



Is there any synergism between physical exercise plus antidepressants in the reduction of depressive symptoms? A systematic review with meta-analysis

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Palavras-chave: physical exercise, depressive symptoms, antidepressant drugs, synergy

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1. Abstract

Introduction: Major depressive disorder (MDD) is a severe mental illness that affects 5–20% of the general population. Current antidepressant drugs exert only a partial clinical efficacy as approximately 30% of depressed patients failed to respond to these drugs and antidepressants produce remission only in 30% of patients. Physical activity (PA) and physical exercise (PE) were shown to be effective as monotherapy and growing evidence supports its capacity as an augmentation strategy for the efficacy of antidepressant medication and psychological treatment. However, this last aspect needs to be systematically assessed, as the evidence is not consistent across studies. **Aim:** Verify whether PE, when combined with antidepressant drugs, has additional effects in terms of reducing depressive symptoms, in comparison with taking antidepressant drugs only. **Methods:** We performed a systematic literature search (randomized and non-randomized studies) in accordance with PRISMA recommendations. We considered studies comparing the effectiveness of usual treatment alone versus when combined with PE to reduce symptoms of depression. We included studies among which participants comprised a wide range of ages (18 years and older). They were assessed with several scales, appropriately validated, that measure the severity of depressive symptoms. The characteristics of the sample are organized by sex, mean age, time in which participants had depression/use of antidepressants, intervention groups, measured outcomes, symptom measurement scales, and specification of results. To specify the dose needed to maximize the benefits of a correct prescription of exercise for the prevention and/or assistance of depressive symptoms, we organize the information of studies by frequency, duration of intervention, volume, and intensity. The random effect meta-analysis was used to estimate the standardized mean difference for pharmacological treatment alone versus pharmacological treatment and exercise. **Results:** For the comparison between groups, we included 12 studies in this meta-analysis. The results suggest that PE is an option that should be seen as an adjunct to depression medication in reducing the severity of depressive symptomatology. Sub analysis suggest that patients who benefit the most are 1) the ones that were already in medication when PE was started, ii) who performed aerobic exercise, iii) engaged on moderate intensity, iv) with a training volume above 60min/session, v) with a good adherence to PE, vi) who participated in short term interventions, vii) with a wide range of ages. **Conclusions:** Data from this meta-analysis suggest that PE is an option that should be seen as an adjunct to depression medication. We conclude that the dose and/ or the type of exercise and medication should always be well adjusted by qualified professionals in their respective areas, according to the particularities of each person. It is important implement strategies to maximize adherence to exercise and medication programs by patients.

Keywords: physical exercise, depressive symptoms, antidepressant drugs, synergy

Resumo

Introdução: O transtorno depressivo maior (MDD) é uma doença mental grave que afeta 5-20% da população geral. Os antidepressivos atuais exercem uma eficácia clínica apenas parcial, uma vez que aproximadamente 30% dos pacientes com depressão não responderam aos fármacos e, por sua vez, estes produziram uma remissão apenas em 30% dos pacientes. A atividade física (AF) e o exercício físico (EF) mostraram-se eficazes, pois a monoterapia e a crescente evidência sustentam a sua capacidade de estratégia em aumentar da eficácia da medicação e do tratamento psicológico. No entanto, este último aspeto precisa de ser avaliado sistematicamente, já que as evidências não são consistentes em todos os estudos. **Objetivo:** Verificar se o EF, quando combinado com medicamentos antidepressivos, tem efeitos adicionais na redução dos sintomas depressivos, em comparação com o uso exclusivo de antidepressivos. **Métodos:** Foi realizada uma pesquisa sistemática na literatura (estudos randomizados e não randomizados), de acordo com as recomendações do PRISMA. Foram considerados estudos que comparavam a eficácia do tratamento habitual sozinho versus estudos que combinavam o tratamento antidepressivo com PE para reduzir os sintomas de depressão. Incluímos estudos em que os participantes compreendiam uma ampla gama de idades (18 ou mais anos). Eles eram avaliados com várias escalas, devidamente validadas, que mediam a severidade de sintomas depressivos. As intervenções diziam respeito só a exercício físico. As características da amostra foram organizadas por sexo, média de idades, tempo em que os participantes apresentaram depressão/usaram antidepressivos, grupos de intervenção, desfechos medidos, escalas de medicação de sintomas e especificação dos resultados dos estudos. Para especificar a dose necessária que maximize os benefícios de uma prescrição correta de exercício para a prevenção de sintomas depressivos, organizamos as informações dos estudos por frequência, duração da intervenção, volume e intensidade. A meta-análise de efeito aleatório foi utilizada para estimar a diferença média padronizada para tratamento farmacológico apenas versus tratamento farmacológico e exercício. **Resultados:** Para a comparação entre grupos, incluímos 12 estudos nesta meta-análise. Os resultados sugerem que o EF é uma opção que deve ser vista como adjuvante à medicação para depressão na redução da gravidade da sintomatologia depressiva. As subanálises sugerem que os pacientes que mais beneficiam são 1) os que já estavam em medicação quando o EF foi iniciado, ii) os que realizaram exercício aeróbico, iii) os que praticavam exercício a uma intensidade moderada, iv) aqueles que praticavam um volume de treino superior a 60min/sessão, v) os que tinham boa adesão ao EF, vi) os que participaram em

intervenções de curto prazo, vii) aqueles com uma ampla gama de idades. **Conclusões:** Os dados desta meta-análise sugerem que a PE é uma opção que deve ser vista como adjuvante à medicação para depressão. A dose e/ou o tipo de exercício e medicação devem ser sempre ajustados por profissionais qualificados nas suas respectivas áreas, de acordo com as particularidades de cada pessoa. Além disso, é importante reforçar as estratégias de aumento de adesão aos programas de exercício e medicação pelos pacientes.

Palavras-chave: exercício físico, sintomas depressivos, fármacos antidepressivos, sinergia

2. Bibliographical

2.1. Introduction

Major depressive disorder (MDD) is a severe mental illness that affects 5-20% of the general population. Current antidepressant drugs exert only partial clinical efficacy as approximately 30% of depressed patients failed to respond to these drugs. In addition, antidepressants produce remission only in 30% of patients. Physical activity (PA) and physical exercise (PE) were shown to be effective as monotherapy for depression and growing body of evidence supports its potential as a strategy to maximize the efficacy of the antidepressant medication and psychological treatment and well-being of patients. However, this last aspect needs to be systematically assessed, as the evidence is not consistent across studies. Based on this gap, we performed a systematic review and meta-analysis dedicated to antidepressant drug therapy, could improve the treatment of depressive symptoms (major outcome).

In order to set the introductory background to the topic, the first part of this work was dedicated to epidemiology, pathophysiology, classification, diagnosis, measurement scales, and risk factors for depression. Following we describe the evidence regarding the role of PA and PE for the prevention and treatment of depressive symptoms, respectively. In the subsequent sections of this dissertation, we present the main aims that guided the systematic review, we describe the methodology, present the results, and discuss the data obtained in the meta-analysis. Finally, based on our data and the limitations that we found on the papers included in the review, we present future perspectives that could be used to plan new studies that will help to establish PE as must-have ally to treat depression.

2.2. Epidemiology

It is estimated that more than 300 million worldwide people are affected by depression ("Institute for Health Metrics and Evaluation,"), with a higher prevalence in women (APA, 2019). The same source indicates that, in Portugal, the prevalence of the number of cases for all ages and in both sexes reaches almost 600,000 people (5.88%). The highest prevalence points to people over 55 years of age (7.21%) of both sexes. This disease can be long-lasting or recurring, leaving an individual unable to cope with their daily life and, at the extreme, affected individuals might even commit suicide. Although suicides are rare events (Isometsa, 2020), according to the World Health Organization (2021), annually, more than 700,000 people commit suicide, making it the fourth leading cause of death among young people aged 15-29. According to the latter source, depressive disorders are characterized by a state of sadness, lack of interest, pleasure, feelings of guilt, and low self-esteem. Besides, sleep disorders, lack of appetite, tiredness, and concentration deficit may also occur. Worldwide, depression is the fourth most common health problem and will soon be the most prevalent, due to the Covid-19 pandemic (World Health Organization). Gujral, Aizenstein, Reynolds, Butters, and Erickson (2017), point out that depressed individuals have recurrent episodes (~50%) and/or chronic depression (~20%).

2.3. Classification

APA (2019) referred to various types of depressive disorders, including major depressive disorder (MDD), minor depression (MD), persistent depressive disorder/"dysthymia" (PDD), subsyndromal depression (SDD), bipolar disorder (BD), intermittent depression, and psychotic depression, these being some of the most prevalent types. The next paragraphs will focus on the characterization and symptomatology of the various types of depression, to understand the differences between them.

MDD may be mild, moderate, or severe, depending on the number and severity of the symptoms, for at least two weeks. It is usually accompanied by at

least three (out of a total of at least five) of the following symptoms: weight loss, change in appetite, insomnia or hypersomnia, psychomotor retardation, agitation, fatigue, lack of energy, excessive/inappropriate guilt, worthlessness feelings, indecisiveness, diminished ability to concentrate or think, recurrent thoughts of death, suicidal ideation, suicide plan or attempt (APA, 2019). It is the most prevalent and severe mental disorder, reaching 5-20% of the general population (Beurel, Toups, & Nemeroff, 2020; Guerrera et al., 2020; Gujral et al., 2017; Kvam, Kleppe, Nordhus, & Hovland, 2016), leading to significant social damage and an increase in mortality (Hasler, 2010). The latter authors considered it one of the largest causes of disability worldwide and state that the high rate of inadequate treatment of the disease remains a serious concern. MDD is associated with individual suffering, prescription of antidepressants, social and health spending, increased morbidity and mortality (Lopez-Torres Hidalgo & Group, 2019; Murri et al., 2021).

PDD is considered a chronic and less intense condition, as well as mild depression (World Health Organization, 2017). Around 20-30% of depressive disorders are chronic, and PDD is a common mood disorder, often, more disabling than major episodic depression (Schramm, Klein, Elsaesser, Furukawa, & Domschke, 2020). Typically, patients have a depressed mood, for at least two years, and a minimum of two of the following symptoms: hopelessness feelings, insomnia or hypersomnia, overeating or poor appetite, fatigue, low energy, low self-esteem, indecision, and concentration deficit (APA, 2019). To Schramm et al. (2020), it can be difficult to detect in a psychiatric environment until they intensify in a severe episode. Dae Jong Oh et al. (2021), report that SDD is prevalent and is associated with poor outcomes at the end of life. In addition, SDD is a predictor of incident dementia when it is chronic or recurrent with increasing severity in cognitively normal elderly. SDD is more prevalent than MDD in older adults over 65 years and is associated with functional disability, cognitive impairment, poor physical health, and mortality (D. J. Oh et al., 2020).

The review by Müller and Leweke (2016) portrayed BD which is a serious psychiatric disorder, characterized by depressive, manic, and mixed episodes affecting about 1-2% of the population. According to the authors, there are two

types: BD I which equally affects both sexes; BD II which is more frequent in women. For Han, De Berardis, Fornaro, and Kim (2019), BD is characterized by recurrent depressive and manic/hypomanic episodes; depressive episodes are the most common mood states during the duration of the illness. Approximately 69% of patients with BD are initially misdiagnosed with unipolar depression (UD). According to Pfeil, Holtz, Kopf, Hegerl, and Rummel-Kluge (2017), MD increases the risk of developing MDD. The authors noted a lack of consensus on the symptoms of sleep disorders and depressed mood since in their study these were the most frequent symptoms in the MD group (followed by fatigue, anhedonia, appetite, and suicidality). According to Baumeister and Morar (2008), sleep and depressed mood disorders were the most frequent in MD.

There are also mixed depressive and anxiety disorder, premenstrual dysphoric disorder (PMDD), other specified depressive disorders and depressive unspecified disorders. Other depressive disorder specified do not justify classification, because they are insufficient symptoms or duration. Mixed depressive and anxiety disorder is characterized by symptoms of both anxiety and depression more days than not for a period of two weeks or more. PMDD comprises a pattern of mood symptoms, somatic symptoms, or cognitive symptoms that begin several days before the onset of menses, start to improve within a few days after the onset of menses, and then become minimal or absent within approximately 1 week following the onset of menses (WHO, 2022). Estimates indicate that approximately 85% of women experience, at least one mild premenstrual symptom and that between 20% and 25% have moderate to severe premenstrual symptoms (Lanza di Scalea & Pearlstein, 2019). Unspecified depressive disorder applies to presentations of symptoms characteristic of a depressive disorder causing clinically significant suffering or disability in social, professional or other important areas of functioning, but do not meet the complete criteria for any of the disorders in the diagnostic class of depressive disorders. It is used in situations where the doctor chooses not to specify the reason why the criteria are not met for a particular depressive disorder and includes presentations for which there is insufficient information to make a

more specific diagnosis, for example, in emergency environments (Diagnostic and statistical manual of mental disorders : DSM-5, 2013).

2.4. Pathophysiology

Hasler (2010), organized the main strengths and weaknesses of the various neurobiological hypotheses of depression (genetic vulnerability, altered hypothalamic-pituitary-adrenal [HPA] axis activity, deficiency of monoamines, dysfunction of specific brain region, neurotoxic and neurotrophic processes, reduced gamma-aminobutyric acidergic activity, dysregulation of glutamate system, impaired circadian rhythms). For the authors, these theories of depression and the relatively low response rate to treatments suggest that this is a clinically and etiologically heterogeneous disorder. According to Hare, Toukhsati, Johansson, and Jaarsma (2014), there are several biological plausible mechanisms (changes in the autonomic nervous system, platelet receptors and function, coagulopathic factors, pro-inflammatory cytokines, endothelial function, neurohormonal factors, and genetic linkages such as with serotonin [5-HT] transporter mechanism), and low adherence to medical treatment. According to B (2017), there are no useful biomarkers or imaging abnormalities to determine the pathophysiology of depression during life and, after death, the brain does not reveal any consistent structural or neurochemical abnormalities. In a recent review, Murawska-Cialowicz et al. (2021), outlined biological markers of depression (a decrease in testosterone and estrogens, monoamines [5-HT, dopamine, melatonin], neurotrophins [brain-derived neurotrophic factor - BDNF], noradrenaline, tryptophan, endocannabinoids, sun exposure, and neurogenesis; an increase in inflammation [cytokines and reactive oxygen species], oxidative stress, and cortisol levels). For the authors, one of the main neurotransmitters of the central nervous system is 5-HT ("happiness hormone"), which influences mood, behavior, cognition, emotion, motor function, pain sensitivity regulation, and neuroendocrine regulations related to appetite, reproduction, circadian rhythms, and sleep. Its metabolite is melatonin, the main regulator of sleep and

rhythm, and according to Kruk, Aboul-Enein, and Duchnik (2021), also of insulin and an appetite influencer. 5-HT is a key to a wide variety of behavioral and cognitive phenotypes (Vahid-Ansari & Albert, 2021). According to these authors, 5-HT neurons are capable of regenerating and reinnervating brain regions after disconnections from the 5-HT system (brain damage, chronic stress, or altered development) which often cause depression, anxiety, and cognitive impairment. They said that unravelling this pathophysiology is a complex challenge because syndromes are heterogeneous, aetiology is diverse, and symptomatology (such as guilt and suicidality) cannot be reproduced in animal models. 5-HT is the most extensively studied neurotransmitter in depression. There is no explanation for the mechanism of serotonin loss in depressed patients, but the decrease in L-tryptophan depletion (amino acid synthesizing 5-HT), the decrease in the availability of the 5-HT receptor 1-A, and temporal lobe epilepsy were found in individuals with MDD (Hasler, 2010). de Menezes Galvao et al. (2021), stated that the pathophysiology in patients with MDD depends on the progression of the disease (severity of symptoms and changes in sleep), sociodemographic characteristics (sex, age, income, and schooling), not occurring with the same intensity in every person. The contributions of Guerrera et al. (2020) to explain the pathophysiology of MDD were concentrated on chronic stress, reduction of synaptic plasticity, impairment of adult hippocampal neurogenesis, and hippocampal neurodegeneration, along with the deregulation of the monoaminergic system. They pointed out that chronic stress leads to a decrease in negative feedback from glucocorticoids on HPA activity, resulting in high cortisol levels and an excess of glucocorticoids, which may induce neuronal death at the hippocampal level and dysfunctional alterations in the prefrontal cortex (two regions strongly involved in cognitive symptoms of depression). The self-regulated HPA axis is the main axis of endocrine system (de Menezes Galvao et al., 2021), necessary for adaptation to stress (J. P. Herman et al., 2016), and its activity is evaluated by measuring the response to cortisol (Oberste et al., 2018). The hypersecretion cytokines are a potential tool to predict biological stressors that can contribute to the activation of inflammatory states and other depressive behaviors (Ho et al., 2021; Li et al., 2017). Pro-inflammatory cytokines stress is

related to the inflammatory hypothesis of depression, due to alterations of metabolism in the self-regulated hypothalamus-pituitary-adrenal pathways, neuronal excitotoxicity, and/or brain trophic factors (Murri et al., 2021). Another mechanism is the neurotrophic hypothesis that low levels of BDNF lead to the condition of depression (Neto, Borges, Torres-Sanchez, Mico, & Berrocoso, 2011).

