes more reductions in depression variables. **Not included in the meta-analysis**	6
Dunn, 2005 USA	**INT:** 35.8 ± 6.1 **INT:** 37.7 ± 5.1 **INT:** 33.2 ± 6.7 **INT:** 37.9 ± 6.3 **CON:** 34.5 ± 7.3	72 **INT:** 16 **INT:** 15 **INT:** 17 **INT:** 15 **CON:** 9	**INT:** 3 **INT:** 4 **INT:** 4 **INT:** 3 **CON:** 4	**INT:** 13 **INT:** 11 **INT:** 13 **INT:** 12 **CON:** 5	**Men** (25) **Women** (75)	Overweight and Obesity	Not reported	Sedentary behavior	Not reported	HAM-D	The main effect of energy expenditure in reducing HAM-D scores at 12	15

								weeks was significant.	
								-2.74, [-3.92, -1.55]	

HAM-D: Hamilton Depression Rating Scale; HDRS: The Hamilton Rating Scale of Depression; BDII, Beck Depression Inventory; BDI-II, Beck Depression Inventory-ll; INT: Intervention; CON: Control; Std. Mean Difference: Effect size; CI: Confidence interval.

4.3 Description of physical exercise interventions

The exercise modality that was most studied was AT, which was examined in eight RCTs (88.88%) (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016). Only one RCT (11.11%) focused on RE (Singh et al., 1997). All PE interventions were supervised (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016; Singh et al., 1997). In one study (Blumenthal, 2007), in addition to a supervised program, unsupervised home AT was also included (Blumenthal et al., 2007). Please refer to *Table 2* for more details.

4.3.1 AT (8 RCTs)

The AT programs included in the studies varied in frequency, duration, and intensity. The programs were typically conducted three to five days a week, with a duration ranging from eight to 16 weeks. Each session lasted between 30 to 45 minutes. The intensity of the AT interventions was determined using different parameters.

Some studies reported using minimum intensities of 60% and maximum intensities of 80% based on maximum heart rate (HRMAX) (two studies, 22.22%) (Krogh et al., 2014; Sadeghi et al., 2016). Another study used an intensity of 65% of maximum oxygen consumption (VO2 max) (one study, 11.11%) (Krogh et al., 2012). Four studies (44.44%) by Herman (2002), Blumenthal (1999), Khatri (2001), and Blumenthal (2007) implemented AT with intensities ranging from 70% to 85% of reserve heart rate (RHR) (Blumenthal et al., 2007; Blumenthal et al., 1999; Herman et al., 2002; Khatri et al., 2001). One study categorized intensity into low and high categories (one study, 11.11%) (Dunn et al., 2005). The total volume of AT per week ranged from 90 to 180 minutes.

Only one study reported exercise progression, with the intensity increasing from 70% in the second month to 80% in the third month (Krogh et al., 2012). Some studies based the progression of exercise on subjective perception of effort (four studies, 44.44%) (Blumenthal et al., 2007; Blumenthal et al., 1999; Herman et al., 2002; Khatri et al., 2001). However, several studies did not provide details on the extent of this progression or the timing of the interventions (Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016).

The modes of exercise used in the AT interventions included the cycle ergometer (two studies, 22.22%) (Krogh et al., 2014; Krogh et al., 2012), a combination of cycle ergometer, fast gait or

jogging (two studies, 22.22%) (Herman et al., 2002; Khatri et al., 2001), walking or jogging on a treadmill (one study, 11.11%) (Blumenthal et al., 2007), running in the same place (one study, 11.11%) (Sadeghi et al., 2016), and treadmill or stationary bike (one study, 11.11%) (Dunn et al., 2005). Please refer to *Table 2* for more details.

4.3.2 RE (one RCT)

This exercise modality was performed with a frequency of three times per week and lasted for 10 weeks. The intensity was set at 80% of the one-repetition maximum (1RM), and each exercise consisted of three sets of eight repetitions. The progression depended on the individuals' tolerance capacity, and the decision for progression was based on their subjective perception of effort. The resistance exercises targeted large muscle groups using machines such as chest press, overhead pulldowns, leg press, knee extensions, and flexion. Each session lasted one hour and was accompanied by five minutes of stretching (Singh et al., 1997), *Table 2.*

Table 2 *FITT-VP parameters and means of the physical exercise program and control group*

Study, year, country	F	I	T/W	T	V	P	P	M	Duration of interventions (Weeks)	Supervised Exercise	CG
Krogh, 2012 Dinamarca	3	65% VO2MAX	90 min	Aerobic Training	30 min	Second Month: 70% Third Month: 80%	NR	Cycle ergometer	12	Yes	Stretching exercise
Krogh, 2014 Dinamarca	3	80 % HRmax	135 min	Aerobic Training	45 min	NR	NR	Cycle ergometer	12	Yes	Stretching exercise
Singh, 1996 USA	3	80% 1RM	180 min	Resistance Training	3 sets of 8 repetitions	Each session was tolerated by the subjects	SPE	Exercise machines	10	Yes	No exercise interventions
Herman, 2002 USA	3	70%–85% HRR	90 min	Aerobic Training	30 min	NR	SPE	Cycle ergometer, or brisk walking or jogging	16	Yes	Medication (sertraline 100 mg)
Blumenthal, 1999 USA	3	70%–85% HRR	90 min	Aerobic Training	30 min	NR	SPE	Cycle ergometer, or brisk walking or jogging	16	Yes	Medication (sertraline 50-200 mg)
Khatri, 2001 USA	3	70%–85% HRR	90 min	Aerobic Training	31 min	NR	SPE	Cycle ergometer, or brisk walking or jogging	16	Yes	Medication (sertraline 50-200 mg)
Blumenthal, 2007 USA	3	70%–85% HRR	90 min	Aerobic Training	30 min	NR	SPE	Walking or jogging on a treadmill	16	Yes	Medication (sertraline 50-200 mg)

Blumenthal, 2007 USA	3	70%–85% HRR	90 min	Home-based aerobic training	30 min	NR	SPE	Walking or jogging on a treadmill	16	No	Medication (sertraline 50-200 mg)
Sadeghi, 2016 Iran	NR	60-80% HRmax	NR	Aerobic Training	30 min	NR	NR	Running in place	8	Yes	12 sessions of cognitive behavior therapy
Dunn, 2005 USA	3	Low Intensity	90 min	Aerobic Training	30 min	NR	NR	Treadmill or stationary bicycle	12	Yes	Stretching flexibility
Dunn, 2005 USA	5	Low Intensity	150 min	Aerobic Training	30 min	NR	NR	Treadmill or stationary bicycle	12	Yes	Stretching flexibility
Dunn, 2005 USA	3	High Intensity	90 min	Aerobic Training	30 min	NR	NR	Treadmill or stationary bicycle	12	Yes	Stretching flexibility
Dunn, 2005 USA	5	High Intensity	150 min	Aerobic Training	30 min	NR	NR	Treadmill or stationary bicycle	12	Yes	Stretching flexibility

F: frequency; I: intensity; RM: repetition maximum; T/W: total working time per week; min: minute; T: type of exercise; V: volume; P: progression; M: means of exercise; CG: control group; NR: not reported; SPE: Subjective perception of effort; VO2MAX: Maximum Oxygen Consumption; HRmax: Maximum heart rate; HRR: Reserve heart rate.

4.4 Comparisons reported in the included studies.

Three studies (33.33%) compared AT with flexibility exercise (Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012). In one trial that implemented RE (11.11%), the control group did not undergo any type of intervention (Singh et al., 1997). Many of the studies used medication, primarily sertraline, as the comparator (five studies, 55.55%) (Blumenthal et al., 2007; Blumenthal et al., 1999; Herman et al., 2002; Khatri et al., 2001). Only one trial (11.11%) reported the use of cognitive behavioral therapy (Sadeghi et al., 2016), *Table 2.*

4.5 Methodological quality evaluation

Few studies in this systematic review had methodological difficulties (mean score 12). The quality assessment results are presented in *Supplement 1.* Two RCTs (22.22%) did not specify the method used for participant randomization (Sadeghi et al., 2016; Singh et al., 1997). Six studies (66.66%) did not describe whether group allocation was concealed from eligible patients (Blumenthal et al., 1999; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016; Singh et al., 1997). One RCT (11.11%) did not report if the assessor of at least one primary outcome measure was blinded to group assignment (Sadeghi et al., 2016). Five studies (55.55%) did not report adherence rates above 85% (Blumenthal et al., 2007; Blumenthal et al., 1999; Herman et al., 2002; Krogh et al., 2014; Sadeghi et al., 2016). Two trials (22.22%) reported no adverse events related to the interventions (Krogh et al., 2014; Sadeghi et al., 2016). Two RCTs (22.22%) did not report individual participation in exercise programs (Khatri et al., 2001; Sadeghi et al., 2016). Four studies (44.44%) did not perform intention-to-treat analyses for the outcomes of interest (Herman et al., 2002; Khatri et al., 2001; Sadeghi et al., 2016; Singh et al., 1997). Two studies (22.22%) did not provide point estimates in their results (Blumenthal et al., 2007; Blumenthal et al., 1999), and two did not collect information on physical activity levels from the control group (Krogh et al., 2014; Sadeghi et al., 2016). Lastly, one RCT (11.11%) did not calculate exercise volume and energy expenditure (Sadeghi et al., 2016). More details on the quality assessment are presented in *Supplement 1.*

4.6 Risk of bias in individual studies

Four studies (44.44%) achieved a low risk of bias in the domain evaluating the randomization process (Blumenthal et al., 2007; Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012). In one RCT (11.11%), the same rating was observed due to deviations from the planned interventions (Blumenthal et al., 2007). On the other hand, eight trials (88.88%) were rated as

low risk of bias in terms of incomplete outcome data (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Singh et al., 1997). Five studies (55.55%) achieved a low risk of bias in outcome measurement (Blumenthal et al., 2007; Blumenthal et al., 1999; Herman et al., 2002; Krogh et al., 2014; Krogh et al., 2012). Only three RCTs (33.33%) demonstrated a low risk of bias in reported outcome selection (Blumenthal et al., 2007; Krogh et al., 2014; Krogh et al., 2012). Overall, only one study (11.11%) received a low risk of bias rating (Blumenthal et al., 2007). Meanwhile, six trials (66.66%) were assessed as having a high risk of bias (Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Sadeghi et al., 2016; Singh et al., 1997), and two (22.22%) were rated as having some concerns (Krogh et al., 2014; Krogh et al., 2012). Please refer to *Supplement 1* for more details.

4.7 Report of exercise interventions in physical exercise programs

The reporting of CERT elements varied widely among the interventions, ranging from 0% to 100%. The most reported items were exercise supervision or lack thereof, detailed description and characteristics of exercises and interventions for replication purposes, adaptation, and initial level of PE programs for individuals, and whether there were any changes in planned exercises (reported in 100% of the interventions, 13 out of 13). On the other hand, the least reported items were motivation strategies (0.0%), qualifications and experience of those conducting the interventions, progression, and environment where exercise programs were conducted (reported in five interventions, 38.46%), and the description of any component at home or activities other than PE (reported in two interventions, 15.38%). Six CERT elements had reporting rates between 0% and 50% (items 2, 6, 7, 9, 10, 12), while six items were reported in 100% of the interventions (items 8, 13-16). Please refer to Supplement 1 for more information.

4.8 Evidence Summary

4.8.1 Qualitative synthesis

In the nine included RCTs, the effect of PE interventions on MDD symptomatology was investigated and compared to second-generation antidepressants or cognitive behavioral therapy, BME, or no-exercise interventions (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016; Singh et al., 1997). Out of these studies, four reported greater

reductions in MDD symptomatology scores because of the PE interventions (Blumenthal et al., 2007; Dunn et al., 2005; Herman et al., 2002; Singh et al., 1997). Conversely, four trials reported lower results in favor of the comparators (medication and BME) (Blumenthal et al., 1999; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012). One study conducted by Sadeghi in 2016 (Sadeghi et al., 2016) included three groups: AT, cognitive behavioral therapy, and no exercise interventions. At the end of the eight weeks, lower scores were found in participants who were part of the AT and psychotherapy group, indicating a positive effect of both interventions on MDD symptomatology.

4.8.2 Adverse Events Summary

One out of seven RCTs (14.2%) reported no adverse events (AEs) during the follow-up period. However, this study specifically mentioned that AEs were caused by performing the oxygen consumption test (Khatri et al., 2001).

On the other hand, six out of seven studies (85.7%) evaluated and reported AEs (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Krogh et al., 2012; Singh et al., 1997). Among these six trials, 5 (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Krogh et al., 2012) mentioned the occurrence of participant withdrawals due to medical or health-related reasons.

4.8.3 Adverse events in aerobic exercise participants

Among the 375 participants in the PE interventions, a total of 25 AEs were reported. These events were classified as grade one (5 events), grade two (10 events), grade three (9 events), grade four (1 event), and grade five (0 events). However, it should be noted that 19 of these events were not related to the intervention.

Among the participants in the PE group, six AEs (31%) occurred. These AEs included muscular events, other painful manifestations, and a medical contraindication. It is worth mentioning that these events were managed by using the cycle ergometer as the primary means of PE and additional medical review. For more details, please refer to *Supplement 1.*

4.8.4 Adverse events in participants on second-generation antidepressants, BME, or no exercise interventions.

Among the participants receiving second-generation antidepressants, BME, or no exercise interventions. a total of 39 AEs were reported among 308 participants. These events were

classified as grade one (0 events), grade two (14 events), grade three (25 events), grade four (0 events), and grade five (0 events).

Out of the 39 reported AEs, 21 (54%) were related to medications. These medication-related AEs included symptoms such as dizziness, drowsiness, agitation, and diarrhea. For more information, please refer to Supplement 1.

4.9 Quantitative synthesis

4.9.1 Primary outcome: depressive symptoms

Fig. 2 displays the results of the meta-analysis, which compares the effects of exercise modalities (AT, RE) with second-generation antidepressants, BME, or no exercise interventions on the symptoms of MDD. The forest plot does not present the results of AEs since they are assessed using a different approach.

The meta-analysis included 7 trials with a total of 12 interventions. The pooled SMD, calculated using the random effects model, was -0.27 with a 95% CI of [-0.58, 0.04). This indicates a small clinical effect in favor of exercise interventions, although the difference was not statistically significant. It is important to note that there was considerable heterogeneity among the included studies, as indicated by an I^2 value of 76%.

Physical exercise and controls

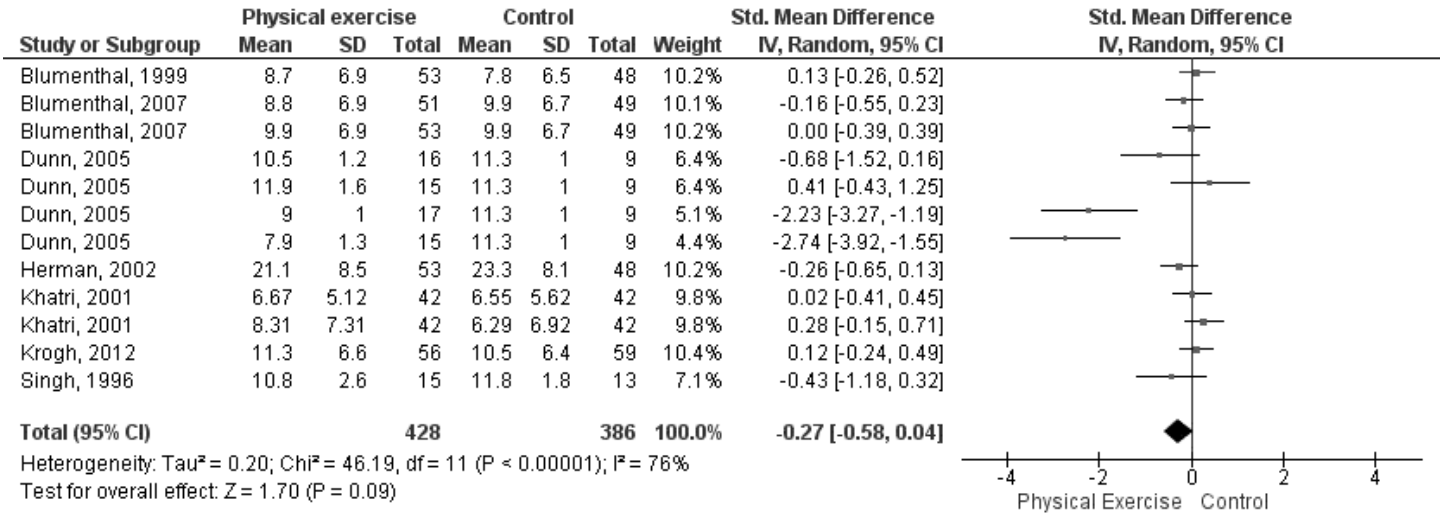

Fig. 2 Analysis of the effect of PE programs on depressive symptomatology in adults with MDD compared to control. I^2: heterogeneity, *p-value* <0,05, standardized mean difference, Random effects model

4.9.2 Subgroup Analysis

The analysis of specific subgroups and comparisons within the review provides additional insights into the effects of PE interventions on MDD symptoms. When focusing on RE, there was a non-significant small effect (-0.43) observed in one study, indicating a potential benefit but not reaching statistical significance (P = 0.26). Similarly, when using the HAM-D, a small effect (-0.46) was found, which approached statistical significance (P = 0.06). However, both analyses showed high heterogeneity (83% and 82% respectively).

A subgroup analysis targeting overweight and obese adults (one study) revealed a large effect size (-1.27), although it did not reach statistical significance (P = 0.07). The analysis based on age (two studies) showed a large effect (-0.94) in individuals under 50 years old, but again, statistical significance was not achieved (P = 0.09). Furthermore, PE performed five days per week (one study) demonstrated a large effect size (-1.13), but with considerable heterogeneity (94%). From one trial of multiple interventions, high-intensity PE interventions displayed a greater effect size (-2.45) compared to the primary outcomes, and it was statistically significant (P < 0.00001), with no heterogeneity observed (heterogeneity = 0%).

In terms of comparisons with different control conditions, when comparing PE (mainly AT) with medication, no significant effect size was found (-0.01, P = 0.94), with low heterogeneity (0%). Conversely, when comparing PE with flexibility exercise, a large effect size (-0.94) was observed, but it did not reach statistical significance (P = 0.09) and showed high heterogeneity

(90%). Only one study compared PE (RE) with no exercise, resulting in a non-significant effect size (-0.43, P = 0.26).

Please refer to *Supplement 1* for further details on these findings.

4.9.3 Sensitivity Analysis

In this review, this analysis was proposed using studies with controls without exercise interventions and a low risk of bias in the domains related to the randomization process and deviations from the intended interventions. Blumenthal et al, (2007) (Blumenthal et al., 2007) was the only study that obtained a low risk of bias rating in both domains. However, 4 studies were judged to have a low risk of bias in the randomization process (Blumenthal et al., 2007; Dunn et al., 2005; Krogh et al., 2014; Krogh et al., 2012). However, Krogh et al, (2014) (Krogh et al., 2014) were not included in the meta-analyses due to its lower methodological quality rating.

The analysis of these selected studies showed a moderate effect size in favor of PE compared to the primary results, with an effect size of -0.58. This effect size was not statistically significant, as indicated by the test for overall effect (Z = 2.00, P = 0.05). It is important to note that the level of imprecision and heterogeneity in these results was considerable. The estimated Tau^2 was 0.45, the Chi^2 value was 39.51 with degrees of freedom (df) = 6 (P < 0.00001), and the I^2 value was 85%. Please refer to *Figure 3* for a visual representation of these findings.

Meta-analyses of the non-exercise interventions control study by Singh et al (1996), reported similar findings to the primary outcomes, with an effect size of -0.26 (95% CI -0.59, 0.07, I^2 = 78%, P = 0.12). This suggests that no significant differences were found between interventions and controls in terms of depressive symptoms when comparing BME and medication (sertraline).

Sensity Analysis

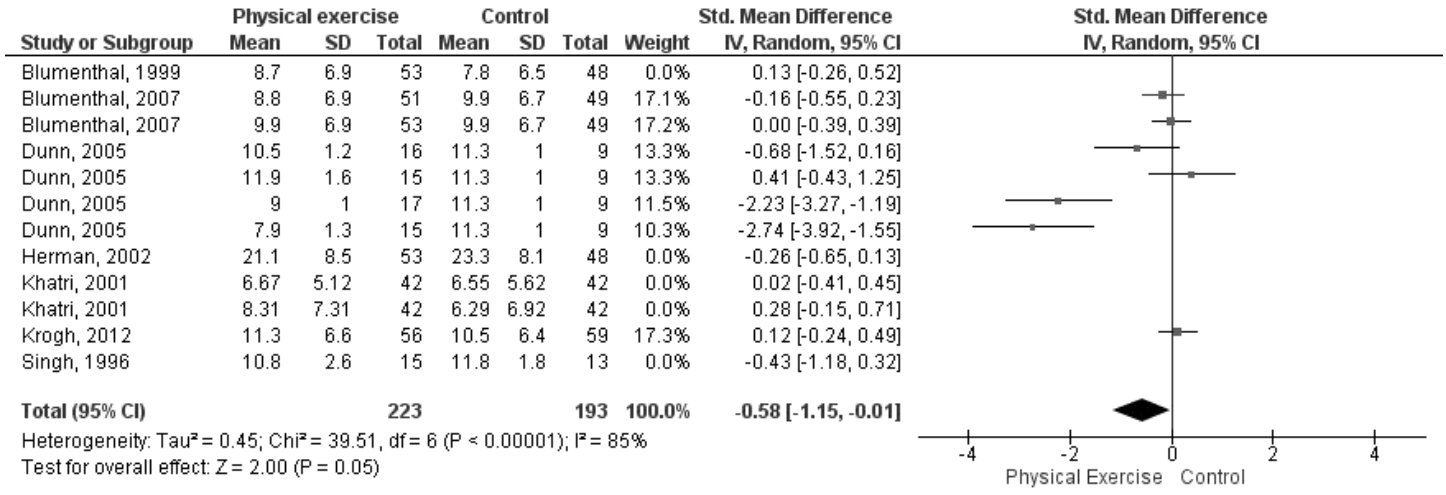

Fig. 3 Sensitivity analysis by removing studies with a high risk of bias. I^2: heterogeneity, *p-value* <0,05, standardized mean difference, Random effects model

4.9.4 Adverse events

The pooled analysis of seven randomized controlled trials (13 exercise arms) involving 812 participants (PE: n=441; BME: n= 371) did not find a significant difference in the risk of grade one to five AEs between PE interventions and second-generation antidepressants, BME or no exercise interventions. The analysis included a total of 65 AEs. The RD was -0.03 with a 95% CI ranging from -0.08 to 0.01. The P-value was 0.17, indicating no statistically significant difference. The I^2 value was 56%, suggesting moderate heterogeneity among the studies. Please refer to *Figure 4* for a graphical representation of these findings.