2.5. Diagnostic

The structured clinical interview for DSM-III has undergone many revisions in the 10 years since it was conceived (Spitzer, Williams, Gibbon, & First, 1992). According to the authors, before the DSM-III, the most common diagnostic instruments for research were Schedule for Affective Disorders and Schizophrenia (SADS) and Schedule for Affective Disorders and Schizophrenia-Lifetime (SADS-L). The latest versions of instruments of SADS family have incorporated DSM-III and DSM-III-R. As the SADS interview contains more items than the DSM-III, some authors complement the latter with a standard rating scale (Brief Psychiatric Rating Scale and the Hamilton Depression Scale). DSM-III evolved to DSM-IV and then to Diagnostic and statistical manual of mental disorders : DSM-5 2013). This evolution had a subtle but important effect on the diagnosis of MDD, mainly due to changes in the exclusion of mourning and persistent depressive disorder (Uher, Payne, Pavlova, & Perlis, 2014). Kroenke, Spitzer, and Williams (2001) concluded that, in addition to diagnoses based on criteria for depressive disorders, the Patient Health Questionnaire-9 (PHQ-9) is also a reliable and valid measure of depression severity, especially given its brevity which makes it a useful clinical and research tool. Kroenke et al. (2009), established PHQ-8 as a valid measure of diagnosis and severity for depressive disorders in large clinical studies. This questionnaire evaluates the conjunction of 8 items that answer the question: in the last 2 weeks, how often were you bothered by any of the following problems? Participants have opportunities to respond "not so much" (0), "several days" (1), "more than half a day" (2), and

"almost every day" (3). At the end, the main thing is to add the answers and the score will evaluate depression. In contrast, Levis, Fischer, Benedetti, and Thombs (2021) said that depression symptom questionnaires and standard cutoffs, such as PHQ-8 scores of 10 and higher, are not intended to estimate disorder prevalence, but are designed for screening purposes; they are intended to identify a higher number of individuals than would be diagnosed with depression if assessed using validated diagnostic criteria.

Mental health disorders (including MDD) are classified through validated diagnostic interviews. For large samples, conducting diagnostic interviews as an estimate of the prevalence of depression is impractical, given the time and the trained personnel that are required. This is why studies classify patients with depression, taking into account the questionnaires that are filled out independently by the participants. The questionnaires evaluate symptoms similar to those evaluated in diagnostic interviews but do not evaluate functional impairment or nonpsychiatric conditions that may produce similar symptoms. Therefore, patients are classified as likely or unlikely to have depression, based on scores above or below a cut-off value (Thombs, Kwakkenbos, Levis, & Benedetti, 2018). These authors point to a number of concerns: the substantial exceeding of the true prevalence of the percentage of patients above a cut-off threshold; the screening tools for depression overestimate the prevalence in true low prevalence populations more than in true high prevalence populations; the error of classifying non-cases as cases of depression (false positives) be disproportionately high in low prevalence populations and minimally compensated by false-negative screens, which occur when true cases are lost by the screening test. After, they provided three alternatives (back-calculation, prevalence matching, and two-stage prevalence estimation) to estimate the prevalence of depression. In the end, the perspective of the authors is that the estimation of the prevalence of disorder with screening questionnaires can contribute to a sobrediagnostic that, consequently, can lead to inadequate labeling and nocebo effects, unnecessary use of health resources, and potentially harmful treatment.

2.6. Scales to measure the depression

To evaluate the symptoms of depression, we considered that in this review it was important that all studies analyzed complied with a properly validated depression scale. The studies in our sample used the following scales:

- "*Hamilton Depression Rating Scale (HDRS)*", a scale containing 17 variables (Hamilton, 1960). The literature also refers to HAM-D and sometimes the authors change the number of items in this scale: 21-item HAM-D or 24-item HAM-D;
- "*Beck Depression Inventory Second Edition: BDI-II*", a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression and is an update of BDI-1 (also used in some studies of our sample) and BDI-1A. (Aaron T. Beck, Robert A. Steer, & Brown, 1996). Measures of the scale: mood, pessimism, sense of failure, lack of satisfaction, guilty feeling, sense of punishment, self-hate, self-accusations, self-punitive wishes, crying spells, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation and loss of libido (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961);
- *The Profile of Mood States (POMS)*, a 65-item scale, is commonly used to measure psychological distress (Curran, Andrykowski, & Studts, 1995). According to Lin, Hsiao, and Wang (2014), this scale evolves to POMS 2, that is, 2nd edition, published in 2012 by Multi-health Systems (MHS) to evaluate transient feelings and mood among individuals aged 13 years or above;
- *Depression, Anxiety and Stress Scale ("DASS-21,")* measured the severity of core symptoms of depression, anxiety, and stress (Carneiro, Fonseca, Vieira-Coelho, Mota, & Vasconcelos-Raposo, 2015);
- *Montgomery-Asberg Depression Rating Scale – MADRS* is a scale with 10 items [apparent sadness, reported sadness, inner tension, reduced

sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts] (Montgomery & Asberg, 1979).

2.7. Depression as a risk factor

It is essential to understand the impact of a depressive and toxic environment on human biology, i.e., the interrelationship between depression and physical health (Kvam et al., 2016). The authors pointed out that, in the face of somatic diseases (such as arthritis, angina, and diabetes), depressive patients have a higher health vulnerability and an increased mortality risk, especially if they suffer from cancer, cardiovascular diseases (CVD), and infections.

According to Sotelo, Musselman, and Nemeroff (2014), depression increases the severity of cancer (especially in patients with pancreatic, oropharyngeal, and breast cancer) and might play a role in the development of the tumor, the inflammatory changes in the disease or its treatment. World Health Organization (2021), stated a dependent relationship between CVD and depression, which may lead to the second and vice versa, and a lot of literature has taken a consistent position in alerting behavioral factors that contribute to the risk of cardiovascular diseases: such as obesity, inactivity, poor diet, smoking and poor adherence to medicines (Hare et al., 2014). More than behavioral mechanisms, this study outlined potential psychosocial and demographic factors, biological mechanisms, and perceived loss that may explain the relationship between CVD and depression. Individuals with major depression display altered influences of the parasympathetic and sympathetic nervous systems on cardiac activity (Toni et al., 2016). The mechanisms associated with increased platelet activation, platelet reactivity, and cardiac events are also related to depression and, in turn, this disease is a risk factor for postoperative myocardial morbidity/mortality (Seligman & Nemeroff, 2015). For Harvey et al. (2018), a biological mechanism is an alteration in the activity of the autonomic nervous system to which regular exercise can contribute to the increase of

parasympathetic vagal tone and lead to physiological changes. Compared to the general population, people with mental illness have a reduced life expectancy of, approximately 10 years, and part of this trend is attributed to the increased rate of cardiometabolic diseases to which exercise can prevent and, consequently, control the associated mortality (Schuch, Vancampfort, et al., 2016).

There is type of depressive disorder that is due to another medical condition. According to *Diagnostic and statistical manual of mental disorders : DSM-5* (2013) the diagnosis is made when the mood disturbance is judged to be attributable to the physiological effect of a specific, usually chronic medical condition (e.g., hyperthyroidism). Tricyclic antidepressants and phenothiazine antipsychotics have demonstrated an association with hypothyroidism in both animals and in vitro studies, a link that is speculated in humans (Zader, Williams, & Buryk, 2019). A study revealed that the prevalence of hyperthyroidism was higher in patients with MDD (2.46%) than in the general population (0.79%) and the increased risk of hyperthyroidism in patients with MDD may be related to an autoimmune response due to thyroid gland antibodies being more prevalent in patients with MDD. The same study revealed that the prevalence of hypothyroidism was also higher in patients with MDD (1.20%) than in the general population (0.30%), and this risk may be related to the disease itself and many patients with MDD suffer from chronic stress and experience fight-or-flight response (Wu, Chien, Lin, Chou, & Chou, 2013).

2.8. Treatment

More than 75% of people in low- and middle-income countries do not receive treatment; in countries of all income levels, many depressive patients are not properly diagnosed and, on the contrary, those who do not have the disease are diagnosed and prescribed antidepressants (World Health Organization, 2021). Several classes of antidepressants are used in depression, such as:

selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, serotonin modulators, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI), NMDA antagonists, each with various types of drugs and various mechanisms of action (Sheffler, Patel, & Abdijadid, 2022). Antidepressants may decrease the ratio of pro-inflammatory/anti-inflammatory cytokines (Sutcgil et al., 2007), stimulating the synthesis of transforming growth factor beta 1 (TGF β 1) and the BDNF levels (neurogenesis, synaptic plasticity, learning, memory, and mood) in depressed patients (Guerrera et al., 2020). The disease is treated with antidepressants and/or psychological therapy, even in populations with CVD (Hare et al., 2014), but as these treatments are not always effective, PE has gained attention, particularly aerobic training (Kramer, 2020; Lopez-Torres Hidalgo & Group, 2019). Sherwood et al. (2016), pointed to about 1.5 to 2.0 times the relative risk that depression represents for the subsequent development of coronary artery disease, showing that PE can be a good strategy for healthy individuals with MDD. According to the authors, medicines have undesirable effects, especially on the elderly population, given their prolonged and unnecessary use. Several authors considered exercise as a viable non-pharmacological treatment for depression and recommended it as a strategy to alleviate clinical depression (Murawska-Cialowicz et al., 2021; Olson, Brush, Ehmann, & Alderman, 2017). Called a good depression manager (Schuch & Stubbs, 2019), unlike antidepressants, the benefits of PE persist after treatment (Gujral et al., 2017). The findings of Heinzl, Lawrence, Kallies, Rapp, and Heissel (2015) suggest that PE can be a viable additional intervention for depression in the elderly, which is very relevant, given that a large number of depressed people in this age group do not receive proper treatment in the usual care. There are also validated psychotherapies for the treatment of depression such as interpersonal, psychodynamic, and cognitive-behavioral psychotherapies and the cognitive-behavioral analysis system of psychotherapy, which focus directly or indirectly on interpersonal difficulties and skills (Hasler, 2010). Acute treatment of unipolar psychotic depression usually involves the combination of an antidepressant and an antipsychotic drug or electroconvulsive therapy (Steven, Biswarup, Jordan, &

Cranwell, 2021). For psychotic depression, the guideline recommends that consideration be given to augmenting treatment with an antipsychotic. The guideline goes on to discuss inpatient care, electroconvulsive therapy, discharge planning, recurrent depression and prevention of relapse, and the transition of child to adult services, areas that are not covered in the APA guideline for children and adolescents (APA, 2019).

2.9. Physical activity (prevention) and physical exercise (treatment)

PA and PE proved to be effective, as monotherapy and increasing evidence supports their ability to increase the effectiveness of antidepressant medication and psychological treatment. However, this last aspect needs to be evaluated, as evidence is not consistent between the studies. For this review, we included aerobic, anaerobic exercises, and a combination of both. In addition, we considered it was pertinent to perceive the effect of other exercises (e.g. yoga, pilates, tai-chi, stretching exercise) whenever the type and dose were specified. Although studies on PA were excluded, we determined it was important to distinguish the impact that PA and PE can have on depression, aiming not only to understand the application of each of them but also the following dualism: prevention versus treatment of the disease.

Low levels of PA are usually associated with the onset of depressive symptoms (Rondina et al., 2018). PA is considered as a protective factor of depressive symptomatology in various age groups (it can decrease the risk of depression by up to 45%) and 60 min per week seems sufficient to prevent 12% of new cases of the disease (World Health Organization, 2019). Josefsson, Lindwall, and Archer (2014) related PA to various physical, mental health, and psychological well-being benefits. Kandola, Ashdown-Franks, Hendrikse, Sabiston, and Stubbs (2019), added information on biological mechanisms (neuroplasticity, inflammation, neuroendocrine response and oxidative stress)

and psychosocial (self-esteem, social support, and self-efficacy), about moderators and confounders of the relationship between PA and depressive symptoms. Kleppang, Hartz, Thurston, and Hagquist (2018) investigated the association between PA and mental health in 17,186 Norwegian adolescents. The authors reported that participation in a sports club was associated with significantly lower odds of depression, highlighting the importance of PA in different contexts and not just the frequency or volume of PA. This idea alerts us to, in addition to training variables, interpret the training environment (whether it is a group and supervised by a professional) as a conduit channel to treat depression more effectively. Several authors emphasized the importance of the state of motivation for the success of any non-drug treatment, noting that it is still a major challenge for patients with depression to increase their PA due to lack of motivation (Cheung & Lee, 2018; Kvam et al., 2016). Like antidepressants, the effects of PA contribute to improving the levels of TGF β 1 and BDNF (Guerrera et al., 2020).

Exercise can be defined as a planned, structured and voluntary activity that improves physical fitness, produced as a result of skeletal muscle contraction and that requires an energy expenditure above the basal metabolic rate (Tasci, Baykara, Gurok, & Atmaca, 2019). The authors concluded that exercise had a positive effect on the therapeutic response in depression treatment. For Knubben et al. (2007), there are several exercise mechanisms that can explain the reduction of depressive symptoms, such as body control capacity, the release of feelings of anger, hostility, the distraction of depressive thoughts, motivation, expectations, and human contact that can influence mood. They concluded that an endurance training program improves symptoms in patients with moderate to severe depression and may be a useful complementary treatment for patients with severe affective disorders in the first 3 weeks of pharmacotherapy. These data are supported by the results of Legrand and Neff (2016) in the sense that endurance training can be a useful adjunct treatment for hospitalized patients with severe affective disorders in the early stages of pharmacotherapy. Heinzl et al. (2015), demonstrated that AE, resistance training, dance, and other alternative forms of exercise (Qi Gong and Tai Chi) are viable for depression in

the elderly. This evidence was reinforced by a meta-analysis of randomized controlled trials that concluded that structural PE should be part of the depression treatment of the elderly (Schuch, Vancampfort, et al., 2016). The authors concluded that aerobic and mixed exercises are associated with major effects in all the studies analysed, and if supervised by professionals with training (physical educators, physiotherapists, and exercise physiologists), the improvements were even bigger. These findings led the authors to consider that there are lower rates of dropout in patients with depression when interventions are governed by qualified exercise professionals. This is also supported by the recommendation made by Madhukar H. Trivedi, Tracy L. Greer, Bruce D. Grannemann, Heather O. Chambliss, and Alexander N. Jordan (2006) that a permanent professional (weekly, or fortnightly) contributes to adherence and solving problems related to the dose of exercise. In a systematic review and meta-analysis that included 23 studies, Kvam et al. (2016) investigated the relief of depressive symptoms through PE in patients awaiting treatment and compared it with several groups of patients with depression. They concluded that PE can be a good alternative for patients who do not respond, do not receive, are waiting treatment, or those who want traditional treatment, and observed a high effect of PE relative to the absence of intervention. This review was based on AE (e.g. walking, running, stationary cycling) and nonaerobic (e.g. endurance exercise, strength exercise, weight lifting) in combination with other antidepressant treatments.

Szuhany, Bugatti, and Otto (2015) in their meta-analytical review of 29 studies demonstrated that both acute and regular PE had a significant impact on increasing BDNF levels. They demonstrated increases in BDNF after a single exercise session (moderate effect size), that regular exercise intensified the effect of an exercise session on BDNF levels and still had a small effect on BDNF levels at rest. This review states that, concerning sex, studies with more women showed lower changes in BDNF through exercise. This study also found that exercise improves cognition and mood, with preliminary evidence suggesting that BDNF mediates these effects. In addition to these improvements, BDNF contributes to improvements in learning processes (Murawska-Cialowicz et al., 2021). For the authors, this evidence reinforces the importance of crosstalk

between skeletal muscle and other distant organs/tissues, such as the nervous system. They considered this biological factor the main actor of neurogenesis, growth, and neuronal survival, whose expression and secretion are intensified with PE, stating that adaptations related to stimulation of neurogenesis are essential for the plasticity of the nervous system. In addition, they explained potential mechanisms of exercise's impact on BDNF in decreasing symptoms of depression. Exercise brings benefits to brain health, intensifying blood supply to the brain, improving its oxygenation, and activating many brain structures (improved brain function, secretion of neurotransmitters that communicate in different regions of the brain, and secretion of different chemicals with growth factors activity). For Zhang and Zhang (2016), exercise can contribute positively to the development of the prenatal and postnatal brain, reduce hyperactivation of the HPA axis, and increase irisin. FNDC5/irisin is a hormone present in several brain regions and can be an important messenger of crossed organs that binds the brain to skeletal muscle, adipose tissue, and the cardiovascular system to coordinate the beneficial effects of exercise. The authors suggest that regular exercise is effective in preventing depression and in reducing average symptoms in clinical and non-clinical populations. For Ross, Saladin, George, and Gregory (2019), individuals with higher aerobic fitness may have better regularization of the hypothalamus-pituitary-adrenal gland, although science has not yet offered a consensus related to a correct prescription.