Adverse Events

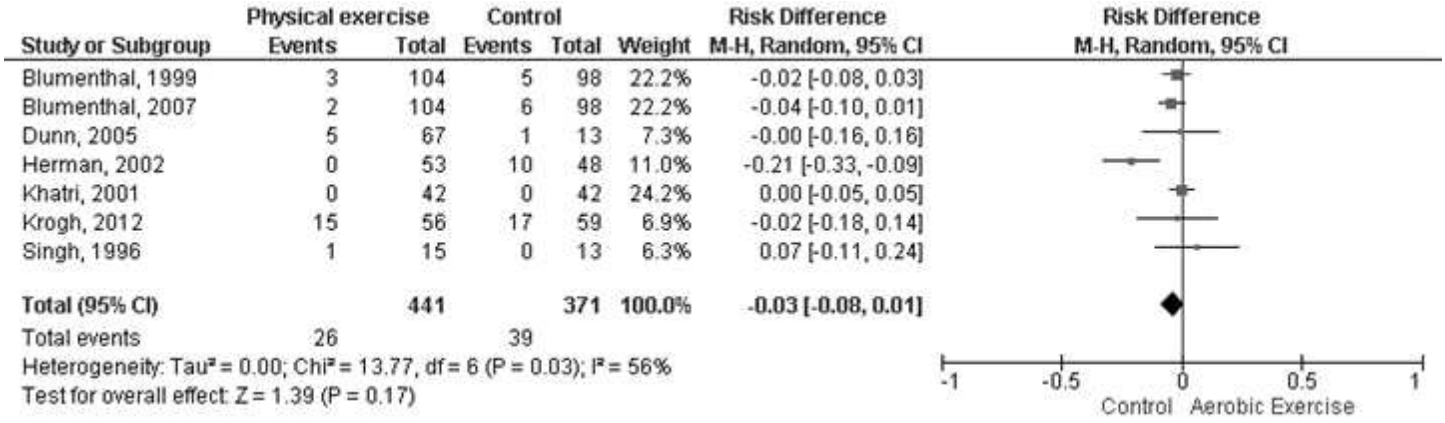

Fig. 4 Analysis of the effect of PE programs on AEs in adults with MDD compared to control. I^2: heterogeneity, p value <0,05. Risk difference. Mantel-Haenszel random effects model.

4.9.5 Quality of life

The two studies included in the meta-analysis, Krogh et al. (2012) (Krogh et al., 2012) and Singh et al. (1996) (Singh et al., 1997), evaluated the effect of PE interventions on general well-being in adults with MDD. Krogh et al. assessed well-being using the Five-Well-Being Index (WHQ-5) and found no statistically significant difference in post-intervention scores between the PE group and the control group ($p = 0.74$). Singh et al. evaluated well-being using the general health dimension of the health questionnaire (SF-36) and found a borderline significant difference between the intervention and control groups ($p = 0.06$).

Although there were only two studies with a total of 147 adults, the reviewers decided to conduct a meta-analysis. The pooled analysis showed a small effect size that slightly favored the control group, with a standardized mean difference of -0.04. However, this effect size was not statistically significant ($p = 0.79$), indicating no significant difference in general well-being between the PE interventions and the control conditions. The heterogeneity among the studies was very low ($I^2 = 0\%$), suggesting consistency in the results. Please refer to *Supplement 1* for further details.

4.9.6 Mortality

In the nine studies included in the review, no deaths were reported among any of the participants (Blumenthal et al., 2007; Blumenthal et al., 1999; Dunn et al., 2005; Herman et al., 2002; Khatri et al., 2001; Krogh et al., 2014; Krogh et al., 2012; Sadeghi et al., 2016; Singh et al., 1997).

4.10 Certainty of the evidence (GRADE)

The overall quality and certainty of the evidence in this review ranged from very low to low. The main factors contributing to the downgrade in quality were the risk of bias and imprecision, which were related to methodological shortcomings in the included RCTs and wide confidence intervals. Here are the key findings based on the level of evidence:

1. Depressive symptoms: There is very low-quality evidence suggesting a potential reduction in depressive symptoms when comparing PE to second-generation antidepressants, BME, or no exercise interventions. The SMD was -0.27 with a 95% CI of [-0.58, 0.04]. However, the statistical significance was not reached ($P = 0.09$), and there was considerable heterogeneity ($I^2 = 76\%$). The evidence was downgraded due to the risk of bias, inconsistency, and imprecision.

2. AEs: There is low-quality evidence indicating no significant difference in the risk of grade 1 to 5 AEs between PE and second-generation antidepressants, BME, or no exercise interventions. The RD was -0.03 with a 95% CI of [-0.08, 0.01]. The statistical analysis showed no significance (P = 0.17), and there was moderate heterogeneity (I^2 = 56%). The evidence was downgraded only for the risk of bias.

3. Quality of life: There is very low-quality evidence suggesting no significant difference in the reduction of quality of life between PE and second-generation antidepressants, BME, or exercise interventions. The SMD was -0.04 with a 95% CI of [-0.37, 0.28]. The analysis did not show statistical significance (P = 0.79), and there was no heterogeneity (I2 = 0%). The evidence was downgraded for risk of bias, indirect evidence, and imprecision.

Regarding mortality, it could not be estimated as there were no reported deaths in the included studies. Therefore, no conclusions can be drawn regarding the impact of PE interventions on mortality based on the available evidence.

It is important to consider the limitations of the included studies and the overall quality of the evidence when interpreting these findings.

5 Discussion

5.1 Summary of main results

In this review, a total of nine trials were included, out of which seven were rated as having high methodological quality (meta-analysis). These trials provided valuable insights into the benefits and potential harms associated with PE (AT and RE) interventions for individuals with MDD without second-generation antidepressants or cognitive behavioral therapy before PE interventions. The study population was heterogeneous, consisting of young and older adults, both sexes, some of whom were overweight or obese and had various comorbidities such as endocrine, cardiac, pulmonary, and orthopedic disorders. Many of the participants were not physically active at baseline.

These trials allowed for comparisons between PE and other interventions such as medication use, flexibility exercise, cognitive behavioral therapy, or no exercise intervention. The main findings indicate that supervised PE, primarily AT, had a small effect size in reducing depressive

symptoms compared to control conditions groups, although the difference was not statistically significant.

Some of the subgroup analyses showed a large effect (overweight and obese adults, individuals under 50 years old, five days per week, and comparing PE with flexibility exercise). However, it is important to note that many of these effects are based on findings from one or two trials, and when compared with control conditions, no statistically significant differences and considerable heterogeneity were observed. Only the supervised PE performed at high intensities (one study with multiple interventions) had a large effect size, presenting significant differences and 0% heterogeneity.

In the sensitivity analyses, moderate and small effects were observed, although they did not show statistically significant differences when performed by selecting low risk of bias in the domains related to the randomization process and deviations from the intended interventions and non-exercise interventions control study.

Regarding safety, 1 RCT (Krogh et al., 2012) provided inconclusive evidence on the safety of exercise interventions. 19 reported AEs were not directly related to PE, and some of them were managed with the use of a cycle ergometer. There was a higher incidence of AEs reported in control groups receiving medication, including symptoms such as dizziness, drowsiness, agitation, and diarrhea. The effect of PE on quality of life, based on data from 147 adults, was rated as trivial and did not reach statistical significance. Lastly, none of the included studies reported any instances of mortality among the participants.

5.2 Overall completeness and applicability of evidence

The findings of this review primarily apply to adults between the ages of 20 and 72 who were diagnosed with MDD and were not receiving second-generation antidepressants or cognitive behavioral therapy. However, it's important to note that some of the included RCTs did not provide sufficient information about the participants' characteristics, such as body composition or the use of medications for other conditions. Additionally, information about the participants' usual or non-usual physical activity levels and employment status was not consistently reported across all trials.

To the best of the reviewers' knowledge, this is the first systematic review to specifically evaluate the effects of PE on MDD symptoms in individuals without prior use of second-generation antidepressants or cognitive behavioral therapy. The subgroup analyses conducted

in the review provide detailed insights into the effects of PE compared to control conditions on specific symptoms associated with MDD. This level of detail enhances our understanding of each intervention and its impact on the symptoms of the disorder.

5.3 Certainty of the Evidence

Indeed, the strength of evidence in this review (GRADE framework) was generally assessed as low to very low. This assessment was influenced by several limitations identified in the included studies, including issues related to risk of bias, inconsistency, and imprecision.

While seven out of the nine included RCTs were evaluated as high quality, some of them had certain shortcomings. For instance, they did not publish the trial protocols in a designated repository and failed to provide detailed descriptions of the statistical or mathematical procedures used for sample size calculations.

The overall risk of bias for the included RCTs was determined to be high, with some concerns. This was primarily due to a lack of reporting regarding the methods used for implementing and concealing randomization, absence of blinding of participants, intervention providers, and outcome assessors, as well as deviations from the intended interventions in some cases.

Additionally, few RCTs provided information on deviations from the planned interventions resulting from the trial setting. These limitations contribute to the overall assessment of the quality of evidence and highlight the need for more rigorous study design and reporting in future research.

5.4 Potential biases in the overview process

This review has some limitations, the first having to do with clinical, methodological, and statistical heterogeneity. From a clinical point of view, the effect of PE was affected by the characteristics of the patients, the interventions, and the results. The true effect of the intervention differed between studies. In methodological terms, some studies do not report blinding and concealment of the allocation sequence, and different instruments were used to measure depressive symptomatology. In summary, the studies suffered from different degrees of bias. Also, in the estimated effect, we obtained a large Chi^2 (statistical test of heterogeneity) and a small P value, which translates into heterogeneity of the effects of the interventions. This is because the review had few studies and small sample sizes (uncertainty in the I^2 value). Therefore, the presence of heterogeneity affected the extent to which generalizable conclusions

can be made. Although we performed an analysis based on random effects, these results need to be taken with caution. On the other hand, we ran a subgroup analysis to explore heterogeneity. There we find that it was substantial and considerable. This further strengthens the cautious interpretation of these findings. By excluding from the meta-analysis two atypical interventions from the study by Dunn et al (2005) (Dunn et al., 2005) (Frequency 3; High intensity; session duration between 90 and 150 minutes for 12 weeks), we found an effect size of -0.01 [-0.16, 0.14] I^2 = 6% (P = 0.39), which evidently demonstrated that the results of these interventions conflicted with the rest of the studies.

The second limitation of this review has to do with the lack of statistical power. An example of this is the subgroup analyses since we have less than 10 studies for each characteristic chosen for the analysis. In summary, this review not only has fewer than 10 included studies but also fewer included studies than analyzes performed.

A potential strength of this review was the performance of random-effects meta-analyses of continuous data (different, but related studies), because the outcome was measured using different scales or units. This model assumes that the differences observed between the results of the RCTs are due to a combination of chance and some genuine variation in the effects of the intervention. We also used the SMD, a recommended test to avoid extreme heterogeneity in the results when cases such as the one described above occur. However, the random effects model also has a drawback in interpreting these findings. This is because, the presence of heterogeneity, gives greater statistical weight to studies with small effects and less weight to those with large effects. Added to this is the asymmetry between the studies (imprecision), which possibly pushed the results of the randomized model toward the findings of the smaller studies.

Indeed, the lack of detailed information on the progression and decision-making related to PE programs is a notable limitation of this review. Without clear and comprehensive descriptions of how the PE interventions were implemented, it becomes challenging for healthcare professionals to replicate and apply these interventions in clinical practice effectively.

On the other hand, this systematic review adhered to the highest methodological standards, following established guidelines (J. C. Andrews et al., 2013; T. J. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors), 2022; Page et al., 2021). Rigorous methods were employed, including comprehensive searches of scientific databases, clinical trial repositories, grey literature, and manual searches. The process of study selection and data

extraction was carried out independently by reviewers who were blinded to minimize bias. This robust methodology strengthens the reliability and credibility of the study.

The experience and expertise of the research team, including university professors and physicians specialized in exercise science and physical activity, undoubtedly constitute a significant strength of this review. However, as the authors themselves acknowledge, the absence of a psychiatrist or mental health expert within the group of reviewers is an important limitation.

The findings and certainty of evidence generated by this study will serve as a valuable resource for the development of future clinical practice guidelines, particularly those focusing on non-pharmacological strategies for the treatment of depressive disorders. However, it is important to acknowledge the methodological limitations identified in the included RCTs. These limitations should be taken into consideration when interpreting the results and applying them to clinical practice.

5.5 Agreements and Disagreements with Other Reviews

In recent years, systematic reviews have been published examining the effect of PE on adults with and without MDD (Cooney et al., 2013; Fernandes et al., 2022; Khazaie et al., 2022; Krogh et al., 2017; Liu et al., 2022; Morres et al., 2019; Sanhueza Pastén & Caneo, 2022; Seshadri et al., 2020; Yu et al., 2022). These reviews generally support the notion that exercise can reduce the symptoms of MDD. However, it is worth noting that some of these reviews did not use the GRADE framework to evaluate and classify the certainty of their findings (Fernandes et al., 2022; Khazaie et al., 2022; Morres et al., 2019; Seshadri et al., 2020), and the level of certainty in others varied from moderate to very low quality (Cooney et al., 2013; Krogh et al., 2017; Sanhueza Pastén & Caneo, 2022; Seshadri et al., 2020; Yu et al., 2022).

One systematic review (Cooney et al., 2013) found a larger effect size than the present review, but this effect was only significant when compared to no intervention or placebo. Additionally, their review did not assess the effect of PE compared to all types of controls, including placebo, psychological therapy, alternative treatments, and medications, among others.

Other systematic reviews have reported findings like our study (Krogh et al., 2017; Morres et al., 2019; Seshadri et al., 2020). For example, Krogh et al. in 2017 (Krogh et al., 2017), reported a trivial effect size of very low quality when pooling studies with low risk of bias. They also found it challenging to assess adverse events due to a lack of information. In our review, we observed a low effect size based on studies of high methodological quality (TESTEX).

Furthermore, our findings suggest that PE is associated with fewer harms compared to medications.

Seshadri et al. 2020 (Seshadri et al., 2020) examined the effects of various forms of exercise (including PE, yoga, and Tai chi) on reducing depressive symptoms in adults with MDD. Some of the included studies in their review involved participants who were concurrently using medication. However, our review did not include exercise as an adjunct to medication but rather compared exercise to other control interventions. Additionally, our review specifically focused on individuals who were not receiving second-generation antidepressants or cognitive behavioral therapy for MDD before PE interventions.

This review employed a specific search strategy guided by the COCHRANE Ibero-America network's expert librarians, resulting in a smaller number of RCTs to screen compared to previous publications. By following the established guidelines and utilizing accurate mapping of studies using Medical Subject Headings (MeSH), we ensured the inclusion of all relevant RCTs related to our PICOTS.

In contrast, Krogh et al. (2017) (Krogh et al., 2017) screened a larger number of trials (25,435) due to different search terms used in their search strategy. Furthermore, their study did not specifically include the term "Depressive Disorder, Major," which is crucial for identifying clinical or major depression. Additionally, their review included RCTs comparing exercise interventions with controls and exercise plus medication with controls. However, it is not specified whether the patients in their included studies were already undergoing second-generation medication or cognitive behavioral therapy before the exercise interventions.

Similarly, Yu et al. (2022) (Yu et al., 2022) reported a larger number of studies in their search results because they aimed to cover various mental health disorders, including depression, anxiety, phobias, post-traumatic stress, mood disorders, among others.

Another study by Wu et al. in 2023 investigated the effects of Yoga interventions on the severity of symptoms associated with MDD (Wu et al., 2023). Their findings indicated a moderate effect, but the certainty of evidence was rated as low to moderate. It is important to note that some of the RCTs included in their review incorporated second-generation antidepressants or cognitive behavioral therapy alongside Yoga interventions. They performed subgroup analyses considering factors such as patients' place of residence, duration of interventions, frequency, and whether the intervention was performed independently or combined with meditation. However, subgroup analyses comparing the interventions to control conditions were not reported.

In contrast, our review specifically focused on the effects of exercise interventions in individuals who were not receiving second-generation antidepressants or cognitive behavioral therapy before the interventions. This was considered a comparator in our study. In our subgroup analysis, when comparing AT with medication (sertraline), the effect size was not statistically significant (-0.01 [-0.17, 0.16], I2 = 0%). This suggests that both treatments may be effective in improving symptoms.

However, it is important to note that this comparison was specific to sertraline, and the effectiveness of exercise compared to other medications such as escitalopram, citalopram, fluoxetine, paroxetine, or duloxetine remains unclear. Considering patient preferences is important, as medications may have adverse events and may be difficult to access in low- and middle-income countries (Evans-Lacko et al., 2018; Qaseem et al., 2016). On the other hand, exercise is a safe and easily accessible non-pharmacological treatment option for various populations.

In our sensitivity analyses, we observed a different effect size when compared to the control groups. These results suggest that, when considering studies with a low risk of bias in important methodological aspects (RoB II), there is a moderate effect size favoring PE interventions in reducing symptoms of MDD. However, it is important to note that this result did not reach statistical significance. Furthermore, the presence of high heterogeneity and imprecision among the included studies emphasizes the need for further research and investigation to better understand the true impact of PE interventions on MDD symptoms. Caution should be exercised when interpreting these findings.

5.6 Implications for Practice

This systematic review offers a comprehensive and current overview of the impact of PE on MDD in adults who have not received second-generation antidepressants or cognitive behavioral therapy before exercise interventions. The findings of this review can be valuable for individuals and their families affected by depression, general practitioners, psychiatrists, professionals in the field of physical activity, and policymakers involved in mental health. However, it should be noted that some of the included RCTs lack complete information on the PE programs, which may hinder their replication in interested communities.

The results of this review suggest that there are some promising effects observed in certain subgroups when it comes to the impact of PE interventions on depressive symptoms in adults with MDD. However, it is crucial to approach these findings with caution, considering the limitations of the included studies and the potential heterogeneity among them. The overall

evidence from the review is inconclusive, mainly due to the risk of bias of the studies. The small number of trials and participants included in some subgroups may have affected the statistical power and precision of the results. Therefore, the lack of statistical significance in certain subgroups should be interpreted with caution, as it may be influenced by the limited sample size.

In conclusion, while this review offers valuable insights into the potential effects of PE interventions on depressive symptoms in adults with MDD, it also highlights the need for further research to address the limitations and strengthen the evidence.

5.7 Implications for Future Research

It is currently not possible to definitively determine the optimal dose of PE required to reduce depressive symptoms in patients with MDD who do not receive second-generation drugs or attend cognitive behavioral therapy.

Future RCTs should be conducted with homogeneous populations, considering detailed and precise definitions of the characteristics of exercise interventions. Specifically, they should assess the effect when exercise is performed at moderate intensities compared to high intensities.

Additionally, it is important to explore the effects of exercise modalities other than AT. Considering RE and its combination with AT for populations with this disorder is crucial. Similarly, these studies should involve multidisciplinary researchers, including psychiatrists and physical educators. Furthermore, future research should place a strong emphasis on providing comprehensive and detailed descriptions of PE interventions, including their progression and decision-making processes. This will enhance the transparency and reproducibility of the studies and enable clinicians to implement evidence-based exercise interventions with greater confidence in managing depressive symptoms in individuals with MDD.

Likewise, the results of this review suggest that future RCTs should be developed in full compliance with protocol construction checklists (Chan et al., 2015) and final reports on non-pharmacological randomized controlled trials (Boutron et al., 2017). Furthermore, it is important to evaluate the methodological quality of these studies using instruments specifically designed for this purpose, such as the TESTEX (Neil A. Smart et al., 2015). Detailed descriptions of exercise interventions should be provided to facilitate replication. Authors should adhere to international reporting guidelines, such as the Consensus on Exercise Reporting Template (CERT) (Susan C. Slade et al., 2016) or the Intervention Description and

Replication Template (TIDieR) checklist and guide (Hoffmann et al., 2014), when formulating and publishing these studies. However, it should be noted that some RCTs included in this review did not publish their protocols in a controlled trial repository. To address this issue, adherence to the CONSORT Statement (Boutron et al., 2017) is recommended. Future systematic reviews focusing on this topic should assess the strength and certainty of the results (J. C. Andrews et al., 2013) to ensure credibility for decision-makers.

Therefore, considering the limitations identified in this review, further research is needed to provide a clearer understanding of the effects of PE interventions on depressive symptoms in individuals with MDD. Larger-scale, well-designed RCTs with consistent methodologies are necessary to establish stronger and more reliable evidence in this area.

6 Conclusion

The available evidence, although of low to very low certainty, indicates that supervised PE (mainly AT) does not show statistically significant differences when compared with second-generation medication or cognitive behavioral therapy, BME, or no exercise interventions in terms of managing symptoms caused by MDD. Additionally, no significant differences were observed in terms of harm or adverse events between these interventions. Subgroup and sensitivity analyses showed moderate and large effects in favor of PE, but without statistical significance and with high heterogeneity.

Indeed, it is crucial to interpret these results with caution due to the limitations mentioned earlier in this review. The identified limitations, such as clinical, methodological, and statistical heterogeneity among the included studies, small sample sizes, and lack of detailed information on progression and decisions related to PE programs, may impact the generalizability and applicability of the findings.

Declarations

This research project did not receive any funding.

Conflicts of interest/competing interests

The authors of this meta-analysis have no conflicts of interest that are directly related to the content of this article.

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Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material

The data sets generated and/or analyzed during the implementation of the study are available from the corresponding author upon request.

Code availability: Not applicable.

Authors Contributions:

Dr. Édison Pérez has all the data from the study and assumes responsibility for the analysis of the data. MSc Luisa Puerta and Professor Daniel López acted as primary co-authors.

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7 CHAPTER 02: FLYWHEEL RESISTANCE TRAINING AND DEPRESSIVE SYMPTOMS IN OLDER WOMEN: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Objective: This trial aimed to compare the effect of resistance training using Flywheel devices versus traditional methods on alleviating depressive symptoms among sedentary older women.