2.10.Exercise prescription

The examples analysed above allow us to realize that the correct prescription of PE can be very useful in combating pharmacological exaggeration, an idea that we try to clarify in this review. Adding to the evidence supporting structured exercise as a therapeutic adjuvant, the fact that 30% to 50% of patients treated with antidepressants do not improve (Eman & Mahmoud, 2017), we consider it important to clarify the type of exercise, the volume, intensity

of training and/or duration of the intervention and the effects of the exercise on various populations.

Vankova et al. (2014), in a study with residents in nursing homes presented evidence that dance-based exercise (1 hour per week [10-min warm-up period, a 40-min main period, and a 10-min cooling-off period], for 3 months) can reduce the number of depressive symptoms. In the study by Hallgren, Kraepelien, Ojehagen, et al. (2015), a 60-min exercise session, 3 times a week, for 12 weeks was more effective than the standard treatment for depression administered by a general practitioner and represents a promising alternative to non-clinical stimulating treatment of patients with mild-moderate depression. Regular exercise of moderate intensity reduces blood lipid levels and blood pressure, which led Doose et al. (2015) to study the benefits of physical and mental health and the possible antidepressant effects of PE. The authors used walking or running 3 times a week for 8 weeks, where effort was self-selected by the participants. This intensity of training is also associated with depression reduction in chronically depressed women taking antidepressant drugs (Craft, 2005). For them, PE acts on self-efficacy as a psychological mechanism for antidepressant effects and is associated with positive changes in response style (reduced tendency to ruminate and increased use of a distractive response style), and the effects were achieved in the first 3 weeks of the study. These findings led the authors to support the use of exercise as an adjunct therapy in the treatment of clinical depression, and aspects of the exercise program related to domain and distraction should be emphasized. Carneiro et al. (2015) results showed that structured and supervised AE (45 to 50 min/week, with intensity between 65%, 73%, 74%, and 76% HR max, 3 times a week, for 4 months) can be effective as adjuvant therapy for treating depression in women, reducing depressive symptomatology, and improving physical fitness. While the group that took medication alone did not improve the BDI-II scale, the group that performed PE had a decrease in this same scale and therefore better parameters at the end of the study. The study by Toni et al. (2016) concluded that the combination of non-progressive PE (mat work and instrumental exercises to improve participant strength and balance, respiration, and motor coordination) and progressive AE

(exercise bicycles) with sertraline was associated with greater improvements in variability heart rate (HRV) compared to the drug alone, which corroborates the use of PE to complement antidepressant therapy, especially in elderly people with high cardiovascular risk. Each session during 1 hour, 3 times per week. Tasci et al. (2019) concluded that patients (most in both groups were women) who practiced walking for at least 30 minutes a day, at least 4 days a week, for 12 weeks, had better improvements in the parameters of depression than the group taking only medication.

Raghavendra et al. (2009) addressed the effects of a yoga program and found a reduction in perceived levels of stress and cortisol. According to the authors, there are several components of yoga that calm, correct autonomic imbalances, and HPA axis disorders precede responses to stress, which can reduce distressing symptoms, improve sleep quality, mood, and life of cancer patients. This effect seems to help reduce perceived stress and poorly adaptive stress excitation patterns, known to cause high distress or depressive symptoms in these patients. A review on neurobiological effects separated the neurobiological effects of acute and chronic exercise in MDD (Schuch, Deslandes, et al., 2016). From the acute point of view, the authors found a significant increase in GH hormone levels through exercise. From the chronic point of view, the authors found significance in more parameters: decreased copeptin levels (12 weeks of exercise); changes on cortical structure and activity hippocampus (large increases on total mean frequency in the anterior region); an increase in hippocampus volume and circulating levels of IL-1 following exercise was positively associated with improvement in depressive symptoms. Gerber, Imboden, Beck, Brand, Colledge, Eckert, Holsboer-Trachsler, Puhse, et al. (2020), in their randomized study, concluded that 6 weeks of indoor cycling, 3 times per week, at 60%-75%% HR.max are insufficient to impact patients' cortisol stress reactivity and suggest new studies to discover more efficient treatments that promote HPA reactivity normalization in patients with MDD. Phillip P.N. Do (2021), concluded that low and moderate exercise intensities (30% and 50% HRR, respectively) do not appear to be significantly different from each other and that vigorous intensity (70% HRR) as it exceeds the lactic threshold, needed to

observe a sharp increase in lactate and a direct response in cortisol from the HPA axis to influence cortisol release. Even so, evidence that aerobic fitness has an impact on significantly increased or decreased cortisol levels at higher exercise intensities is inconclusive. This is supported by the lack of consensus in the literature since most works in this area have small samples and different methodologies. The studies vary in the type of modality (treadmill, ergometric cycle), chosen duration (15-90 min), intensity (%HRR or %Vo2max), time of collection of cortisol samples (the diurnal rhythm plays a role in the amount of secreted cortisol) and the nutritional condition. This review also pointed out that the use of psychological screening for psychological diseases (depression and anxiety) is rarely used by researchers. Imboden et al. (2021), in a supervised intervention of AE (3 times a week of indoor cycling for 6 weeks to 60-75% of HRR), realized that increased cardiorespiratory fitness seems to have a positive effect on depression severity and sleep parameters related to depression. Szymura, Kubica, Wiecek, and Pera (2020), reported that PE also induced an increase in BDNF, an effect that depends on the intensity and duration of exercise (moderate intensity of training seems to be more effective in inducing changes in BDNF concentration). They realized that systematic moderate-intensity balance training influences cytokine levels and anti- and pro-inflammatory neurotrophic factors, at the end of 12 weeks of balance training (in the first week the sessions lasted 30 min and then were extended to 60 min). Concentrations of TGF-1 and BDNF increased in both training groups, but not in groups without training. Mackay, Kuys, and Brauer (2017), in their systematic review with meta-analysis where most of the studies analysed (10 out of 11) used a bicycle ergometer as an intervention (moderate intensity of 60% of the maximum oxygen consumption - VO2max most used), showed that regular AE has an impact on the increase of BDNF levels in neurological populations, respectively in neuroplasticity and motor performance. However, the authors emphasized the need for high-quality clinical trials to confirm these results, with attention to the study design and factors that may influence the BDNF results.

However, the effect of PE may not always be the most effective for treating depressive symptoms and/or considered an obvious solution to science, as it

depends on several factors (for example, many people with certain diseases have an absolute contraindication for exercise). Danielsson, Papoulias, Petersson, Carlsson, and Waern (2014), separated one group of participants who performed aerobic exercises from another who took antidepressant medication and found no differences between treatments. They realized that 2 weekly exercise sessions over 10 weeks in a rehabilitation center had a greater effect in the medium term, but also caused more adverse effects. First, participants had 2 individual sessions with a physical therapist and then trained with 5 to 8 participants. Each training session lasted 1 hour and included: a warm-up phase (5-10 min), interval training (45 min), and a cooling phase of stretching exercises (5 min). Arvidson, Dahlman, Borjesson, Gullstrand, and Jonsdottir (2020), randomized a study whose participants were free to choose the type of activity to be performed and whether they wanted to exercise individually or together with others. This training intervention lasted 6 months, 3 times a week, 45-60 min per session, and with an average HR of at least 75% of the HR.max (calculated by VO2max). The authors concluded that this regularity of AE (the most studied form of exercise in this field) did not affect physiological responses to acute stress compared to untrained controls. To Cooney (2014), exercise does not seem to be more effective than psychological or pharmacological therapies. In regards to the reduction of depression among patients, Blumenthal et al. (1999), stated that the therapeutic response of antidepressants is faster than that of PE, corresponding to the conclusion of 16 weeks of exercise. Nevertheless, the authors considered that exercise and exercise training program may be an alternative for the treatment of depression in older persons.

3. Objectives (general and specific) and hypotheses

The main objective of this work is to verify whether PE, when combined with antidepressant drugs, has additional effects in terms of reducing depressive symptoms, in comparison with taking antidepressant drugs only. Thus, we intend to interpret the dose of exercise (by intensity, session volume and weekly frequency) that can best suit the treatment of depression, according to randomized, non-randomized, pilot (if randomized) and observational studies. In this sense, we will identify the primary outcome (severity of depressive symptoms) and that the difference between groups, before and after treatment, through a valid scale that measures depressive symptomatology. We will also formulate secondary outcomes that may interfere with the maximization the treatment benefits and sources of heterogeneity (medication, type of exercise, duration of intervention, sex, age, groups, intensity and volume of training). After that, we will calculate the random effect meta-analysis to estimate the standardized mean difference for standard treatment only versus standard exercise treatment, and we will discuss the results in order to establish a valid path for the application of exercise against this disease. In this sense, this dissertation will formulate a set of scientifically validated recommendations, where readers can extract ideas for practical application in the context of clinical exercise, to effectively reduce depressive symptoms for patients and contribute to the improvement of public health.

4. Methods

To carry out this work, we performed a systematic literature search in accordance with PRISMA recommendations (21). The protocol of this work has not been published in advance.

4.1. Eligibility criteria

A study was considered eligible if it included the following criteria:

Participants: people of both genders, any age with depressive disorders.

Intervention: we included aerobic exercise (running, walking*, cycling, "aerobic training", "endurance training", "endurance exercise", "interval training"), anaerobic exercise ("endurance training", "strength training", "strength exercise", "endurance exercise", "weightlifting") and a combination of both ("interval training", "combined exercise", "combined training"). We also think it appropriate to include yoga, pilates, tai-chi, or swimming/hydrogymnastic lessons, when the type of exercise is well specified. Studies in which the doses of stretching are not specified are also excluded. Also excluded were studies concerning PA, all that did not include an experimental group that performs physical exercise combined with antidepressant medication, and studies that belonged to rodents.

Comparison: to be included, a study had to compare the effectiveness of exercise when combined to taking antidepressants with a control group receiving usual care plus antidepressants (without exercise).

Outcomes: studies should be addressing the change in depressive symptoms. Studies on depressive symptoms were included if they used a specific and duly validated scale. If the information is available from the studies, we also planned to perform sub analysis to investigate the impact of several training variables (such as volume, weekly frequency and intensity) in order to determine

the precise dose of exercise needed to maximize the benefits for depression. As a secondary outcome we also consider interesting to understand if the type and adherence to medication and exercise interferes in the maximization of these same benefits.

Study design: randomized and non-randomized controlled clinical trials, pilot studies (if randomized), and observational studies. Only studies published in English were considered eligible.

4.2. Sources of information

The search was conducted by one researcher on PubMed and Scopus databases for papers published from inception to 30-04-2022. The search in the PubMed and Scopus databases was conducted by inserting the following sequence:

(depression OR "depressive disorder" OR "major depression" OR "atypical depression" OR "mental depression" OR "bipolar disorder") AND ("physical exercise" OR "physical training" OR "exercise training" OR "strength training" OR "resistance training" OR "strength exercise" OR "resistance exercise" OR "aerobic training" OR "aerobic exercise" OR "endurance training" OR "endurance exercise" OR "interval training" OR "combined exercise" OR "combined training" OR "exercise therapy" OR walk* OR run OR jogging OR cycling OR bicycling OR swimming OR exercise* OR exercising) AND ("psychological treatment" OR "pharmacologic treatment" OR "antidepressant medication" OR "antidepressant drug") AND ("depressive symptoms" OR "quality of life"). A manual search was also carried out by checking the references of primary articles and systematic reviews. All retrieved articles were download for a reference manager software (EndNote).

4.3. Data extraction and management

The selection of studies was carried out by one researcher. The first stage of screening included reading the title and abstract, followed by reading the full articles to verify eligibility. Studies not meeting the eligibility criteria were excluded and the reason was registered. A second researcher was recruited to confirm exclusion of any paper (D.M.G). For each eligible study, we collected general information (title, authors, place and date of publication), characteristics of the study (study design, sample size, age, gender, time that the participants presented depression, and time that participants were on medication) intervention (type of exercise, frequency, intensity, volume, duration of intervention), and outcome measures (primary and secondary). Whenever necessary, data was transformed to allow further use in quantitative analysis using mathematical formulas previously described (22, 23). In case of need for addition or missing information, the authors of the studies were contacted. In case of no response, the study in was removed from the analysis.

4.4. Risk bias

For the analysis of the risk of bias, the selected articles were assessed by researcher and a second evaluator (D.M.G) was requested in situations of indecision. For this assessment we used the Cochrane risk-of-bias tool for randomized trials (Rob 2) (Cochrane, 2022), which evaluated each study based on the domains presented in Figure 2.

4.5. Data analysis

We processed data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (22). Data are expressed as standardized mean difference (SMD) and 95% confidence intervals for each outcome.

Heterogeneity was tested statistically using the χ^2 test of heterogeneity and I^2 statistic. Values of 0% to 25% were considered low heterogeneity, 26% to 50% moderate heterogeneity, 51% to 75% high heterogeneity and > 75% very high heterogeneity. In addition, I^2 was considered statistically significant if the p value <0.10 (42). Data from each study were pooled using the random model when heterogeneity > 50% or by the fixed model when the heterogeneity was <50% (42).

We completed data synthesis and analyses using the Review Manager 5.2 software (RevMan 2016) for all outcome measures that were reported in at least 2 articles.

5. Results

The study selection process is outlined in Figure 1. Initially, we identified 1479 studies, of which 11 were duplicated. After reading the title and abstract, we excluded 1417 studies, leaving only 62 works to read in full. After a complete analysis of these scientific articles, we eliminated 50 for the reasons shown in Figure 1 and Table 1. In the end, this review included the analysis of 12 studies.