Methods: This randomized controlled trial, conducted from May to December 2023 at the Federal University of Viçosa, Brazil, involved 29 sedentary women over 60 without clinical depression. Participants were randomly assigned to Flywheel or traditional resistance training for eight weeks, performing six exercises twice a week. The primary outcome was depressive symptoms. Randomization used blocks of two and four via random number software. Blinding was maintained by concealing group assignments in sealed envelopes, managed by an external investigator, with both the outcome assessor and principal investigators blinded.

Results: Twenty-nine women were assigned to Flywheel (n=14) or traditional (n=15) training. The trial concluded with no significant deviations from the planned interventions. Data from all participants were included, with one dropout in the control group necessitating multiple imputation analyses. Adjusted depressive symptom scores were 2.7 ± 2.7 for Flywheel (a 2.5-point decrease) and 2.0 ± 2.8 for traditional (a 2.0-point decrease), with no significant differences (p=0.193). The effect size was small ($\eta p^2 = 0.03$) with low statistical power ($1-\beta = 0.25$). Reported adverse events were mild (grade 1), with no severe events.

Conclusion: Both resistance exercise interventions, Flywheel and traditional, may reduce depressive symptoms in sedentary older women. Further research with larger samples and greater power is needed to confirm these findings.

Trial registration: ClinicalTrials.gov NCT05910632

Keywords: depression; elderly; exercise; resistance training; harms.

8 Background

Depression, recognized as a dominant contributor to global disability, impacts an estimated 280 million individuals (Yin et al., 2022). Among older adults, its prevalence stands at 5.7% (Iemmi, 2022; Nakamura et al., 2022). Furthermore, it is noteworthy that depression is 50% more prevalent in women (Woody et al., 2017) and manifests as a sustained loss of interest and pleasure in daily activities for a minimum duration of two weeks. Diagnostic indicators encompass substantial changes in weight or appetite, disruptions in sleep patterns, psychomotor agitation or retardation, fatigue, feelings of worthlessness, difficulties in concentration, and contemplation of suicide (Sanhueza Pastén & Caneo, 2022).

Alarmingly, over 50% of suicide cases occur in individuals without documented psychiatric conditions (Bachmann, 2018), culminating in a staggering 700,000 annual suicides (Villarroel & Terlizzi, 2020). In 2019, the Americas witnessed 97,339 incidences of suicide, predominantly affecting men (PAHO, 2021). Of particular concern, Brazil reported a suicide rate of 6,400 per 100,000 inhabitants, with 41% of its populace grappling with depression in 2022 (Nakamura et al., 2022). The severity of depressive symptoms is notably higher among adults, with a particular emphasis on women (Grigolon et al., 2023). Adults diagnosed with depression are at a heightened risk of developing comorbid conditions, including diabetes, heart attacks, lower back pain, and a decreased quality of life. These conditions contribute to elevated morbidity and mortality rates among this population (Amiri, 2022; Orsolini et al., 2022). In 2010, the economic burden associated with depression in the United States amounted to $210.5 billion. Over a decade, this figure escalated to almost $390 billion by 2020. Notably, direct treatment costs represented a mere 11.2% of this financial load (Greenberg et al., 2021). An efficacious treatment regimen has the potential to engender a global economic advantage of $230 billion by the year 2030 (Dishman et al., 2021).

Standard interventions comprise second-generation pharmaceuticals and cognitive-behavioral therapy (Qaseem et al., 2016), A significant number, exceeding 75%, of individuals in low- and middle-income countries are deprived of appropriate medical care as a result of limited resources, insufficiency of healthcare professionals, and prevalent social stigma (Evans-Lacko et al., 2018). It is important to note that commonly prescribed medications may also be associated with significant adverse events (Qaseem et al., 2016). Engaging in physical exercise provides a secure and readily available approach to mitigate depressive symptoms (Pérez-López et al., 2017).

Some Randomized Controlled Trials (RCTs) (Cunha et al., 2023; Leng et al., 2018; Soori et al., 2022), systematic reviews (Pérez Bedoya É et al., 2023), and 1 umbrella review (Križaj et al., 2022) have assessed how effective physical exercise is in reducing depressive symptoms in sedentary adults and those with comorbidities. RCTs conducted by Soori et al. (2022) (Soori et al., 2022) and a systematic review by Pérez-López et al. (2017) (Pérez-López et al., 2017) have provided evidence of the efficacy of short-duration aerobic exercise and Pilates interventions in reducing depressive symptoms and regulating serotonin levels. In a RCT conducted by Cunha et al. (2023) (Cunha et al., 2023), the effects of extended resistance training on depressive symptoms in elderly women were investigated, demonstrating potential enhancements in mental well-being.

An umbrella review showcased the advantages of eccentric exercise for elderly individuals, although it did not specifically address depressive symptoms (Križaj et al., 2022). RCTs evaluating the impact of flywheel resistance training have shown significant improvements in functional performance, mobility, muscle strength, and postural stability among the elderly (Floreani et al., 2022; Sañudo et al., 2022; Sañudo et al., 2019). The effect of flywheel resistance training on depressive symptoms among older women has not yet been investigated. This trial was designed to assess the effect of an 8-week flywheel resistance training program on depressive symptoms and adverse events in sedentary older women. Secondary outcomes encompassed quality of life, strength manifestations, and blood pressure. Our hypothesis posited that participants in the intervention group would manifest greater reductions in depressive symptoms relative to those in the control group.

9 Methods

9.1. Procedures

This study employed a parallel two-arm randomized controlled trial design, adhering to the recommendations outlined by the CONSORT Statement guideline for controlled trials of non-pharmacological interventions (Boutron et al., 2017). The methodological quality of this RCT was assessed using the Tool for Assessing Study Quality and Reporting in Studies of Physical Training (TESTEX) (N. A. Smart et al., 2015).

Following sample size calculation, an external researcher randomized women into either the intervention or control groups using blocks 2 and 4, facilitated by sealed envelope software. The study commenced after approval from the ethics committee of the Federal University of

Viçosa, with reference number 1,821,139. Additionally, this trial was registered in the clinical trials repository under the identifier NCT05910632. Before enrollment, all participants provided written informed consent, which included information about potential benefits and harms.

Eligible participants were women aged 60 or older residing in the community of Viçosa, Brazil. Recruitment methods included email communication, newspaper articles, visits to specialized centers for the elderly, and distribution of flyers. Inclusion criteria required women to be aged 60 or older, proficient in Portuguese, willing to participate in all trial procedures, have good vision, engage in at least 4 hours of sedentary behavior daily, and not diagnosed with major depressive disorder or taking second-generation medications. Exclusion criteria included uncontrolled chronic diseases, psychiatric illness, scheduled surgeries, joint diseases, and recent participation in resistance training programs.

Sedentary behavior was assessed using a self-developed question, with all participants reporting an average of 6 hours per day spent in sedentary activities. Participants were provided detailed information about the research phases, including potential benefits and risks, and assured of confidentiality throughout the study.

9.2. Sample size

Sample size calculation was based on a RCT that evaluated resistance training's effect on general depressive symptoms in older women, utilizing the Korean version of the short form of the Geriatric Depression Scale (GDS-SK) (Jin et al., 2019). This study reported a mean difference of 2.3 between intervention and control groups, with a common standard deviation of 1.3. With a 95% confidence level, alpha error of 0.05, and desired power of 90%, the initial minimum sample size required was 20 women. However, the sample size was increased to 29 women to ensure robustness and internal validity, with a 1:1 allocation ratio between groups. Sample size calculation was performed using the EPIDAT 4.2 computer program.

9.3. Randomization and blinding

The allocation of women to intervention and control groups was blinded by an external investigator using sequentially numbered and sealed envelopes. The primary investigator and all other personnel involved remained unaware of group assignments. Professionals administering interventions and participants were also blinded until initial evaluations were

completed. Additionally, the principal investigator and those assessing study results were blinded to treatment assignments.

9.4. Assessments

9.4.1. Medical history, and blood pressure

During the initial visit, demographic and medical history data were collected via an interviewer-administered questionnaire.

Blood pressure (BP) was measured on the right arm using a Minimus® III aneroid sphygmomanometer, with systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) calculated accordingly. MAP was calculated as ((2×DBP) + SBP)/3.

9.4.2. Depression symptoms

Depressive symptoms were assessed using a validated Brazilian version of the Geriatric Depression Scale (GDS) in its abbreviated form, comprising 15 questions regarding emotional well-being and the frequency of specific life circumstances. Responses were categorical (yes or no). Ten items affirmed depression with positive responses, while the remaining items indicated depression with negative responses. Total scores exceeding 0 indicated depression, with higher scores indicating greater symptom severity (Milena Sampaio Castelo et al., 2010). Participants completed the questionnaire at baseline and after the 8-week intervention.

9.4.3. World Health Organization Quality of life assessment-Bref (WHOQOL-Bref)

Quality of life and general health were evaluated using a twenty-six-item questionnaire on a 5-point Likert scale across four domains: physical health, psychological health, social relationships, and environment. The WHOQOL-Bref questionnaire was utilized to derive scores ranging from 0 to 100, with higher scores indicating better quality of life. The Brazilian version of the WHOQOL-Bref (Rocha & Fleck, 2009), adhering to international standards for reliability, validity, test-retest, and sensitivity analysis, was employed. Participants completed the questionnaire at baseline and after the 8-week intervention.

9.4.4. Different manifestations of muscle strength

To assess maximum isometric voluntary contraction (MIVC) of the lower limbs, a load cell (MK®, model CSL/ZL-1 T, MK Controle, Brazil) was affixed to a BH Fitness® Nevada Pro-t leg extension machine, sampling at 1000 Hz. Participants executed maximal isometric quadriceps femoris contractions for 5 seconds with knees at a 90° flexion angle, measured with a goniometer (Carci®, São Paulo, Brazil). The highest of two attempts, recorded for subsequent analysis, was selected (Patrocinio de Oliveira et al., 2018).

For the 1RM test, participants extended their knees from a 90° to 180° angle on the same machine. A warm-up session with a 30% MIVC load preceded, and perceived exertion was assessed with the OMNI-RES scale (Gearhart et al., 2011). Load adjustments were made based on participant feedback until they could perform one proper repetition.

Lower limb muscular power was assessed with loads at 40%, 60%, and 80% of 1RM, randomized for each participant. Participants performed knee extension movements at maximal speed for each load, followed by a controlled return. Power was measured using a Chronojump Encoder (Chronojump® Boscosystem, Barcelona, Spain) at 1000 Hertz, with mean power (MP) and peak power (PP) calculated from the highest of three repetitions using Chronojump Software, version 1.6.2 (Chronojump® Boscosystem, Barcelona, Spain) (Moreira et al., 2022).

9.4.5. Harms

AEs were systematically assessed using a self-designed questionnaire with categorical "yes" or "no" responses. Administered and supervised by laboratory personnel, participants completed the questionnaire before and during interventions, overseen continuously by the principal investigator. All potential AEs, including exercise-unrelated events, were recorded. Exercise-related events were categorized based on severity using the "Common Terminology Criteria for Adverse Events" version 5.0 (CTCAEv5.0), with grades ranging from 1 to 5 (Health & Human, 2020). Incidences between groups were reported, distinguishing if they were attributed to exercise. Withdrawals prompted by medical reasons were classified as grade 3 AEs, while grades 1 to 2 represented typical physiological responses to exercise, recorded but not considered preventable (see supplementary material: Table 6. Adverse Events).