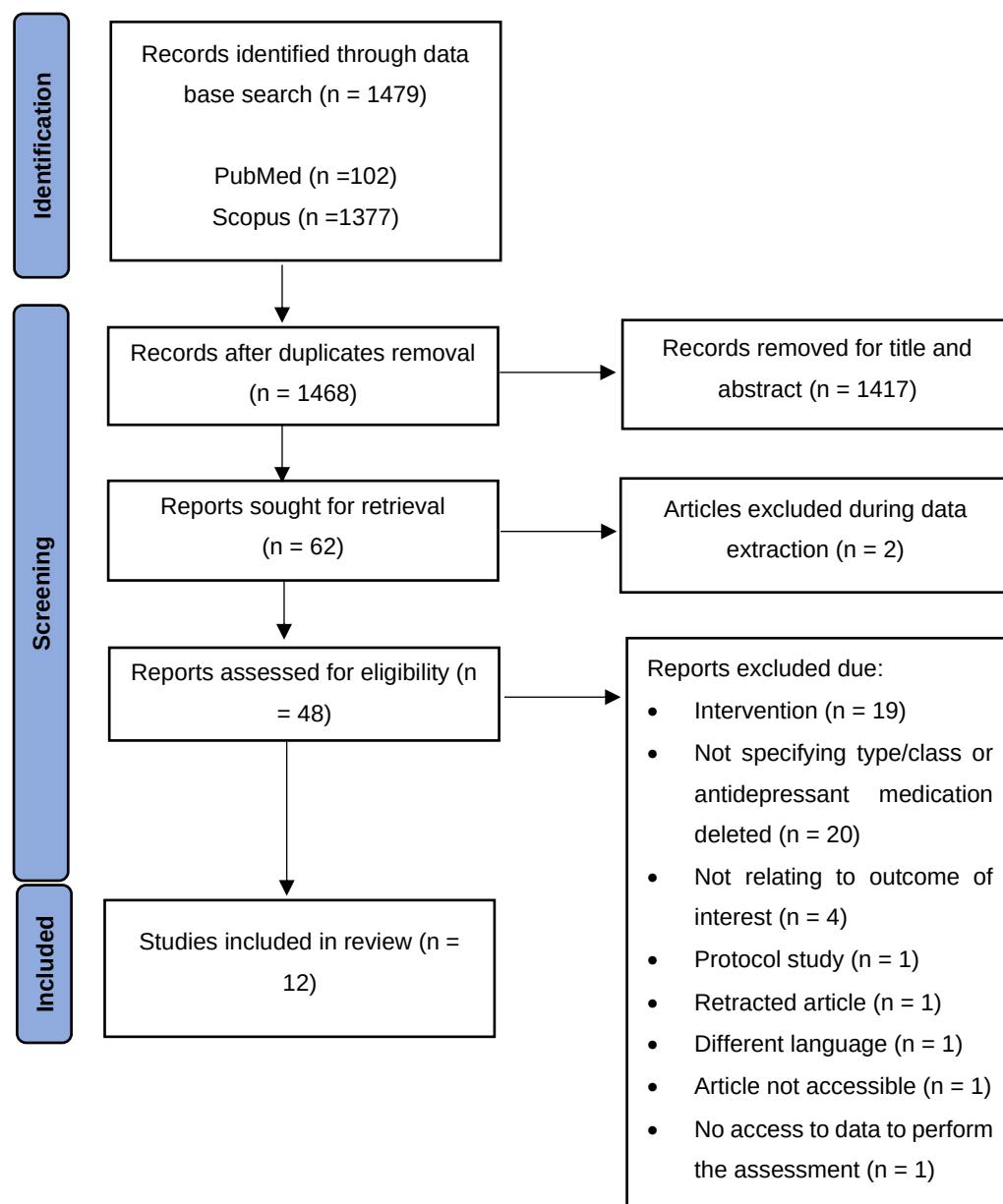


Figure 1. Flow Diagram of the Study Selection Process

Table 1. Reasons for exclusion

Study name	Grounds for excluding
M. H. Trivedi, T. L. Greer, B. D. Grannemann, H. O. Chambliss, and A. N. Jordan (2006)	Intervention: a study with only one exercise group
M. H. Trivedi, T. L. Greer, B. D. Grannemann, T. S. Church, et al. (2006)	Intervention: both groups exercised
Blumenthal et al. (2012)	Intervention: the intervention group does not combine exercise with the drug
Shachar-Malach, Cooper Kazaz, Constantini, Lifschytz, and Lerer (2015)	Intervention: both groups exercised
Trombello et al. (2018)	Outcome: does not evaluate depressive symptoms
López-Torres Hidalgo et al. (2019)	Doesn't specify the type/class of antidepressant
Blumenthal et al. (1999)	Inability to access the data to perform the evaluation
Knubben et al. (2007)	Intervention: both groups exercised
Da Costa et al. (2009)	Antidepressant medication not indicated
Legrand and Mille (2009)	One of the exclusion criteria was taking antidepressants
Raghavendra et al. (2009)	Antidepressant medication not indicated
Schuch, Vasconcelos-Moreno, Borowsky, and Fleck (2011)	Doesn't specify the type/class of antidepressant
Trivedi et al. (2011)	Intervention: both groups exercised
Carter, Callaghan, Khalil, and Morres (2012)	Protocol of a study
Kruisdijk, Hendriksen, Tak, Beekman, and Hopman-Rock (2012)	Doesn't specify the type/class of antidepressant
Sturm et al. (2012)	Intervention: both groups exercised
Hughes et al. (2013)	Intervention: both groups exercised
Van der Waerden, Hoefnagels, Hosman, Souren, and Jansen (2013)	Doesn't specify the type/class of antidepressant
Helgadóttir, Ekblom, and Forsell (2014)	Antidepressant medication not indicated
Salehi et al. (2014)	Retracted
Vankova et al. (2014)	Doesn't specify the type/class of antidepressant
Pibernik-Okanović et al. (2015)	Antidepressant medication not indicated
Salehi et al. (2016)	Intervention: none of the groups did only medication
Sherwood et al. (2016)	Outcomes: CHD Risk Assessments, but doesn't measure depression symptoms

Strid, Andersson, Forsell, Öjehagen, and Lundh (2016)	Doesn't specify the type/class of antidepressant
Yeltepe Ercan, Yargiç, and Karagözoglu (2016)	Language
Cahn, Goodman, Peterson, Maturi, and Mills (2017)	Antidepressant medication not indicated
Kvæl, Bergland, and Telenius (2017)	Relates to PA
Neviani et al. (2017)	Intervention: both groups exercised
Olson et al. (2017)	Intervention: both groups exercise
Prathikanti et al. (2017)	Doesn't specify the type/class of antidepressant
Sadeghi, Ahmadi, Moghadam, and Parvizifard (2017)	Antidepressant medication not indicated
Radovic, Melvin, and Gordon (2017)	Paper not accessible
Ahmed et al. (2018)	Outcomes: Measured outcomes did not include depressive symptoms
Cheung and Lee (2018)	Doesn't specify the type/class of antidepressant
Haller et al. (2018)	Doesn't specify the type/class of antidepressant
Oberste et al. (2018)	Intervention: both the groups conducted exercise
Verrusio et al. (2018)	Antidepressant medication not indicated
De Cassia Rondina et al. (2018)	Does not specify well whether the intervention refers to PA or physical exercise
Murri et al. (2018)	Article does not display data in a form that allows its use
Philippot et al. (2019)	Intervention: both groups exercised
Ross et al. (2019)	Intervention: one of the groups had healthy people
Vargas-Terrones, Barakat, Santacruz, Fernandez-Buhigas, and Mottola (2019)	Antidepressant medication not indicated
Gerber, Imboden, Beck, Brand, Colledge, Eckert, Holsboer-Trachsler, Pühse, et al. (2020)	Intervention: both groups exercised
Hellem, Sung, Ferguson, and Hildreth (2020)	Intervention: both groups exercised
Imboden et al. (2021)	Intervention: both groups exercised
López-Torres Hidalgo et al. (2021)	Relates to PA
Lu, Liu, and Yuan (2021)	Antidepressant medication not indicated
Nugent et al. (2021)	Outcomes: IL-6 concentrations, but doesn't measure depression symptoms
Gilbert, Earleywine, and Altman (2021)	Antidepressant medication not indicated

5.1. Study characteristics

Table 2 contains describes the type and country of the study. Fourteen studies were included in this meta-analysis: ten randomized clinical trials, one was non-randomized trial, and one was a quasi-experimental randomized trial. All the articles compared the effectiveness of usual treatment alone or when combined with physical exercise to reduce symptoms of depression.

Table 2. Description of studies

Study name	Kind of study	Country
Lavretsky et al. (2011)	Randomized	USA
Carneiro et al. (2015)	Randomized	Portugal
Legrand and Neff (2016)	Randomized	France
Khatri et al. (2001)	Randomized	USA
S. Herman et al. (2002)	Randomized	USA
Craft (2005)	Quasi-experimental design	USA
Vieira, Porcu, and Buzzo (2009)	Randomized	Brazil
Danielsson et al. (2014)	Randomized	Sweden
Hallgren, Kraepelien, Öjehagen, et al. (2015)	Randomized	England
Doose et al. (2015)	Randomized	Germany
Toni et al. (2016)	Randomized	Italy
Tasci et al. (2019)	Non-randomized	Turkey

Table 3, 4, 5 and 6, summarizes the information retrieved from 12 selected studies divided by: medication, type of exercise, duration of intervention, frequency, intensity, and volume, mean age, time that the participants presented depression, time that participants were on medication, measured outcomes, how the outcomes were assessed, and results.

Table 3. Methodology of the studies by medication, type of exercise, duration of intervention

Study name	Medication	Type of exercise	Duration of intervention
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Lavretsky et al. (2011)	SSRIs: Escitalopram (10mg/day and after 4 weeks 20mg/day)	Tai Chi Chih	10 weeks
Carneiro et al. (2015)	SSRIs: fluoxetine, escitalopram, sertraline, and paroxetine; When convenient, benzodiazepines diazepam, lorazepam and estazolam were used as anxiolytic or hypnotics	AE: traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing	16 weeks
Legrand and Neff (2016)	AE group: SSRIs (paroxetine, fluoxetine) n= 9; SNRIs (milnacipran): n= 3; dopamine agonist (bupropion): n= 2; ST group: SSRIs (paroxetine, fluoxetine) n= 8; SSNRI (milnacipran): n= 2; dopamine agonist (bupropion): n= 1; NI group: SSRIs (paroxetine, fluoxetine) n= 7; SSNRI (milnacipran): n= 2; dopamine agonist (bupropion): n= 1	AE: daily brisk walking or jogging; ST: several muscle groups: thighs, calves, gluteal, shoulders, back)	10 consecutive days
Khatri et al. (2001)	SSRIs: Sertraline (Zoloft) - initiated with 50mg and up to 200mg. The median dosage was 100mg	AE: continuous cycle ergometer or brisk walking/jogging	16 consecutive weeks
S. Herman et al. (2002)	SSRIs: Sertraline (Zoloft) - initiated with 50mg and up to 200mg)	AE: continuous cycle ergometer or brisk walking or jogging	16 consecutive weeks
Craft (2005)	SSRIs and Atypical SSRIs	Brief (5min) session of stretching followed by PE	9 weeks

		on stationary cycle ergometers and treadmills	
Vieira et al. (2009)	SSRIs: Citalopram 20mg; Alprazolam 0,05mg; Amitriptyline 20mg; Fluoxetine 20mg; Clonazepam 0,05mg; Clomipramine 10mg; Paroxetine 10mg; Clomipramine 20mg; Paroxetine 20mg Benzodiazepine: Alprazolam 0,05mg; Clonazepam 0,05mg TCAs: Amitriptyline 20mg; Clomipramine 10mg; Clomipramine 20mg Clomipramine 75mg; Imipramine 20mg	Hydrogymnastics	12 weeks
Danielsson et al. (2014)	TCA: clomipramine SSRIs: sertraline, fluoxetine SNRI: venlafaxine Other agents: mirtazapine, bupropion	AE: cross-trainer, stationary bikes, step-up boards, rowing machine, treadmill, jumping ropes, balls, free weights and cable machines	10 weeks
Hallgren, Kraepelien, Öjehagen, et al. (2015)	1/3 of all patients were taking antidepressants (primarily SSRIs)	Light exercise: yoga classes (or similar) with a focus on gentle ST and controlled breathing; moderate exercise: an intermediate-level aerobics class; vigorous exercise: a higher intensity aerobics/strength-training and balance class	12 weeks
Doose et al. (2015)	SSRIs, SNRIs, TCAs	AE: walking/running	8-week

Toni et al. (2016)	SSRIs: Sertraline (starting dosage of 50mgs)	NPE: exercise bicycles PAE: mat work and instrumental exercises to improve participant strength and balance, respiration and motor coordination	24 weeks
Tasci et al. (2019)	TCA: n= 1; SSRIs: n= 15; SNRIs: n= 4; Others: n= 3	Brisk walking	12 weeks

SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin and norepinephrine reuptake inhibitors; TCAs: tricyclic antidepressants; NPE: non-progressive exercise; PAE: progressive aerobic exercise; ST: stretching training; PE: physical exercise; NI: not intervention

All studies combined PE with antidepressant medication, specifically, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). Knowing the type and/or class of antidepressants and the mechanism of action is important for several reasons: for example, it is known that there are drugs that are directly related to depression and antidepressants that can induce other diseases. For example, TCAs are related to hypothyroidism (Zader et al., 2019) or higher doses of SNRIs have been reported to mildly increase blood pressure (B, 2017). For the last authors: TCAs block the reuptake of both norepinephrine and serotonin; SSRIs can block the reuptake of serotonin and increase the synaptic transmission of serotonin. For Galecki, Mossakowska-Wojcik, and Talarowska (2018), the mechanism of anti-inflammatory action may serve as a possible explanation for the efficacy of antidepressants from the groups of SSRIs and SNRIs Lavretsky et al. (2011) used escitalopram (10mg/day and after 4 weeks 20mg/day). Carneiro et al. (2015) used fluoxetine, escitalopram, sertraline, and paroxetine. When convenient, benzodiazepines (diazepam, lorazepam and estazolam) were used as anxiolytic or hypnotics. Legrand and Neff (2016) used SSRI (paroxetine, fluoxetine), SNRIs (milnacipran); dopamine agonist (bupropion). Khatri et al.

(2001) used sertraline (zoloft) initiated with 50mg and up to 200mg. The median dosage was 100mg. S. Herman et al. (2002) used sertraline (zoloft) initiated with 50mg and up to 200mg. Craft (2005) used SSRIs and Atypical SSRIs, but did not specify what the drug was. Vieira et al. (2009) used SSRIs (citalopram 20mg, alprazolam 0.05mg, amitriptyline 20mg, fluoxetine 20mg, clonazepam 0.05mg, clomipramine 10mg, paroxetine 10mg, clomipramine 20mg, and paroxetine 20mg; Benzodiazepine (alprazolam 0,05mg, and clonazepam 0,05mg); tricyclic antidepressants (amitriptyline 20mg, clomipramine 10mg, clomipramine 20mg, clomipramine 75mg, imipramine 20mg). Danielsson et al. (2014) used tricyclics (clomipramine), SSRIs (e.g sertraline, fluoxetine), SNRI (venlafaxine), and other agents (e.g mirtazapine, bupropion). In the study of Hallgren, Kraepelien, Öjehagen, et al. (2015), 1/3 of all patients were taking antidepressants (primarily SSRIs). Doose et al. (2015) used SSRI, SNRI, and tricyclic antidepressants. Tasci et al. (2019) used tricyclic antidepressant, SSRI, SNRI, and others, not specifying what the drug was.

Table 4. Methodology of the studies by frequency, intensity and volume of the session

Study name	Frequency	Intensity	Volume
Lavretsky et al. (2011)	2 times per week	Not reported	2h per week Each session: 120min with 10min warm-up (e.g., ST and breathing) and 5min of cool-down exercises
Carneiro et al. (2015)	3 times per week	65%, 73%, 74% and 76% HR max. respectively (RPE: 12e13)	40-50min per session: 10min of a general low-intensity warm-up; 30min of AE; 5min low-intensity cool-down period
Legrand and Neff (2016)	Not referred	65–75% HR max.	AE group: 30min;

			ST group: 30min with stretching by 60sec and equivalent resting intervals between stretching series
Khatri et al. (2001)	3 sessions per week	70% to 85% HRR	AE: 10min warm-up; 30min; 5min cool-down exercises
S. Herman et al. (2002)	3 group exercise sessions per week	70% to 85% HRR	AE: 10min warm-up; 30min; 5min cool-down exercises
Craft (2005)	3 days per week	Weeks 2-3: "comfortable" pace; For the remaining 6 weeks: to ride or walk at 50– 75% of HRR	Weeks 2-3: "comfortable" pace in a total of 20min; For the remaining 6 weeks: 30min
Vieira et al. (2009)	2 sessions per week	Through the RPE scale, but not referred	50min per week
Danielsson et al. (2014)	2 sessions (first 2 weeks) and 2 sessions per week (8 weeks)	Higher perceived intensity 16–17 on the RPE and intermittent intervals of lower perceived intensity 13–14 on the RPE	Each session lasted for 60min: a warm-up phase of 5–10min, 45min of interval training, and a 5min cool-down with stretching exercises
Hallgren, Kraepelien, Öjehagen, et al. (2015)	3 times per week	Light, moderate, and vigorous exercise (not reported)	Sessions were 60min in duration and most included between 5 and 20 participants
Doose et al. (2015)	3 times weekly	Self-selected according to perceived effort (not reported)	Each session lasted for 60min and included: 10-15min warm-up and 10-15min cool down/flexibility exercise time, with an exercise bout in between 30-45min
Toni et al. (2016)	3 times per week	NPE: mat work and instrumental exercises to improve participant strength and balance, respiration and motor coordination	Each session with 60min (in groups of 3-6 participants)

		PAE: Warm-up was followed by cycling at an intensity that would increase along the weeks according to a standardized protocol	
Tasci et al. (2019)	4 days a week	Not reported	30min a day

AE: aerobic exercise; NAE: non aerobic exercise; ST: stretching training; NPE: non-progressive exercise; PAE: progressive aerobic exercise; h: hours; min: minutes; RPE: rate of perceived exertion