9.5. Resistance training interventions

The resistance training interventions were described using the Consensus Exercise Reporting Template (CERT) (S. C. Slade et al., 2016) to ensure standardized reporting. The interventions

were based on findings from the National Strength and Conditioning Association (Fragala et al., 2019).

Materials: Participants in the flywheel group used multi-station equipment with a flywheel (Physical Solutions, Multi Leg model, Santo Amaro/São Paulo/Brazil) while the control group used gym machines and free weights.

Image 1: Physical Solutions, Multi Leg model, Santo Amaro/São Paulo/Brazil

Provider: Physical Education students, trained by the principal investigator, supervised the sessions.

Delivery: Sessions were conducted in groups or individually, with close supervision to ensure proper technique. Adherence was monitored, and participants were encouraged through feedback and progress discussions.

Progression: Flywheel participants progressed by mobilizing the flywheel at maximum speed, while controls increased weight if they completed more than 12 repetitions with proper form.

Exercise Routine: Each resistance workout consisted of 6 generic exercises targeting various muscle groups, including leg extension, leg curl, biceps curl, seated row, shoulder flexion, and calf raise.

Non-Resistance Components: No home exercise or non-resistance components were included.

Safety Measures: Adverse events were documented and reported promptly.

Location: Flywheel sessions were held at the Human Morphophysiology Analysis Laboratory (HUMANLAB), while control sessions took place in the university gym.

9.5.1. Flywheel resistance training (intervention group)

During flywheel resistance training, participants utilized a multi-gym flywheel device engaging both upper and lower extremities. Sessions consisted of 6 exercises targeting each muscle group twice weekly over 8 weeks (Fernandez-Gonzalo et al., 2016; Patrocinio de Oliveira et al., 2018). Supervised by Physical Education students, participants underwent a 2-week familiarization period before training.

Each session included a 5-minute warm-up focusing on joint mobility, followed by 50 minutes of resistance training with the flywheel. A 5-minute cool-down concluded each session. The protocol comprised 4 sets of 8 repetitions per exercise with 2-minute rests between exercises and sets.

Participants exerted maximal effort during the concentric phase, with the flywheel generating resistance during the eccentric phase. Exercise intensity was evaluated using the OMNI-RES scale (Gearhart et al., 2011). Verbal encouragement emphasized maximal effort and avoiding the Valsalva maneuver. Table 3 outlines frequency, intensity, total work time, type of exercise, volume, and progression.

9.5.2. Traditional resistance training (control group)

Older women engaged in muscle group stimulation twice weekly over 8 weeks under the supervision of undergraduate and graduate students majoring in physical education. Before starting interventions, participants underwent a 2-week familiarization period to master resistance training techniques. Each session followed a structured format: a 5-minute warm-up focusing on joint mobility, a 50-minute resistance training segment utilizing machines and free weights, and a 5-minute cool-down phase, replicating warm-up movements. Participants were reminded to avoid the Valsalva maneuver. Both groups refrained from other physical activities, reporting their activity levels before and after the trial (see Table 3).

Table 3
Dose characteristics of resistance training programs.

	FLYWHEEL RESISTANCE TRAINING (Intervention)	TRADITIONAL RESISTANCE TRAINING (Control)
FREQUENCY	2x/week	2x/week
INTENSITY	Moderate to high 6 - 10 in OMNI-RES Scale*	Moderate to high 6 to 10 on OMNI-RES Scale*
TOTAL RESISTANCE TRAINING TIME PER WEEK (MIN)	120	120
VOLUME	4 sets, 8 rep.	4 sets, 8-12 rep.
PROGRESSION	Execution speed	2 – 5% of the mobilized load
REST BETWEEN EXERCISES (s)	120	120
REST BETWEEN SETS (s)	120	120
PROGRAM DURATION (W)	8	8
	TIME UNDER TENSION	
CONCENTRIC PHASE (s)	1	1
ECCENTRIC PHASE (s)	2	2

*OMNI-RES Scale: to monitor and ensure that the women's group is performing resistance training at moderate to vigorous intensities. Score 6 to 10.
The progression will be made when, with a weight in kilograms, the woman performs more than 12 repetitions.

9.6. Statistical analysis

To assess the normality of the distribution of quantitative variables, the Shapiro-Wilk test was utilized, and the Levene test was employed to examine the homogeneity of variance. These statistical tests determined that the variables conformed to a normal distribution ($p > 0.05$). Given the normal distribution of these variables, we present them in terms of means and standard deviations. The student t-test for independent samples was applied to compare the initial results between groups. The statistical differences were confirmed assuming equal variances and were further substantiated by examining the 95% confidence interval.

Regarding AEs reported during the exercise interventions, the frequency of occurrence for each participant was recorded before and after the sessions. A descriptive analysis was performed to determine the absolute frequency and proportion of events. The Chi-square test was used to compare these proportions between groups.

To evaluate differences within and between groups, a Multivariate Analysis of Covariance (MANCOVA) was conducted. This robust statistical test allowed for the examination of the relationship between multiple dependent variables, spanning dimensions such as depressive symptoms and quality of life, among others, and independent variables (group and time). This analysis was performed while controlling for one or more covariates: years of schooling, monthly income, number of children, number of chronic non-communicable diseases, and hours spent sitting, bending, or lying down.

The effect size, measured through partial eta squared (ηp^2), was utilized to quantify the magnitude of the observed effects. A value of 0.01 was considered indicative of a small effect, 0.06 suggested a moderate effect, and 0.14 or more signified a substantial effect size. Furthermore, a rigorous assessment of statistical power was conducted, set at the conventional threshold of 80% ($1-\beta = 0.80$), thereby elucidating the study's robustness in discerning genuine differences.

Simultaneously, intragroup changes from baseline were calculated using a manual mathematical procedure. This involved subtracting the final mean of each variable from its corresponding initial mean.

During the resistance training interventions, one participant in the control group withdrew from the research for personal reasons. Consequently, we conducted multiple imputations for her data. The level of statistical significance considered for the analysis was $\alpha = 5\%$. Data analysis was carried out using SPSS version 25 for Windows.

10 Results

10.1. Baseline characteristics

The study randomly assigned twenty-nine eligible participants, expressing interest in the research, into two groups: the Intervention group (Flywheel resistance training, n=14) and the Control group (Traditional resistance training, n=15). A flowchart detailing study participation and group allocation is provided in Figure 5.

The normality of the variables was confirmed via the Shapiro-Wilk test. Additionally, the Levene test indicated no statistically significant differences among baseline variables, including medical history, blood pressure, depressive symptoms, quality of life, and strength assessments (refer to Table 4).

Regarding demographic distribution, 51.7% identified as white, 27.6% as mestiza, and 20.7% as black. In terms of retirement status, 65.5% were retired, while 34.5% were not retired, with 31% actively working. Marital status varied, with 41.4% married, 24.1% widowed, 17.2% separated, and 17.2% single. Lifestyle habits revealed that 93.1% did not use tobacco, while 55.2% reported alcohol consumption. Moreover, 82.8% of participants reported medication use. Educationally, 27.6% completed education up to basic primary, while one participant (3.4%) had 23 years of schooling. Ten women (34.5%) earned 2 minimum wages per month, while one (3.4%) reported earning 34 minimum wages.

Adherence and compliance rates were slightly higher in the control group (86.7%) compared to the intervention group (85.7%) p>0,05. Notably, one participant from the intervention group discontinued due to a surgical procedure, while one from the control group attended only 9 sessions (6.7%).

Perceived effort, assessed using the OMNIRES scale, averaged 7 in the intervention group, indicating exercises were perceived as somewhat difficult to difficult. In the control group, perceived effort remained consistently at 7 throughout the sessions, suggesting similar difficulty and demand.