The literature indicated several types of exercise, with different intensity, frequency and volume decreases depressive symptoms. Lavretsky et al. (2011) used Tai Chi Chih 2 hours a week, 2 times a week, for 10 weeks. Each Tai Chi Chih session lasted 120min (10min warm-up and 5min cooling exercises). Most parts of the studies resorted to AE. Carneiro et al. (2015) for 16 weeks, applied AE (traditional games, indoor/outdoor natural circuit workouts with resistance bands, jump ropes, fitness balls, brisk walking, and dancing), 3 times a week to 65%, 73%, 74% and 76% HR max (RPE: 12 and 13). Each session had a duration of 40-50min (10min of low intensity general heating; 30min of aerobics; low intensity cooling period of 5min). Legrand and Neff (2016) divided the sample into a group that performed AE (walking or daily running, with an intensity between 65-75% HR max, for 30min) and other group performed stretching exercises for the various muscle groups, for 30min with rest intervals of 60s and equivalent between stretches: thighs, calves, buttocks, shoulders, back. Khatri et al. (2001) used AE (continuous cycle ergometer or brisk walking/jogging: 10min warm-up; 30min; 5min cool-down exercises) during 16 consecutive weeks, 3 sessions per week at 70% to 85% HRR. S. Herman et al. (2002), during 16 consecutive weeks, with 3 group exercise sessions per week, used AE (continuous cycle ergometer or brisk walking or jogging at 70% to 85% HRR). Each session had a 10min warm-up; 30min of continuous cycle ergometer or brisk walking or jogging; 5min cool-down exercises). In the study of Craft (2005), during 9 weeks, the participants performed a brief (5min) session of stretching followed by PE on stationary cycle ergometers and treadmills, 3 days per week. The intensity of exercise in weeks 2-3 was at a “comfortable” pace during 20min, and for the remaining 6 weeks it

was 30min to ride or walk at 50–75% of HRR. Vieira et al. (2009) the participants did 2 hydrogymnastics sessions per week, during 12 weeks, accumulating 50min per week. The intensity it was measured with the PSE, but the authors did not report the exercise intensity. In the study of Danielsson et al. (2014) each session of AE lasted 1h: a warm-up phase of 5–10min, 45min of interval training, and a 5min cool-down with stretching exercises. The participants started in the first 2 weeks with 2 sessions and the following 8 weeks with 2 sessions per week. Regarding exercise intensity, they used the highest perceived intensity (16–17 on the Borg Scale) and intermittent intervals of lower perceived intensity (13–14 on the Borg Scale). During 12 weeks, Hallgren, Kraepelien, Öjehagen, et al. (2015) conducted the participants to join 60min sessions, 3 times per week, (between 5 and 20 participants) with light, moderate, and vigorous exercise intensity. Doose et al. (2015) asked the participants to perform AE (walking/running in a self-selected intensity according to perceived effort) 3 times per week, during 8-weeks. Each session had 60min of duration and included: 10-15min warm-up and 10-15min cool down/flexibility exercise time, with an exercise bout in between 30-45min. Tasci et al. (2019) used 30min a day of brisk walking, during 12 weeks, 4 days a week. The authors did not report the exercise intensity.

Table 5. Methodology of the studies by population, mean age, time that the participants presented depression, time that participants were on medication

Study name	Participants (by gender)	Mean age (SD) in years	Time that the participants presented depression	Time that participants were on medication
Lavretsky et al. (2011)	N= 73 esCIT + TC: n= 23 women; esCIT+ HE: n= 22 women	esCIT+ TC: 69.1 (7.0); esCIT+ HE: 72.0 (7.4)	Age at depression onset in years: esCIT+ TC: 41.4 (24.1); esCIT+ HE: 46.8 (24.1)	14 weeks: first, for 4 weeks, for selection processes of the response to medication. Then, for 10 weeks, accompanied with TC and HE interventions

Carneiro et al. (2015)	N= 26 women	Combined medication and exercise: 52.78 (7.66); Medication treatment: 47.80 (15.05)	Not reported	Participants had been taking medication for at least 6 weeks
Legrand and Neff (2016)	N= 35 AE group: n= 9 women; Placebo (ST): n= 8 women; No intervention (control): n= 7 women	AE group: 45.3 (10.6); ST group: 41.8 (13.2); NI group: 49.1 (16.5)	At least, between July 2011 and July 2015	Started less than 2 weeks
Khatri et al. (2001)	N= 84 Men: n= 20 Women: n= 64	56.73 (6.45)	Not reported	Not reported
S. Herman et al. (2002)	N= 156 N= 43 (men); N= 113 (women)	56.72 (6.45)	Not reported	16 consecutive weeks (potential participants were excluded if they were already taking antidepressant medications)
Craft (2005)	N= 19 women	43.21	Lasting a mean of 17.47 (28.75) months	Participants were receiving pharmacological treatment for their depression (for at least 4 weeks prior to study entry). They had been taking their current medications for a mean of 47.26 months
Vieira et al. (2009)	N= 16 women	36.45 (9.45)	Not reported	Participants took medication only during the intervention (3 months)

Danielsson et al. (2014)	N= 62 48 women and 14 men	Ex: 44.7 (12.5); BBAT: 45.4 (13.5); Advice: 46.3 (13.9)	Not reported	Antidepressant duration, n (%): Ex: 6 w–3 months: 3 (14) 3–9 months: 7 (32) > 4-9 month: 12 (54) BBAT: 6 w–3 months: 1 (5) 3–9 months: 7 (35) > 4-9 month: 12 (60) Advice: 6 w–3 months: 1 (5) 3–9 months: 8 (40) > 4-9 months: 11 (55)
Hallgren, Kraepelien, Öjehagen, et al. (2015)	N= 257 men; N= 689 women Ex: n= 317; ICBT: n= 317; TAU: n= 312 Post-treatment assessment (3 months): Ex: n= 249; ICBT: n= 259; TAU: n= 232	18-34: 30 men and 30 women; 35-49: 37 men and 36 women; 50-71: 33 men and 33 women 73% of women with a mean of age: 43 (12)	Not reported	Participants took medication throughout the intervention
Doose et al. (2015)	N= 46 Intervention: 18 (60) women Control: 11 (68.8) women	Intervention: 46.07 (10.32) Control: 51.25 (10.22)	Years since first episode: Intervention: 8.10 (7.09) Control: 10.78 (10.63)	Ongoing pharmacological antidepressant treatment, n (%): Intervention: 15 (50) Control: 12 (75)
Toni et al. (2016)	S: 72.0% women; S+EX: 71.1% women	S: 73.5 (6.9) S+EX: 75.0 (6.4)	Duration of depressive disorder:	Lifetime use of antidepressants: S: 70.0%

			S: 10.4 (15.3) S+EX: 24.1 (20.1)	S+EX: 73.7%
Tasci et al. (2019)	N= 33 G1: n= 14 women; G2: n= 14 women	G1: 37.24 (7.926); G2: 39.81 (8.352)	Not reported	Continuing treatment for a while: G1: 10 G2: 12

N: number of participants; esCIT: escitalopram; HE: health education; TC: Tai Chi Chi; ST: stretching training; BBAT: basic body awareness therapy; G: group; S: sertraline; EX: exercise; ICBT: internet-based cognitive-behavioural therapy; TAU: treatment as usual

Table 5 shows the methodology of the studies divided by: population (by gender), mean age (in years), time that the participants had depression, how long they were on medication, groups, measured outcomes, how long the outcomes were evaluated, and results. A total of 2022 participants were included in the meta-analysis, with the majority being women (n= 1354, i.e., approximately 66.96%). The average age of our sample is 51.43 years, without the study of Hallgren, Kraepelien, Öjehagen, et al. (2015) which represents ages with intervals (18-34 years; 35-49 years; 50-71 years). Young people, adults, and the elderly correspond to the age groups of our entire sample.

We collected information about "how long the participant had been depressed" and "how long the participant had been taking antidepressants," but not all articles provided this data. Some articles indicated different aspects such as: "number of depressive episodes", "onset of depression after 55 years" and "age at onset of depression". Lavretsky et al. (2011) refer to the average age at which participants began to have depression (70.55 years). The first 4 weeks of the study were used to evaluate the processes of selecting the response to medication. For the next 10 weeks, antidepressants were followed up with other interventions. In the study by Carneiro et al. (2015), one of the exclusion criteria is that participants change the medication in the last 6 weeks. In the study of Legrand and Neff (2016) participants had been depressed for at least 5 years and started taking antidepressants less than two weeks before the study began.

Craft (2005) found that participants reported recurrent episodes of depression for a lasting mean of 17.47 (28.75) months and that they were taking their current medications for an average of 47.26 (47.55) months. Participants received pharmacological treatment for depression at least 4 weeks before entering the study. Hallgren, Kraepelien, Öjehagen, et al. (2015) only 8% of participants had depression, but the time when the disease was diagnosed is not reported. Participants took medication throughout the intervention. Doose et al. (2015) revealed the average age since the participants had their first episode (intervention group: 8.10 (7.09)); control group: 10.78 (10.63) and ongoing pharmacological antidepressant treatment (intervention group: 15 (50), control group: 12 (75)). Toni et al. (2016) indicated the duration of depressive disorder for both groups (S: 10.4 15.3; S+EX: 24.1 20.1), on average, and the percentage of participants who previously took antidepressants (S: 70.0; S+EX: 73.7). Danielsson et al. (2014) pointed out the time that participants ingested antidepressants (6 weeks-3 months; 3-9 months; 4-9 months). Most participants, approximately 11.67%, took antidepressants between 4-9 months. The participants of the study by Vieira et al. (2009) intake antidepressants for 3 months, and those of the study by S. Herman et al. (2002) for 16 consecutive weeks, both during the intervention process. Tasci et al. (2019), only revealed that group 1 (10 people) and group 2 (12 people) had a continuing treatment for a while. One study did not reveal any of this information (Khatri et al., 2001).

Table 6. Methodology of the studies by groups, measured outcomes, evaluation of outcomes, results

Study name	Groups	Measured outcomes	Evaluation of outcomes	Results
Lavretsky et al. (2011)	esCIT+ TC: (n= 36) 3 withdraw (1 after 1 week, 2 after 4 weeks);	Primary outcomes: depression remission;	24-item HDRS score of 16 or higher at baseline.	TC participants: • Baseline: 17.8 (2.0) • End of Treatment: 5.1 (3.5)
	esCIT+ HE (n= 37): 2 withdrew (1	Secondary outcomes: the severity of anxiety,	24-item HDRS: scores of 6 or	HE participants:

	after 10 weeks, 1/2 after 2 weeks: the study indicated 2)	apathy, psychomotor retardation, resilience, health-related quality of life, and cognition	less. The response was defined as HDRS scores of 10 or less. Nonresponse was defined as less than 30% improvement on HDRS scores from baseline	- Baseline: 17.0 (1.6) - End of Treatment: 6.7 (4.4)
Carneiro et al. (2015)	Combined medication and exercise: N= 9; Medication treatment: N= 10	Primary outcomes: depression Secondary outcomes: anxiety; stress; self-esteem	BDI-II (Portuguese Version). Total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms	BDI-II scores (baseline) - Exercise: 45.56 ± 9.65; - Control: 46.10 ± 11.52 BDI-II scores (after 4 months) - Exercise: 34.89 (10.56); - Control: 49.40 (16.72) Depression scores (baseline) - Exercise: 12.78 (6.82) - Control: 11.30 (5.48) Depression scores (after 4 months) - Exercise: 7.33 (6.12) - Control: 11.90 (6.52)
Legrand and Neff (2016)	AE group: n= 14; ST group: n= 11;	Primary outcome: change in the BDI-II total score from	21-item BDI-II (evaluating symptoms and attitudes related	BDI-II scores (baseline) AE group: 36.1 (5.9);

	NI group: n= 10	baseline to the end of the study period	to MDD in the past week). Total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms	- ST group: 37.8 (8.3); - NI group: 35.7 (6.7) BDI-II scores (end of treatment) - AE: 18.92 (6.11); - Stretching interventions: 28.43 (7.46) - NI group: 29.29 (12.57)
Khatri et al. (2001)	AE: n= 42; Antidepressant medication: n= 42	Primary outcomes: - Assessments of cognitive functioning; - Depression; - Physical fitness;	17-item HAM-D: participants were eligible if they met DSM-V criteria for MDD and obtained a HAM-D score of > 12; 21-item BDI	HAM-D scores (baseline): 18.04 (3.63) BDI scores (baseline): 21.55 (7.54) HAM-D scores exercise group (baseline): 17.52 (3.17); HAM-D scores exercise group (pos): 6.67 (5.12); HAM-D scores medication group (baseline): 18.55 (4.00); HAM-D scores medication group (pos): 6.55 (5.62) BDI scores exercise group (baseline): 21.14 (7.48); BDI scores exercise group (pos): 8.31 (7.31)

				BDI scores medication group (baseline): 21.95 (7.67); BDI scores medication group (pos): 6.29 (6.92)
S. Herman et al. (2002)	Medication only: N= 48; Exercise only: N= 53; Combination of antidepressant medication plus exercise: N= 55	Primary outcomes: • Depression; • Additional measures	• 17-item HRSD ranged from 13 to 29; • 21-item BDI ranged from 7 to 41	HRSD scores (baseline): 17.87 (3.58); BDI scores (baseline): 22.17 (7.21) Full-cohort success (BDI): 21.7 (7.4); Full-cohort success (HDRS): 17.1 (3.5) Success HRSD scores • Medication only: 17.1 (4.2); • Exercise only: 16.8 (2.8); • Combination of antidepressant medication plus exercise: 16.6 (3.3) Failure HDRS scores • Medication only: 19.3 (3.6); • Exercise only: 18.0 (3.41); • Combination of antidepressant medication plus exercise: 19.2 (3.6) Success BDI scores

				• Medication only: 23.3 (8.1); • Exercise only: 21.1 (8.5); • Combination of antidepressant medication plus exercise: 20.8 (5.6) Failure BDI scores • Medication only: 21.6 (7.8); • Exercise only: 21.0 (5.3); • Combination of antidepressant medication plus exercise: 25.3 (7.3)
Craft (2005)	10 women chose to participate in the CG; 11 women chose the exercise intervention group (2 women dropped out of the study, both in the exercise intervention group)	Primary outcomes: • Distraction; • Severity of depression; • Coping self-efficacy; • Rumination	21-item BDI-II ranged from 0 to 63: scores of 0–13 indicate “minimal” depression, 14–19 indicate “mild” depression, 20–28 indicate “moderate” depression, and 29–63 indicate “severe” depression; 24-item DCSSES that asks participants to assess their confidence in their ability to engage in a	BDI-II scores Study entry: • CG: 24.9 (12.6) • Ex: 21.2 (8.4) 3 weeks: • CG: 24.7 (12.0); • Ex: 9.3 (4.8) 9 weeks: • CG: 21.8 (16.4) • Ex: 6.4 (5.4) DCSES scores Study entry: • CG: 6.0 (1.2) • Ex: 6.8 (1.0) 3 weeks: • CG: 5.2 (1.3); • Ex: 7.3 (0.9) 9 weeks:

			variety of coping responses from 0 (not at all confident) to 10 (confident)	- CG: 5.3 (1.8); - Ex: 7.5 (0.9)
Vieira et al. (2009)	GE: N= 8: submitted to the hydrogymnastics program); GC: N= 8: non-PE group, only medication	Primary outcomes - Anxiety; - The mood states (tension, depression, anger, vigor, tiredness, confusion).	POMS: the subject scores from 0 (when he feels there is no manifestation) to 4 (when he believes he is extremely affected by feeling)	GE Pre-session: - Baseline: 3.87 (6.10); 6 weeks: 2.37 (4.60); 12 weeks: 2.62 (5.04) GE Pos-session: - Baseline: 1.12 (6.10); 6 weeks: 1.00 (4.60); 12 weeks: 0.75 (5.04) GC: - Baseline: 4.87 (5.14); 6 weeks: 7.12 (5.38); 12 weeks: 9.00 (8.36)
Danielsson et al. (2014)	Ex: n= 22 (16 women and 6 men); BBAT: n= 20 (16 women and 4 men); Advice: n= 20 (16 women and 4 men)	Primary outcome: evaluation of depression (MADRS) Secondary outcomes: global function, self-reported depression symptoms, using the MADRS-S, anxiety symptoms, body awareness,	MADRS (10 items reflecting key features of depression, each item scoring 0–6 points) at baseline and at 10 weeks	MADRS Baseline - Ex: 24.6 (4.1); - BBAT: 23.9 (5.0); - Advice: 23.4 (5.0) MADRS 10 weeks (ITT) - Ex: -10.37 (1.6); - BBAT: -5.8 (1.7); - Advice: -4.6 (1.7) MADRS 10 weeks (ITT) - Ex: -12.8 (1.6) - BBAT: -8.4 (1.8)

		cardiovascular fitness		Advice: -5.1 (1.8)
Hallgren, Kraepelien, Öjehagen, et al. (2015)	12-week PE intervention: n= 317; 12-week ICBT intervention: n= 317; 12-week TAU intervention: n= 312 Post-treatment assessment (3 months) 12-week PE intervention: n= 249; 12-week ICBT intervention: n= 259; 12-week TAU intervention: n= 232	Primary outcome: severity of depression Secondary outcomes: self- rated work capacity	MADRS (higher scores indicate more severe depression; each item produces a score ranged from 0 to 6). Total scores range between 0 and 60.	MADRS baseline (all participants) 12-week PE intervention: 22.2 (6.8); 12-week ICBT intervention: 21.5 (6.7); 12-week TAU intervention: 20.9 (7.5) MADRS 3 months (all participants) 12-week PE intervention: 13.8 (8.9); 12-week ICBT intervention: 11.3 (7.9); 12-week TAU intervention: 11.2 (7.3) MADRS baseline (men) 12-week PE intervention: 21.9 (6.7) 12-week ICBT intervention: 22.2 (5.4) 12-week TAU intervention: 21.5 (8.1); MADRS 3 months (men) 12-week PE intervention: 10.8 (8.2);