Figure 5

CONSORT 2010 Flow Diagram

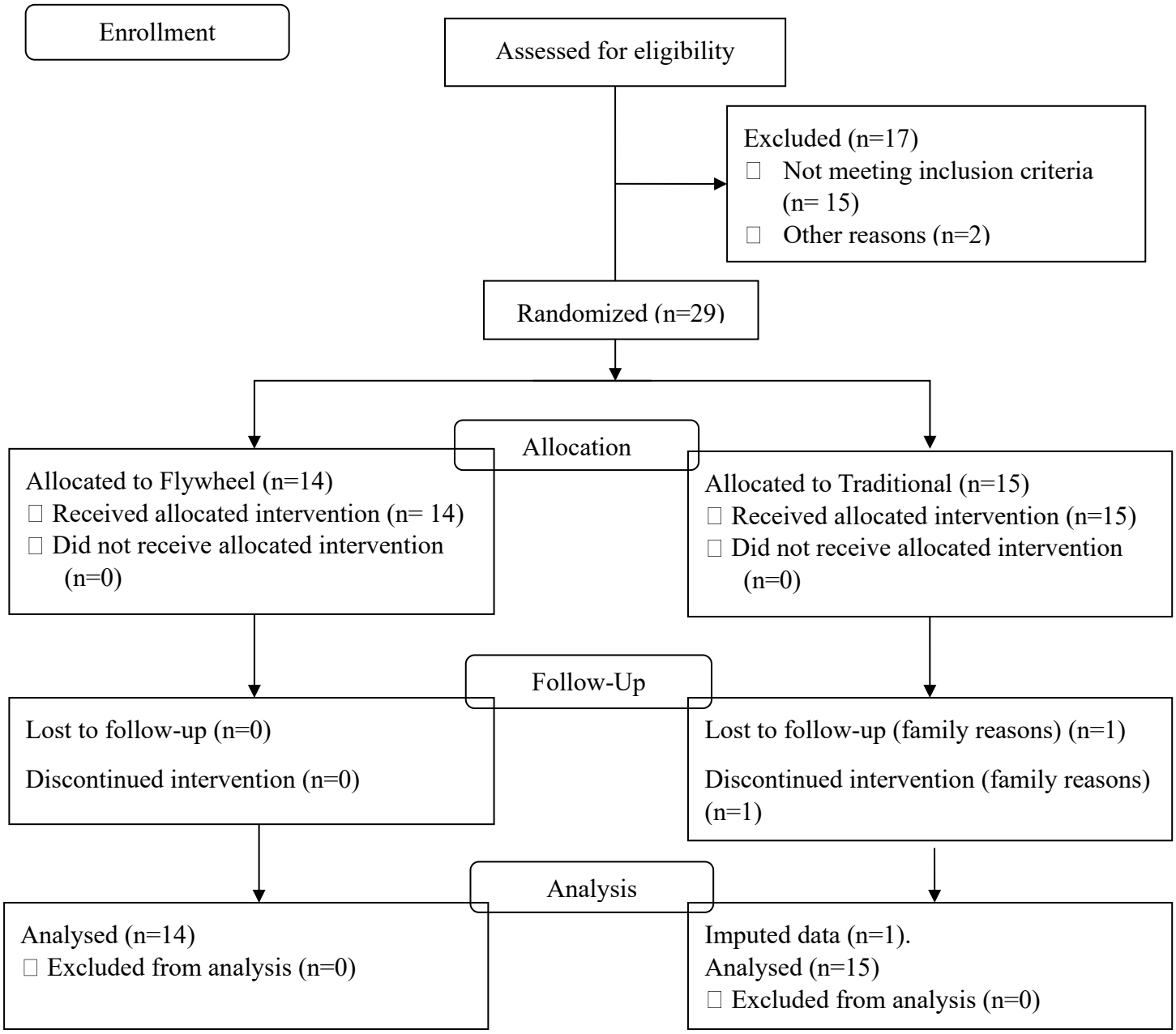

Table 4
Baseline characteristics of older women

Variable	Total ± SD n=29	Traditional resistance training ± SD n=15	Flywheel resistance training ± SD n=14	P	CI 95%
Medical history, and blood pressure					
Age (Years)	65,38 ± 5,01	66,40 ± 5,50	64,29 ± 4,35	0,26	-1,6 - 5,9
SBP (mmHg)	136,21 ± 12,93	138,00 ± 14,73	134,29 ± 10,89	0,45	-6,2 - 13,6
DBP (mmHg)	83,10 ± 12,84	84,00 ± 15,49	82,14 ± 9,75	0,70	-8,0 - 11,8
MAP (mmHg)	100,80 ± 9,94	102,00 ± 11,18	99,52 ± 8,65	0,51	-5,1 - 10,1
Depressive symptoms					
GDS (total score)	4,6 ± 3,5	4,0 ± 3,5	5,2 ± 3,5	0,39	-3,8 - 1,5
Quality of life					
WHOQOL-Bref (total score)	60,00 ± 8,41	62,64 ± 7,29	57,17 ± 8,85	0,08	-0,6 - 11,6
Strength Assessments					
MVIC (Kg)	33,41 ± 11,65	32,03 ± 10,84	34,88 ± 12,69	0,52	-11,8 - 6,1
1RM (Kg)	32,28 ± 10,34	31,07 ± 11,27	33,57 ± 9,49	0,52	-10,4 - 5,4
MP 40%1RM (W)	90,9 ± 40,8	85,3 ± 43,8	97,1 ± 38,8	0,44	-43,2 - 19,6
MP 60%1RM (W)	105,8 ± 40,49	97,4 ± 37,5	114,8 ± 42,9	0,25	-48,0 - 13,3
MP 80%1RM (W)	116,7 ± 43,1	110,5 ± 40,1	123,3 ± 46,6	0,43	-45,8 - 20,3
PP 40%1RM (W)	190,86 ± 87,42	175,9 ± 92,1	206,7 ± 82,4	0,35	-97,5 - 35,9
PP 60%1RM (W)	209,9 ± 71,2	203,2 ± 72,4	217,2 ± 71,8	0,60	-69,0 - 41,0
PP 80%1RM (W)	214,5 ± 73,4	208,0 ± 70,9	221,4 ± 78,1	0,63	-70,2 - 43,3

Data are presented as mean ± SD.
Abbreviations: SD: standard deviation; CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; GDS: geriatric depression scale; WHOQOL-Bref: World Health Organization Quality of life assessment-Bref; MVIC: maximum voluntary isometric contraction; RM: maximum repetition; MP: mean power; PP: peak power.
A significance level of $p < 0.05$ was employed to ascertain statistical significance between the control and intervention groups.

10.2. Primary outcomes

10.2.1 Depressive symptoms

When adjusting for potential confounding factors, no statistically significant differences were found between the groups ($p=0.193$, $\eta p^2=0.03$, $1-\beta=0.25$). Notably, significant intragroup differences were observed ($p=0.001$, $\eta p^2=0.21$, $1-\beta=0.92$). This suggests that there are statistically significant differences within at least one of the groups. As a result, the Flywheel group achieved a post-intervention mean of 2.7 ± 2.7, while the final score in the traditional group was 2.0 ± 2.8. However, considering baseline values, older women in the intervention group experienced a reduction of -2.5 points, while the control group showed a reduction of -2.0 points (Table 5).

10.3. Secondary outcomes

10.3.1 Quality of life (WHOQOL-Bref Brazilian version)

After adjusting for possible confounding factors, an intragroup analysis revealed a p-value of 0.057, ηp^2=0.07, and 1-β=0.48. While not reaching conventional statistical significance ($p<0.05$), this suggests potential differences within at least one of the groups. Comparing the final means between the groups yielded a p-value of 0.115, ηp^2=0.05, and 1-β=0.34. The small to moderate effect size, both within and between groups, indicates that the variability explained by differences within groups is modest. The statistical power below 0.80 highlights potential limitations in detecting significant differences due to the sample size. In summary, there are indications of differences within at least one group, but no statistically significant differences were found between the groups in the final means, as shown in Table 5.

Table 5
Differences Within and Between Groups Related to Depression, and Quality of Life.

Outcome	Traditional resistance training (Control Group)			Flywheel resistance training (Intervention Group)			Intragroup differences			Between groups differences		
	Pre-intervention Mean ± SD n=15	Post Intervention Mean ± SD n=15	Intra-group changes from baseline	Pre-Intervention Mean ± SD n=14	Post Intervention Mean ± SD n=14	Intra-group changes from baseline	P	ηp^2	Power (1-β = 0.80)	P	ηp^2	Power (1-β = 0.80)
Depressive symptoms												
GDS (total score)	4,0 ± 3,5	2,0 ± 2,8	-2,0	5,2 ± 3,5	2,7 ± 2,7	-2,5	0,001*	0,21	0,92	0,193	0,03	0,25
Quality of life												
WHOQOL-Bref (total score)	62,64 ± 7,29	66,32 ± 5,63	3,68	57,17 ± 8,85	61,18 ± 8,54	4,01	0,057	0,07	0,48	0,115	0,05	0,34

Data are presented as mean ± SD.
Differences within and between groups were compared using the MANCOVA test (covariates: years of schooling, monthly income, number of children, number of chronic non-communicable diseases, and hours spent sitting, bending, or lying down).
Abbreviations: SD: standard deviation; GDS: geriatric depression scale; WHOQOL-Bref: World Health Organization Quality of life assessment-Bref.
*A significance level of $p<0,05$ was used to determine statistical significance.
ηp^2 Test: small = 0,01; medium = 0,06; large = 0,14.

10,3,2 Manifestations of strength

Compared to the baseline, both older women in the control and intervention groups exhibited increased values in variables assessing strength manifestations (MVIC, 1RM test, and muscle power). However, for most variables, no statistically significant differences were found between the groups ($p > 0.05$). Only Peak Power (PP) at 80% of 1RM showed a value of $p=0.049$, $\eta p^2=0.08$ (moderate), and $1-\beta=0.50$ (low) when adjusting for the potential effect of covariates. In terms of intragroup differences, values of $p<0.05$, large effect sizes ($\eta p^2=0.16$), and high statistical power ($1-\beta=0.83$) were found in the MVIC and 1RM variables. Although mean power at 60% of 1RM and PP at 40% of 1RM showed values of $p<0.05$, they presented moderate effect sizes and low statistical power, as shown in supplementary material, Table 4.

10.3.3 Blood Pressure

P values > 0.05 for systolic, diastolic, and mean blood pressure, small effect sizes, and low statistical power were observed when comparing final means between groups. Despite not reaching statistical significance, systolic blood pressure decreased 16.27 mmHg in the control group and 15.72 mmHg in the intervention group. For diastolic blood pressure, the control group experienced a reduction of 12.55 mmHg, while the intervention group showed a reduction of 7.85 mmHg. Mean arterial pressure also showed reductions in both groups: Traditional = -13.53, Flywheel = -10.47. In intragroup comparisons, it was found that systolic, diastolic, and mean blood pressure obtained values of $p<0.05$. Likewise, large effect sizes $\eta p^2>0.16$ and substantial statistical powers $1-\beta>0.80$, see supplementary material, Table 4.

10.3.4 Harms

In this RCT, only grade 1 to grade 3 AEs were recorded, including hypotension, dizziness, nausea, airway, or inner ear infections, falls, excessive fatigue, arthritis, blurred vision, and non-intervention-related retinal surgery. These AEs were mild, minimal, and non-invasive, not impeding daily activities for the participants. In the intervention group, incidents of dizziness (in sessions 5, 7, and 10), nausea (in session 15), and excessive fatigue (in sessions 6, 15, and 16) were observed, all during exercise. Similarly, the control group reported episodes of dizziness during exercise (in sessions 8, 12, and 13). Additionally, 1 control group participant experienced blurred vision during exercise due to a pre-existing condition of high blood pressure. 2 participants in the Flywheel group reported falls unrelated to the interventions.

Although events were more frequent in the intervention group, not all were attributed to the interventions. See supplementary material for more details.

11 Discussion

11.1 Depressive symptoms

The current study represents a pioneering effort in clinical investigation, being the initial RCT specifically formulated to examine the impacts of resistance training, facilitated by the innovative Flywheel apparatus, on the reduction of depressive symptoms among older women with sedentary behaviors in community settings. Despite a marginally higher adherence rate observed in the control group and sporadic reports of minor adverse events during and after exercise (grade one and two), both supervised interventions, characterized by moderate to high intensities, demonstrated a statistically significant decrease in depressive symptoms, as evidenced by within-group analyses. The observed antidepressant effects of resistance training, whether employing the Flywheel or not, may reasonably be attributed to the cascading release of endorphins and the augmented availability of neurotransmitters such as serotonin, dopamine, and norepinephrine during and after exercise bouts (Jin et al., 2019). The initial analysis revealed that the total sample did not demonstrate significantly high scores on the GDS (4.6 points). However, the intervention group exhibited scores of 5.2, implying the potential presence of clinical depression according to validation studies (cutting point 5) (M. S. Castelo et al., 2010). After completing the 16 sessions, a reduction in depressive symptoms was noted, although it did not demonstrate statistical significance between the groups ($p>0.05$). This observation suggests the potential presence of a type 2 error in the intergroup comparisons, reflecting diminished effect sizes and statistical power. Hence, there is a clear indication that further comprehensive investigations should be conducted.

In our study, we executed 16 resistance training sessions, encompassing six exercises targeting both major and minor muscle groups, administered biweekly, with 8 sets and 64 repetitions per muscle group per week. Parameters related to frequency, intensity, session duration, and rest periods were consistent across all groups, although differing values associated with exercise volume and progression were implemented. Both Flywheel training and the control group offer secure and viable interventions for mitigating depressive symptoms in older women living in the community, showcasing the ability to ensure women's adherence and participation. While the majority of prior studies center on traditional resistance training in the mental health of the

elderly (Cunha et al., 2024), this study underscores the reduction in depressive symptoms, irrespective of whether the contraction involves an eccentric overload. Further research specific to the use of the Flywheel device is necessary to validate these findings.

The effectiveness of traditional resistance interventions in alleviating depressive symptoms among the older adult population has been substantiated by research. Cunha et al.'s systematic review revealed that a resistance training program comprising three sessions per week, with three sets per person and fewer than six exercises per session and conducted for less than 12 weeks, exhibited significant improvements in mental health parameters (Cunha et al., 2024). Additionally, a network meta-analysis conducted by Noetel et al. established that vigorous resistance training in women resulted in moderate reductions in depressive symptoms (Noetel et al., 2024). Similarly, isolated resistance exercise was found to have a moderate and noteworthy effect in reducing symptoms in individuals over 18 years of age, with and without major depression. It was noted that factors such as the duration and frequency of interventions, as well as the number of series and repetitions, played pivotal roles in determining the antidepressant effect (Rossi et al., 2024).

In a study conducted by Cavalcante et al. (2020) (Cavalcante et al., 2020), it was found that resistance training on unstable surfaces did not yield significant modifications in depressive symptoms among older adults with self-reported cognitive disorders. Conversely, a supervised resistance training program implemented by Cunha et al. (2022) (Cunha et al., 2022), demonstrated a decrease in depressive symptoms independent of age, muscle strength, and cognitive function. Furthermore, Sahin et al. (2018) (Sahin et al., 2018) discovered that both low-intensity and high-intensity resistance training led to a reduction in depressive symptomatology among older adults with frailty. Notably, none of these primary and tertiary studies used exercise interventions as control conditions.

Currently, it is understood that resistance training utilizing a flywheel, in contrast to conventional resistance training, elicits greater muscle strength, necessitates reduced motor activation, diminishes oxygen consumption within muscle fibers, and entails lower energy expenditure. Additionally, it augments cortical excitability while reducing motor unit discharge. Furthermore, it incites greater muscle damage and mechanical stress, particularly impacting type II muscle fibers (notably IIb) to a greater extent than type I fibers (Hody et al., 2019; Kowalchuk & Butcher, 2019). These observed effects are not exclusive to athletes or elite sportsmen (Allen et al., 2023; Murton et al., 2023) but are also apparent in older adults (Hill et al., 2022). However, it remains undetermined whether, beyond the effects, flywheel training

could significantly influence the modification of depressive symptoms in older adult women, or consistently account for it.

11.2 Quality of life (WHOQOL-Bref Brazilian version)

In both study groups, an increase in quality of life scores was observed. Nevertheless, the conducted comparisons failed to reveal statistically significant differences, indicating moderate effect sizes and low statistical power. It is noteworthy that the Flywheel group yielded a higher score compared to the control group, which also exhibited an increased score. This implies that resistance exercise may have a notable impact on enhancing the quality of life domains in sedentary adult women in a community setting.

Evidence with a high to moderate level of certainty expounds that this form of exercise, when not coupled with dietary control and combined with aerobic exercise, enhances the quality of life of older adults with sarcopenia (Shen et al., 2023). Additionally, it elevates scores across most domains of this outcome in older adults aged 60 years and above, although not in overall results (Khodadad Kashi et al., 2023). Consistent findings have also been reported in adults with prostate cancer and type 2 diabetes mellitus, with the effect of diabetes being deemed slight (Jia et al., 2024; Nader et al., 2024).

Regarding the Flywheel device, evidence suggests that improves shoulder muscle strength and quality of life in female breast cancer survivors (Naczk et al., 2022). However, the available evidence supporting its effect on the quality of life of older adults is grounded in a single study (Kowalchuk & Butcher, 2019). The evidence endorsing the effect of Flywheel on the quality of life in adult women is currently insufficient.

11.3 Manifestations of muscle strength

This study evaluated strength outcomes in the adult population, with specific emphasis on community-dwelling women. The assessment employed measures such as MVIC, 1RM, and muscle power of the lower extremities via the knee extension test. Both groups exhibited improvements, with notable differences in MVIC, 1RM, MP at 60% of 1RM, and PP at 40% of 1RM within each group, showcasing moderate and large effect sizes. Notably, PP at 80% of 1RM demonstrated distinctions between groups, potentially attributed to participants' familiarity with executing the concentric phase at a higher speed in the Flywheel group.

Previous primary investigations propose that this approach may be more efficacious in enhancing muscle power in the lower and upper limbs (Floreani et al., 2022). Specifically, the increase in muscle strength resulting from these interventions is correlated with decreased mortality. Studies have indicated an association with a noteworthy reduction in mortality in adults, with potential reductions in mortality from all causes, cardiovascular disease, and cancer (Shailendra et al., 2022). Conversely, a decline in muscle mass (atrophy) could lead to heightened mortality from all causes (Zhou et al., 2023). It is estimated that a 5 kg increase in muscle strength could potentially reduce mortality in the clinical population by 28% (Jochem et al., 2019). Systematic reviews suggest that it could reduce mortality from all causes by 21%, although there is no evidence of an association with cancer (Saeidifard et al., 2019). In seemingly healthy populations, handgrip strength could diminish the risk of death from all causes by 31%, with a slightly stronger association in women, implying a 14% reduction when higher levels of strength are observed in the knee extension test (García-Hermoso et al., 2018). Moreover, it is inversely associated with depression (Cabanas-Sánchez et al., 2022).

It is imperative to note that while a relationship has been documented between increased muscle strength and reduced mortality, this association does not necessarily imply causality. Furthermore, it remains undetermined whether this link extends to reducing the risk of mortality by suicide in both clinical and non-clinical populations. Similarly, it is yet to be ascertained whether this correlation persists when exercising with Flywheel devices.

11.4 Blood pressure

These research findings indicated no significant variances in systolic and diastolic blood pressure between the groups; however, notable clinical differences were observed in both outcomes within each group. These discrepancies are of importance as the reduction in mmHg values may suggest a lowered risk of heart failure among the participants (Baffour et al., 2023).

Furthermore, the documented decreases resulting from the interventions may signify a reduced likelihood of cardiovascular events. Attainment of systolic blood pressure values below 120 mmHg after 16 sessions potentially correlates with diminished all-cause mortality risk for women in the Flywheel group (Seidu et al., 2023).

It is noteworthy that tertiary evidence has ascertained the ability of traditional resistance exercise, with a minimum intervention duration of three weeks, to decrease blood pressure in adults over 60 years of age, in comparison to being sedentary (Henkin et al., 2023).

Additionally, it has been proposed that higher intensities and volumes of strength exercise could exert a more pronounced effect on reducing blood pressure when compared to physical inactivity (Schneider et al., 2023).

Moreover, it is pertinent to acknowledge the existence of non-linear associations between blood pressure and depression; hypotension could potentially increase the risk of depression (Lim et al., 2023). Notably, results from other studies exhibit inconsistencies (Jeon et al., 2020; Yang et al., 2015). Nonetheless, the impact of Flywheel devices on blood pressure remains unexplored, particularly within the older adult population residing in the community.

11.5 Harms

The study documented minor AEs and identified events unrelated to the resistance training interventions. Interestingly, recent research on traditional resistance training, eccentric overload Flywheel training, mental health issues such as clinical depression and depressive symptoms and standing balance did not report any AEs in their respective study cohorts (Cavalcante et al., 2020; Cunha et al., 2022; Cunha et al., 2024; Noetel et al., 2024; Rossi et al., 2024). Evaluating the consistency of these findings and their potential association with exercise is crucial.

12 Strengths and limitations

The study exhibits various noteworthy strengths as the first randomized controlled trial evaluating the effect of Flywheel devices in contrast to traditional resistance training on depressive symptomatology among older women with sedentary lifestyles living in the community. Notable elements include high adherence, participation, and compliance with the sessions, alongside meticulous recording of potential adverse events before and during the interventions. To ensure the study's integrity, checklists like the CERT were utilized, and the protocol was transparently published in the Clinical Trials repository. The study also maintained internal validity by employing validated instruments in Brazil to measure primary and some secondary outcomes, such as quality of life. Adequate sample size calculation and allocation concealment before the resistance sessions were carried out. Furthermore, blinding of key personnel was implemented to minimize bias. However, limitations arose due to the small size of the intervention group of older women, leading to insufficient sample size for detecting significant statistical differences. Moreover, the specific equipment used in this trial may not be widely available and requires logistical procedures for implementation.

13 Conclusion

This study indicates that supervised resistance training, conducted at moderate intensities with or without Flywheel devices, is both safe and feasible for sedentary older women residing in the community. These interventions showed promising reductions in depressive symptoms and clinically significant improvements in blood pressure, quality of life, muscle strength, and maximal isometric voluntary contraction. Furthermore, greater gains in muscle power at 80% of 1RM were noted with Flywheel devices. Caution is advised in interpreting these findings due to small effect sizes and low statistical power in the study.

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Data availability statement

Due to the sensitive nature of this research, participants did not agree for their data to be shared publicly, so supporting data is not available.

General Conclusions

In general, the current evidence concerning physical exercise and depression faces methodological challenges that hinder a comprehensive understanding of exercise intervention reports, thereby complicating decision-making for guideline developers such as clinical practice guidelines. Moreover, we are gradually exploring the specific characteristics that strength training must adopt in terms of frequency, intensity, volume, and progression to alleviate depressive symptoms in clinical and non-clinical populations.

Practical Applications

Supervised aerobic exercise at moderate to vigorous intensities is safe and may reduce depressive symptoms in adults with major depressive disorder. Recommended exercise sessions should last between 30 to 45 minutes, conducted 3 to 5 times per week, throughout 8 to 16 weeks. Such exercises can include indoor cycling, outdoor running, or treadmill workouts.

Regarding resistance training, it has been established as safe for older adult women residing in the community, whether using Flywheel devices or traditional methods. It is advised to perform 16 sessions targeting muscle groups such as quadriceps, hamstrings, calves, biceps brachii, deltoids, and rhomboids, twice a week. Each session should involve 3 to 4 sets of 8 to 12 repetitions, ranging from moderate to vigorous intensity. Proper familiarization with the training process is crucial, particularly for Flywheel exercises, where progression is achieved by increasing execution speed during the concentric phase, and in traditional training, by gradually increasing the load beyond the suggested number of repetitions.

Recommendations for Future Research

Future RCTs should explore the effect of resistance training at different intensities and volumes and compare free weights versus machine exercises. Furthermore, the role of supervision in achieving expected outcomes should be evaluated. It is essential to develop studies aimed at validating specific effort perception instruments for older adults residing in the community, as existing instruments may confuse this population.

Finally, it is recommended that future RCTs increase sample sizes (minimum of 50 women) and study durations (minimum of 16 weeks) to detect potential differences between groups and determine if reductions in depressive symptoms are sustained over time. Additionally, integrating other training modalities such as combined and multicomponent training should be considered. These trials should be rigorously designed and transparently reported, utilizing

checklists like CONSORT, CERT, TIDieR, and TESTEX to enhance methodological quality and report transparency.

Summary for communities

This thesis looks at how different types of physical exercise can help reduce symptoms of depression in adults with MDD and in older women who do not exercise regularly. The first part of the research reviewed and analyzed nine previous studies involving 678 adults with MDD who were not taking certain medications or receiving therapy. The analysis found that exercise might help reduce depressive symptoms, but the effect was small and not strong enough to be considered reliable. Factors like how often and intensely the exercise was done, and the age and weight of the participants, might have influenced the results. However, the overall quality of the evidence was low, meaning the findings should be interpreted with caution.

The second part of the research was a new study conducted at the Federal University of Viçosa in Brazil. This study involved 29 women over 60 years old who were not physically active. They were divided into two groups: one did a special type of resistance training called Flywheel training, and the other did traditional resistance exercises. Both groups trained twice a week for eight weeks. The study found no clear difference between the two types of exercise in reducing depressive symptoms. Although some participants experienced mild side effects, there were no serious issues.

In summary, while both studies suggest that exercise, including resistance training, may help reduce depressive symptoms, more research is needed with larger groups of people and better study designs to confirm these results. The findings should be interpreted carefully due to limitations in the research methods and variability in the outcomes.

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