				• 12-week ICBT intervention: 12.7 (8.1); • 12-week TAU intervention: 16.9 (10.3) MADRS baseline (women) • 12-week PE intervention: 22.4 (6.9); • 12-week ICBT intervention: 21.3 (7.1) • 12-week TAU intervention: 20.7 (7.3) MADRS 3 months (women) • 12-week PE intervention: 11.6 (7.7); • 12-week ICBT intervention: 10.6 (6.9) • 12-week TAU intervention: 12.9 (8.2)
Doose et al. (2015)	Intervention: n= 30) Control: n=16	Primary outcome: HRSD-17 Secondary outcome: BDI-II	Primary outcome: 17-item scale is derived from the 21-item scale by leaving out the last 4 items examining (diurnal variation, derealisation, paranoia and obsessive	HRSD-17 • Intervention: - 9.48 (-11.38; - 7.58); • Control: -1.24 (- 3.85; 1.37) BDI-II • Intervention: - 8.20 (-11.39; - 5.01); • Control: -3.54 (- 7.92; - 0.85)

			compulsive symptoms)	
			Secondary outcome: BDI-II (German version)	
Toni et al. (2016)	S: n= 50 (sertraline alone) S+EX: n= 38 (NPE + PAE)	Primary outcomes: • HRV indices; • Psychiatric and medical assessments	17-item HAM-D (Remission from depression was defined as an HAM-D score of 10 or less at study end)	HAM-D total score (baseline) • S: 20.3 ±3.9 • S+EX: 20.1 ±3.1 HAM-D total score (end of study) • S: 13.8 ±5.8 • S+EX: 7.1 ±3.2
Tasci et al. (2019)	G1: n= 17 (antidepressant medication and were asked for brisk walking); G2: n= 16 (only antidepressant medication)	Primary outcomes: • Anxiety; • Depression levels	HDRS: a total score of 0-13 indicates no depression, 14-27 mild depression, 28-41 moderate depression, and 42-53 severe depression	HDRS-1 (baseline) • G1: 18.88 ± 5.036 • G2: 22.50 ± 7.554 HDRS-2 (6 weeks) • G1: 7.06 ± 7.909 • G2: 15.94 ± 9.855 HDRS-3 (12 weeks) • G1: 5.76 ± 6.61 • G2: 14.13 ± 9.57

N: number of participants; HDRS/HAM-D: Hamilton depressive rating scale; POMS: Profile of Mood States; BDI: Beck depression inventory; MADRS: Montgomery-Asberg Depression Rating Scale; DCSES: Development of the Depression Coping Self-Efficacy Scale; GE: experimental group; GC: control group; ST: stretching training; BBAT: basic body awareness therapy; G: group; S: sertraline; Ex: exercise; ICBT: internet-based cognitive-behavioural therapy; TAU: treatment as usual; N: not intervention

Table 6 shows the methodology of the studies divided by: groups, measured outcome, evaluation of outcome, and results. Lavretsky et al. (2011) used 24-item HDRS score of 16 or higher at baseline. 24-item HDRS: scores of 6 or less. The response was defined as HDRS scores of 10 or less. Nonresponse was defined as less than 30% improvement on HDRS scores from baseline. Carneiro et al. (2015) used BDI-II (Portuguese Version). Total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms.

Legrand and Neff (2016) used 21-item BDI-II and total scores ranged from 0 to 63 points, with a high score reflecting a higher level of depressive symptoms. Khatri et al. (2001) used 17-item HAM-D. S. Herman et al. (2002) used 17-item HRSD (ranging from 13 to 29) and 21-item BDI (ranging from 7 to 41). Craft (2005) used 21-item BDI-II (ranging from 0 to 63): scores of 0–13 indicate “minimal” depression, 14–19 indicate “mild” depression, 20–28 indicate “moderate” depression and 29–63 indicate “severe” depression. In addition, they used 24-item DCSES where participants were assessed on questions of confidence and ability to engage in a variety of coping responses where 0 corresponded to "not at all confident" and 10 meant "confident". Vieira et al. (2009) used POMS scale: the subject scores from 0 (when he feels there is no manifestation) to 4 (when he believes he is extremely affected by feeling). Danielsson et al. (2014) used MADRS (10 items reflecting key features of depression, each item scoring 0–6 points) at baseline and at 10 weeks. Hallgren, Kraepelien, Öjehagen, et al. (2015) used MADRS scale (higher scores indicate more severe depression; each item produces a score ranged from 0 to 6). Total scores range between 0 and 60. Doose et al. (2015) used the 17-item scale is derived from the 21-item scale by leaving out the last 4 items examined (diurnal variation, derealisation, paranoia, and obsessive-compulsive symptoms) and BDI-II scale (German version). Toni et al. (2016) used 17-item HAM-D, where the remission from depression was defined as an HAM-D score of 10 or less at study end. Tasci et al. (2019) used HDRS: a total score of 0-13: no depression; 14-27: mild depression; 28-41: moderate depression; and 42-53: severe depression.

Regarding to the risk of bias, 11 studies scored “High-risk” and 1 scored “Some concerns”. Figure 2 summarizes the classification of bias by domain.

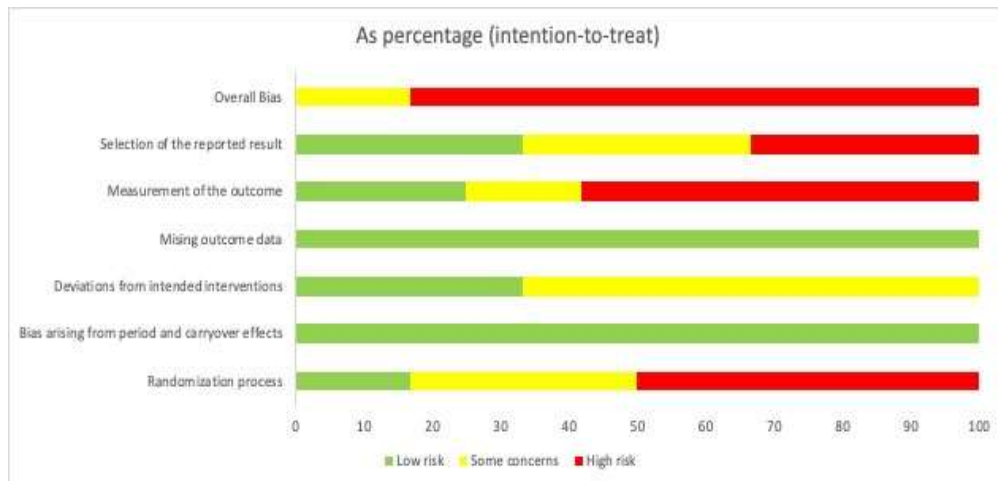


Figure 2. Risk Bias

5.2. Synthesis of the findings

A forest plot of the distribution of effects is presented in the Figure 3. For the comparison between the groups, it was possible to include 12 studies: 1 of them had two different experimental groups, so it was named as Legrand and Neff (2016) (b). Six studies showed a significant effect in favour of exercise combined with antidepressant medication, and seven studies showed no significant effects both in favour of the intervention group and the control group. Four studies were larger than zero indicating a reduction in depressive symptoms favouring the group of antidepressant medication, but that effect was not significant. The cumulative effect of the studies, suggests that there is a significant reduction in depressive symptoms in favour of the experimental group compared to the control group (SMD= -0.75 (95% CI – 1.24, -0.25); P= 0.003). However, we observed very high and significant heterogeneity ($I^2= 91\%$ (P < 0.00001)).

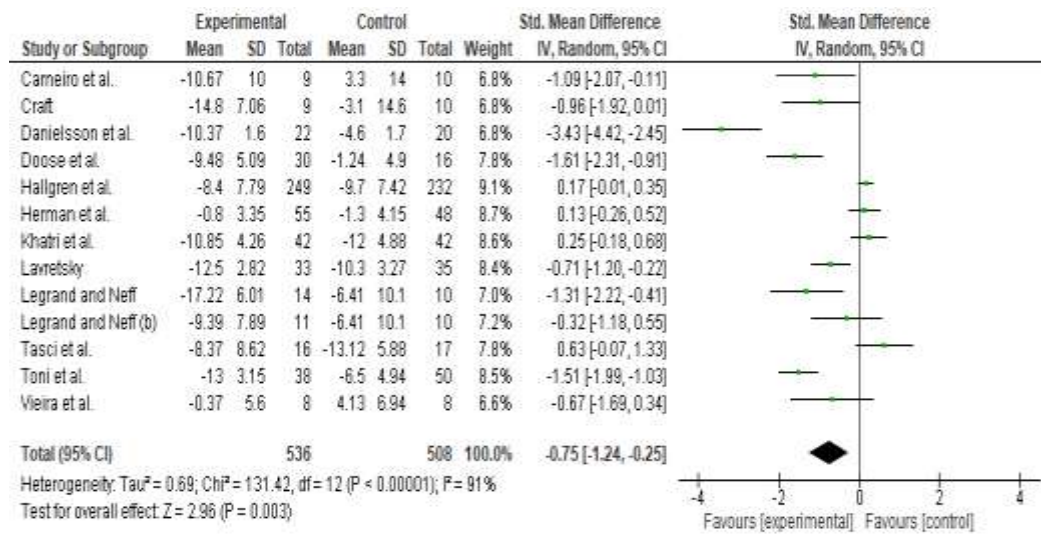


Figure 3. Forest plot of primary outcome: severity of depressive symptoms

Visual inspection of the funnel plot to access publication bias in the effects of exercise plus medication on depressive symptoms suggest no bias (Figure 4).

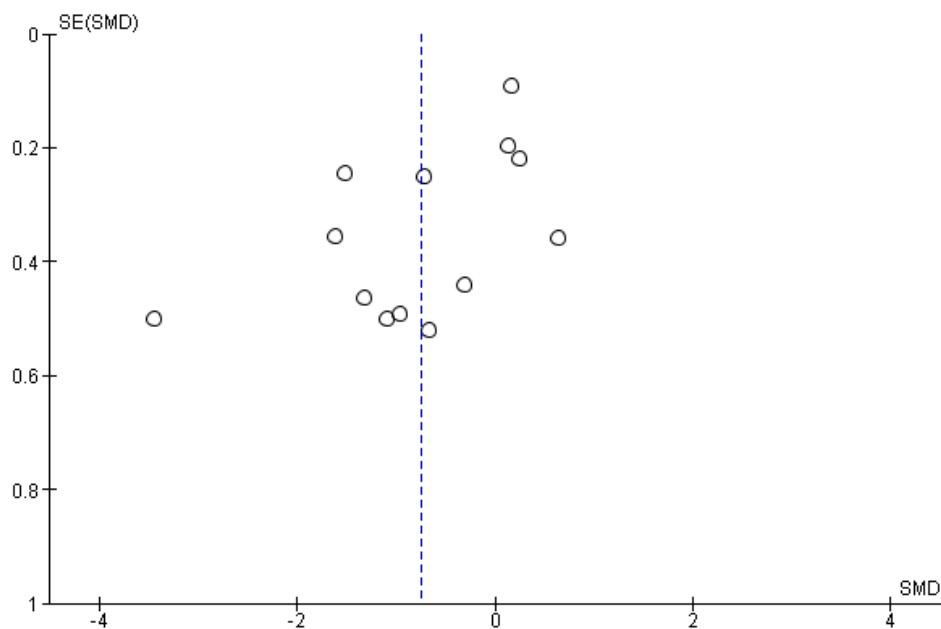


Figure 4. Funnel plot of primary outcome

Table 7 shows the sensitivity analysis using the following values: SMD, heterogeneity, and test for overall effect. When we removed a study from the sample, significant differences continued to be observed in all cases favoring the group that combined exercise and pharmacology.

Table 7. Analysis of sensitivity

Study name	SDM	Heterogeneity	Test for overall effect
Lavretsky et al. (2011)	-0.75 [-1.29, -0.22]	Tau ² = 0.76; Chi ² = 126.95, df = 11 (P < 0.00001); I ² = 91%	Z = 2.75 (P = 0.006)
Carneiro et al. (2015)	-0.72 [-1.24, -0.21]	Tau ² = 0.70; Chi ² = 128.22, df = 11 (P < 0.00001); I ² = 91%	Z = 2.75 (P = 0.006)
Legrand and Neff (2016)	-0.70 [-1.21, -0.19]	Tau ² = 0.69; Chi ² = 125.50, df = 11 (P < 0.00001); I ² = 91%	Z = 2.70 (P = 0.007)
Legrand and Neff (2016) (b)	-0.78 [-1.31, -0.26]	Tau ² = 0.72; Chi ² = 131.34, df = 11 (P < 0.00001); I ² = 92%	Z = 2.93 (P = 0.003)
Khatri et al. (2001)	-0.85 [-1.39, -0.30]	Tau ² = 0.79; Chi ² = 126.86, df = 11 (P < 0.00001); I ² = 91%	Z = 3.03 (P = 0.002)
S. Herman et al. (2002)	-0.84 [-1.39, -0.28]	Tau ² = 0.83; Chi ² = 128.28, df = 11 (P < 0.00001); I ² = 91%	Z = 2.94 (P = 0.003)
Craft (2005)	-0.73 [-1.25, -0.22]	Tau ² = 0.70; Chi ² = 128.99, df = 11 (P < 0.00001); I ² = 91%	Z = 2.78 (P = 0.005)
Vieira et al. (2009)	-0.75 [-1.27, -0.23]	Tau ² = 0.71; Chi ² = 130.56, df = 11 (P < 0.00001); I ² = 92%	Z = 2.85 (P = 0.004)
Danielsson et al. (2014)	-0.54 [-0.97, -0.10]	Tau ² = 0.46; Chi ² = 88.89, df = 11 (P < 0.00001); I ² = 88%	Z = 2.43 (P = 0.01)

Hallgren, Kraepelien, Öjehagen, et al. (2015)	-0.84 [-1.41, -0.28]	Tau ² = 0.84; Chi ² = 98.93, df = 11 (P < 0.00001); I ² = 89%	Z = 2.94 (P = 0.003)
Doose et al. (2015)	-0.67 [-1.17, -0.17]	Tau ² = 0.64; Chi ² = 115.13, df = 11 (P < 0.00001); I ² = 90%	Z = 2.63 (P = 0.008)
Toni et al. (2016)	-0.67 [-1.15, -0.18]	Tau ² = 0.59; Chi ² = 100.50, df = 11 (P < 0.00001); I ² = 89%	Z = 2.70 (P = 0.007)
Tasci et al. (2019)	-0.86 [-1.38, -0.34]	Tau ² = 0.71; Chi ² = 125.86, df = 11 (P < 0.00001); I ² = 91%	Z = 3.26 (P = 0.001)

To explore the possible sources of heterogeneity, we performed various sub analysis: medication, type of exercise, duration of intervention, gender, age, groups, intensity, and volume of training.

Regarding medication (Figure 5), we divided this sub analysis into single medication (participants took only SSRIs) versus miscellaneous medication (participants took several drugs for depression). Analysing the studies that intervened with a single antidepressant drug (seven studies), two of them showed a significant effect. The other two studies were in favour of the control group without significance. In the analysis of miscellaneous medication (nine studies), four studies favoured the experimental group with significant evidence and the rest did not favour neither medication treatment nor combined treatment with significance. Although the sub analysis of the diverse medication is the only one with significant statistics in favour of the experimental group, there was a very high and significant heterogeneity of I²= 91% (P < 0.00001).

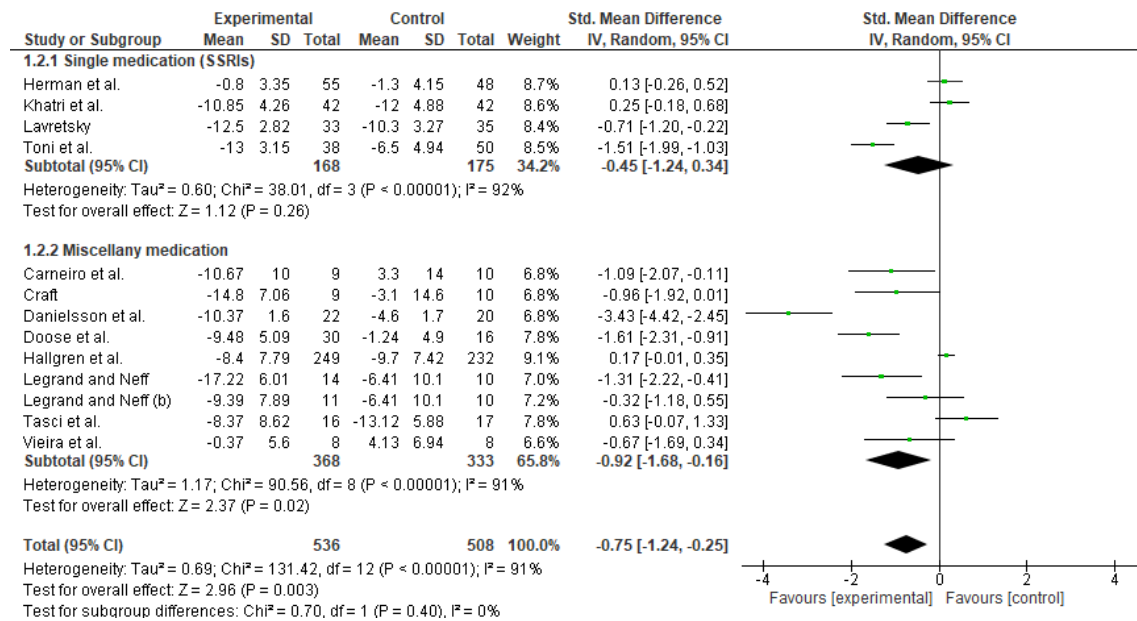


Figure 5. Forest plot of the comparison for the outcome medication in experimental and control group

Next, we compared the studies in which participants used antidepressants before the intervention and studies in which participants took tablets during the interventions (Figure 6). When participants were already involved in taking antidepressants before the intervention began, the results were significant (-1.43 (95% CI -2.17, -0.69; $p = 0.0002$), in favour of the experimental group, but heterogeneity remained high and significant ($I^2 = 79\%$; $P = 0.0002$).

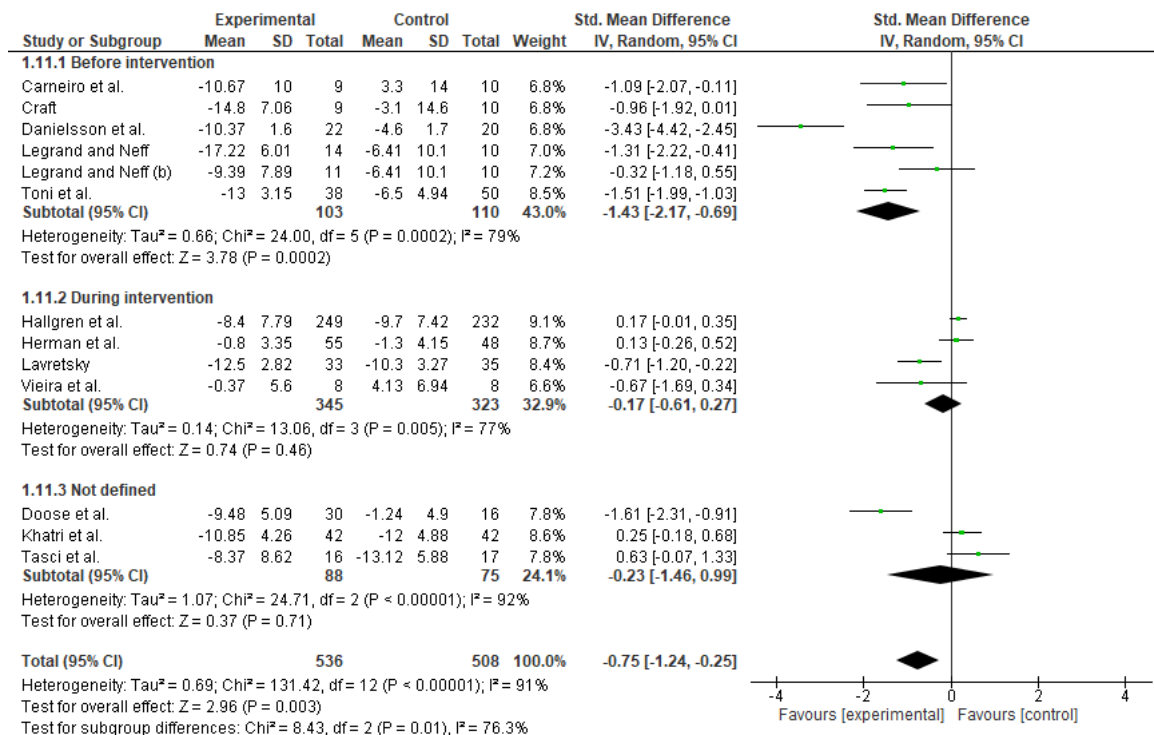


Figure 6. Forest plot of the comparison for the outcome antidepressant intake (before, during the intervention or defined) in experimental and control group

In adherence to the protocol, we divided the studies as follows: good adherence (seven studies), poor adherence (two studies) and unreported adherence (three studies) (Figure 7). Five of the studies in which participants' adherence was good presented significant statistics in favour of the exercise group. The other two studies, one of them favoured the experimental group and the other the control group, but both without significant results. In total, this sub analysis presented with significance ($SMD = -4.80$ (95% CI -7.98, -1.63)) in the decrease of depressive symptoms in favour of the experimental group, despite the high heterogeneity $I^2 = 90\%$ ($P < 0.00001$).

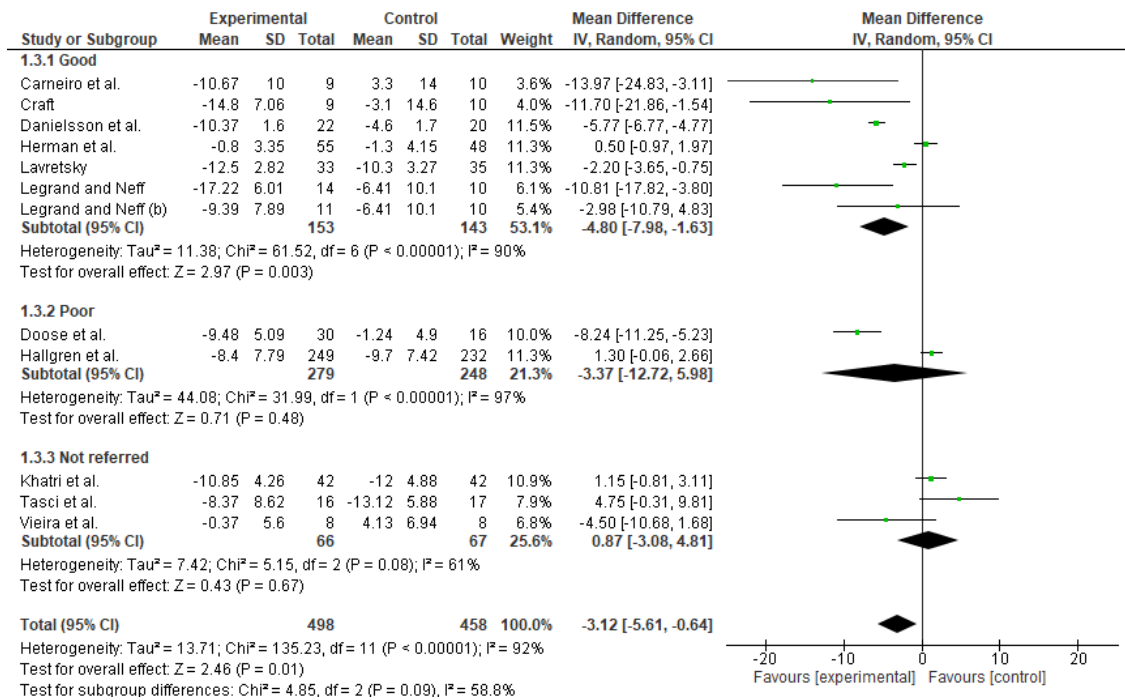


Figure 7. Forest plot of the comparison for the outcome adherence in experimental and control group

The combined exercise is the only one that does not present significant statistics in favour of the experimental group (Figure 8). According to our sub analysis, AE and other types of exercise (stretching and Tai Chi Chih) favour the reduction of depressive symptoms when combined with antidepressant pharmacology, showing significant differences. In AE (9 studies), 4 of them presented significant results in favour of exercise and the remaining two were not significant. The three studies that fell to the treatment side only with medication showed no significant results. The cumulative effect favoured the intervention with AE (SMD -85 (95% CI -1.58, -0.12); $p = 0.02$) but the heterogeneity in this sub analysis was very high ($I^2 = 90\%$; $P < 0.00001$). The two studies referring to stretching and Tai Chi Chih demonstrated effectiveness in reducing depressive symptoms in favour of combined intervention (SMD = -0.61 (95% CI -1.04, -0.19); $p = 0.005$), with no heterogeneity ($I^2 = 0\%$; $P = 0.44$).

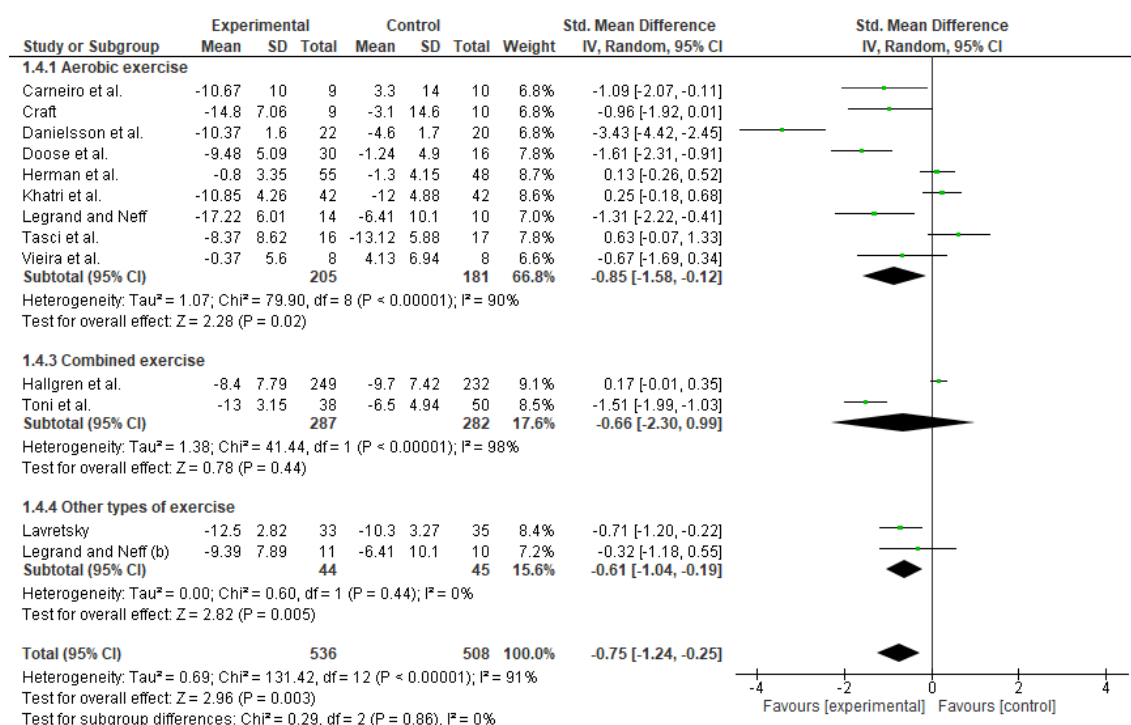


Figure 8. Forest plot of the comparison for the outcome type of exercise in experimental and control group

Regarding the duration of the intervention, we divided the studies into short interventions (10 days to 12 weeks) and long interventions (13 weeks or more) (Figure 9). Regarding short interventions (nine studies), four of them showed significant evidence in favour of exercise. Three of them also favoured the experimental group and only two the control group, but both without significant effect. In long interventions (four studies), two of them showed significant evidence in favour of exercise. The other two fell to the side of the drug therapy group, but without significance. In total, this sub analysis allowed us to verify that shorter exercise interventions showed significant improvements in depressive symptoms, -0.87 (-1.56 , -0.18), unlike longer interventions. However, heterogeneity was high $I^2 = 91\%$ ($P < 0.00001$).

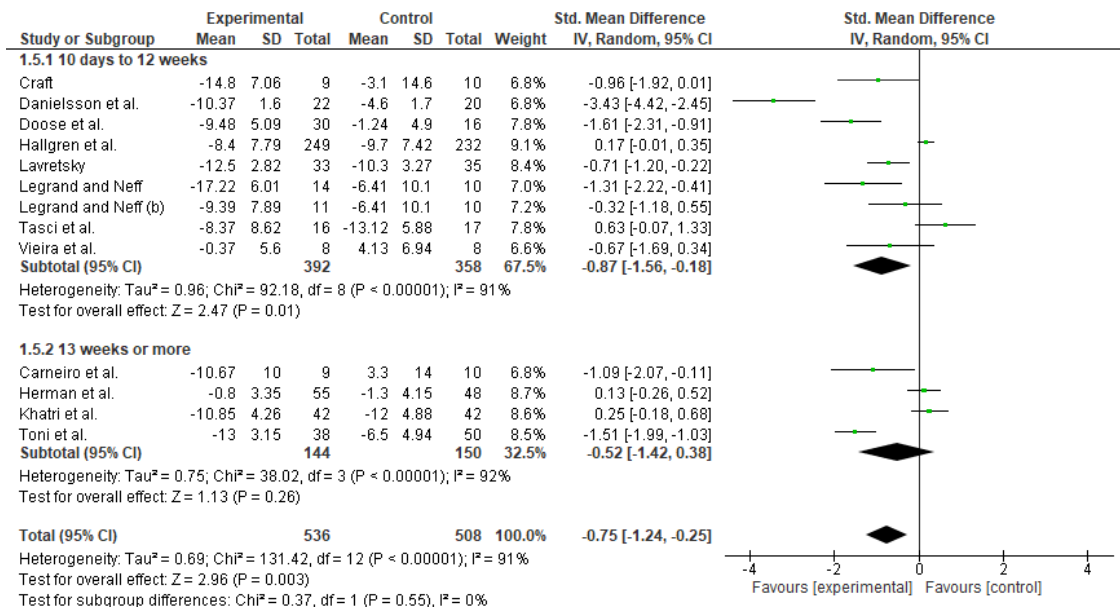


Figure 9. Forest plot of the comparison for the outcome duration of intervention in experimental and control group

On gender issues, we divided the interventions as follows: one of them included only females and the other included both sexes (Figure 10). Regarding the studies that included only females, three studies favoured the experimental group, but only one of them with significant statistics. Cumulative data favours the experimental group (SMD = -0.91 (95% CI -1.48; -0.34); $p = 0.002$) with no evidence of heterogeneity $I^2 = 0\%$ ($P = 0.84$). As for the sub analysis for both sexes, six studies favoured the exercise group, where five of them showed significant evidence. The remaining four studies favoured antidepressant medication, but without significant evidence. For both sexes, the cumulative analysis favoured the experimental group (SMD = -0.71 (95% CI -1.28 -0.14; $p = 0.01$), but with very high and significant heterogeneity ($I^2 = 93\%$; $P < 0.00001$).

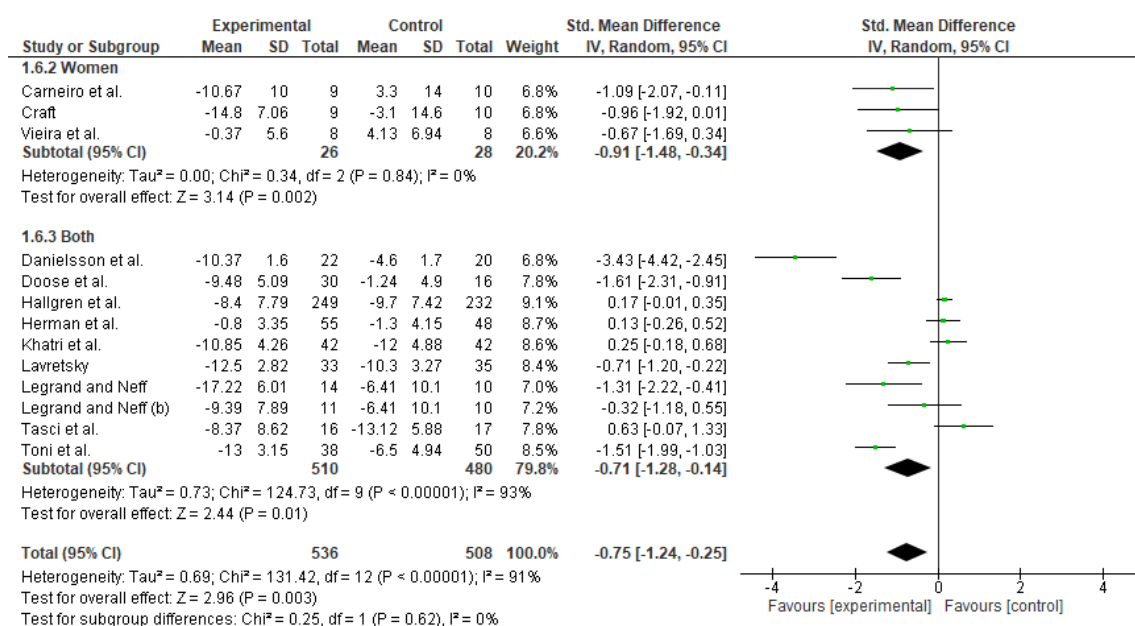


Figure 10. Forest plot of the comparison for the outcome gender in experimental and control group

For age groups, we performed a sub analysis by young/adult/old (18-71 years), adult/old (50 years or older), and age not defined (Figure 11). In the young age group to the elderly, four studies were in favoured of the experimental group (significant results), and two studies favoured pharmacological therapy (no significant results). The cumulative data supports the experimental group (SMD = -1.10 (95% CI -2.14, -0.06); $p = 0.004$), but high heterogeneity was observed ($I^2 = 96\%$; $P < 0.00001$). From the age of 50, the cumulative results of the three studies (two of them in favour of the control group and one in favour of the experimental group) did not show statistical differences between experimental and control group (SMD = -0.09 (95% CI -0.65, 0.46); $p = 0.74$; $I^2 = 79\%$; $P = 0.008$).

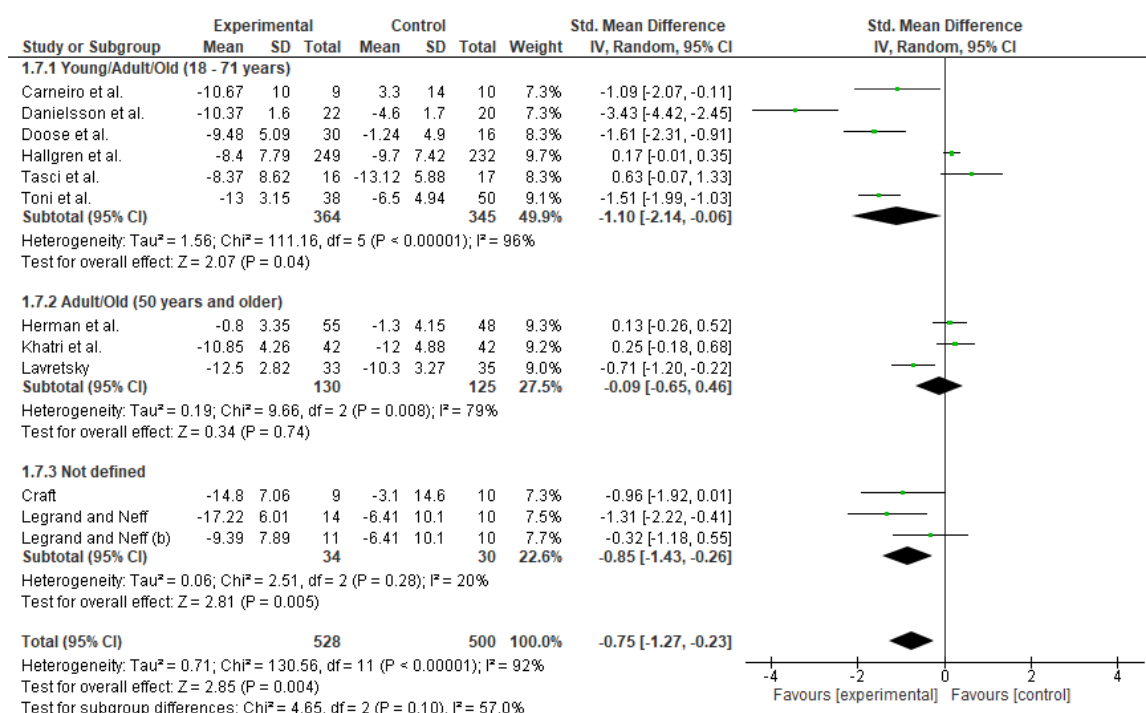


Figure 11. Forest plot of the comparison for the outcome age groups in experimental and control group

In intensity of training, we differentiated sub analysis into moderate intensity (two studies), moderate to vigorous intensity (two studies), vigorous intensity (two studies), and no intensity defined (seven studies) (Figure 12). Moderate intensity is the only one in which the results favoured the combined treatment group (experimental) (SMD = -1.21 (95% CI -1.88, -0.54; $p = 0.0004$), with no evidence of heterogeneity ($I^2 = 0\%$; $P = 0.0004$). For moderate to vigorous intensities studies tend to favour combined therapy, for vigorous intensities, studies go back to favour of pharmacological therapy, both interventions without significance in the results. When training intensity is not defined studies are divided: three of them demonstrate efficacy of combined therapy with significant evidence and two of them without significance; the other two tend to drug therapy, but without statistically significant results.

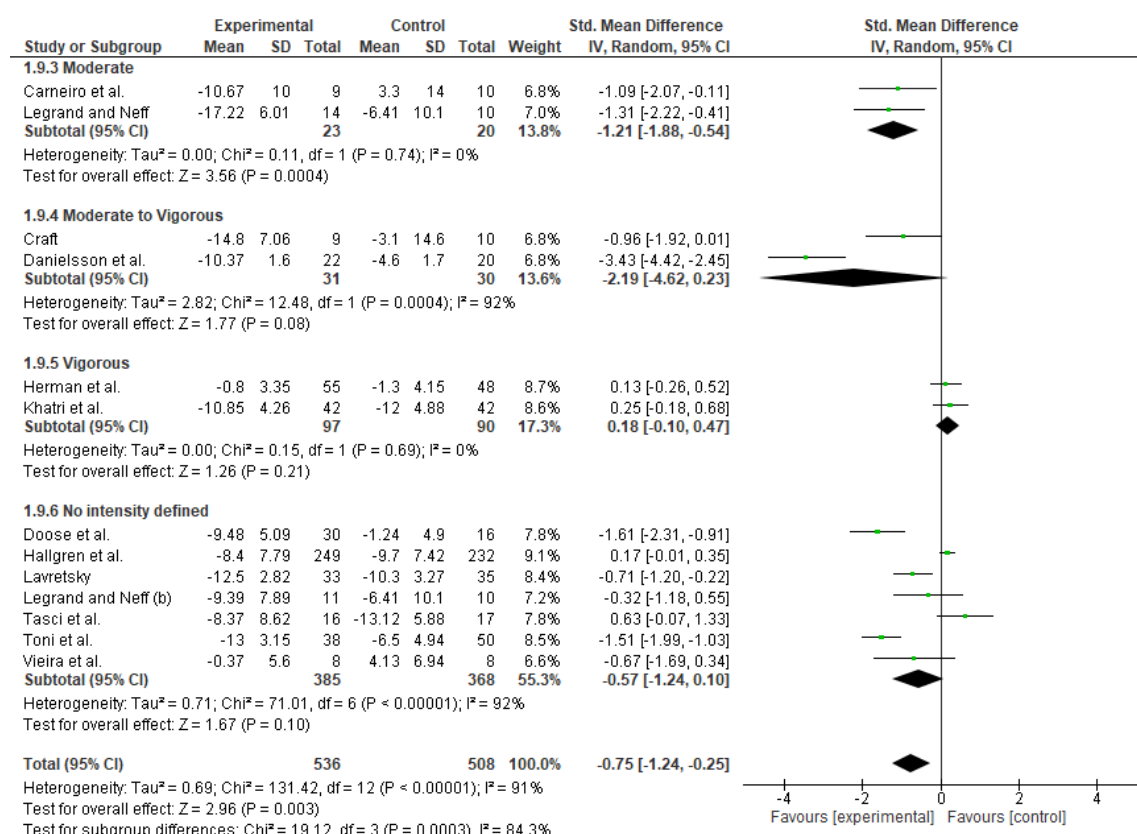


Figure 12. Forest plot of the comparison for the outcome exercise intensity in experimental and control group

Regarding the training volume, our analysis was divided into shorter sessions (up to 50 minutes per session) and longer sessions (between 60 and 120 minutes per session) (Figure 13). In the shorter interventions, two studies showed significance and other three did not favour exercise significantly. The cumulative analysis did favoured the exercise intervention group but significance was detected. Regarding to studies using longer training sessions, four studies were in favour of the experimental group and one study in favour of pharmacological therapy, but none was significant. Our cumulative data show a significant effect in favour of the experimental group for longer exercise interventions (SMD = -1.36 (95% CI -2.43, -0.29; $p = 0.01$), although heterogeneity was high ($I^2 = 96\%$; $P < 0.00001$).

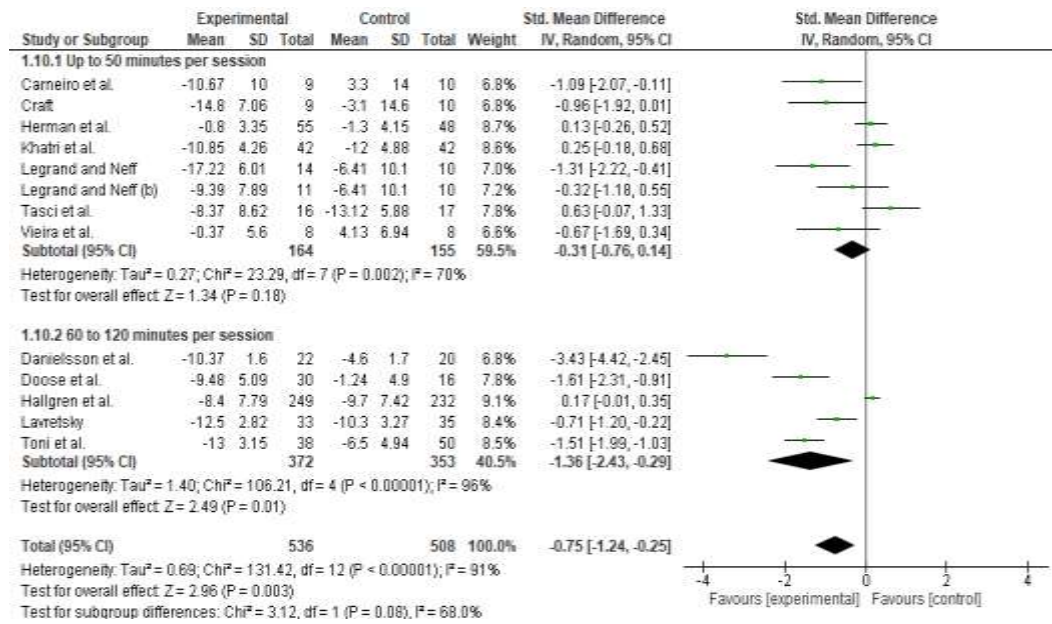


Figure 13. Forest plot of the comparison for the outcome volume training in experimental and control group

6. Discussion

More exercise than pharmacological therapy, a weapon against depression?

The main objective of our review is to clarify whether physical exercise, when combined with antidepressant pharmacology, leads to the decrease of depressive symptoms. Our data suggest that there is evidence in favour of exercise for the decrease of depressive symptoms and that it should be used as in combination to pharmacological treatment for better outcomes. This result is in line with other reviews that concluded that exercise is an effective intervention for depression and may be a viable adjuvant treatment in combination with antidepressants (Kvam et al., 2016; Mura, Moro, Patten, & Carta, 2014; Netz, 2017; Schuch, Vancampfort, et al., 2016).

Although it was already demonstrated in the literature that exercise is capable of favouring clinical depression, our meta-analysis is an update on what has already been studied, especially by the various sub analysis that we performed on different outcomes. 75% of the analysed sample set studies applied AE in combination with antidepressants and the results showed that this may be an interesting treatment for depression. Regarding intensity, our study showed that moderate exercise seems to be the most effective dose for the treatment of the disease. A range of 65-75% HR.max seems to be a good training proposal for individuals undergoing treatment (Carneiro et al., 2015; Legrand & Neff, 2016). This pattern corresponds to other results that the literature has been supporting over the years: to Craft (2005), a moderate PE program was associated with a reduction in depression among chronically depressed women taking antidepressant drugs; Mota-Pereira et al. (2011) suggested that moderate intensity AE can be used as an effective therapy adjuvant to pharmacological therapy, in resistance to MDD; Meyer et al. (2022) concluded that performing short bouts of moderate intensity exercise appears to be effective for the management of key symptoms (anhedonia, depressed mood state) in adults with

MDD; a recent review concluded that AE of moderate intensity is the better choice for adolescents with depression and depressive symptoms (Wang et al., 2022). This consistency of results emphasizes the importance of a moderate exercise dosage to increase therapeutic efficacy. Legrand and Neff (2016) compared AE and stretching exercise and, although the results of combined therapy were more motivating in the group that practiced AE, participants who underwent stretching also reduced depressive symptomatology but not significantly. Stretching exercise and TCC also demonstrated efficacy in drug combination therapy, according to our results. Lavretsky et al. (2011) performed the first RCT to test the efficacy of TCC as an adjuvant to standard antidepressant drug treatment of geriatric depression and found significant differences in the change in C-reactive protein (CRP) levels over time. According to the same source, there are effects on relaxation training described in the literature that led to a reduction of clinical somatic symptoms, with additional effects on symptoms of anxiety and depression, blood pressure, and recovery from immunomediated diseases. In addition, TCC administration decreases sympathetic production, improves specific viral immunity and vaccine response, has effects on sleep quality, and increases overall health functioning in healthy older people. Among our sample, the RTC that applied TCC was the one in which the training sessions were longer (120min). This data goes against a recent meta-analysis that argued that only a high amount of TCC can reduce IL-6 and CRP (Shu, Feng, Cui, Cheng, & Wang, 2021). Mental exercise can also help to reduce negative emotions, relieve fatigue, and prevent cardio and cerebrovascular diseases (J. L. Zhao et al., 2020). The evidence highlights the importance of exercise for both the body and mind, and as a possible option for depressive treatment. Regarding volume of training, the results showed statistically significant evidence in sessions ranging from 60min to 120min for all types of exercise. Concerning the frequency of training, 3 times a week corresponded to 66.6% of the interventions, which led us not to do any sub analysis on this outcome.

For the result of the combined treatment to be positive it is necessary to have a good adherence to the program. In this sense, our results showed significant improvements when participants had good adherence to PE. In turn,

when participants' adherence was weak or undisclosed, therapeutic efficacy was not significant. Regarding the duration of the intervention, our results were significant when the intervention periods were shorter (from 10 days to 12 weeks). Thus, we believe that the interpretation of the adherence to the intervention program has a strong dependence its duration. Sirey et al. (2017), considered the Participation in Treatment Program as effective to improve early adherence to pharmacotherapy and promote improvements in the disease. The monoamine depression hypothesis was articulated 50 years ago and only then was the first pharmacological treatment for MDD discovered (Hillhouse & Porter, 2015). The authors made it clear that SSRIs are the first stage of treatment, due to their safety, effectiveness, and tolerability (Chu & Wadhwa, 2022). Our results showed no significant evidence for improving depressive symptoms in participants who were taking SSRIs only. According to our analysis, making miscellaneous medication combined with exercise seems to significantly improve the state of individuals with depression. This pattern is supported in the literature because as patients progress in the stages of treatment, new antidepressant drugs with different mechanisms of action are needed (Hillhouse & Porter, 2015).

As the literature has pointed out, there is a higher prevalence of disease in women than in men. This may be due to numerous reasons, but it should be noted that at early ages (11-14 years), girls report significantly higher prevalence (Juul, Hjemdal, & Aune, 2021). Our sample comprised a smaller number of interventions performed only in women (25%) than those performed in both sexes (75%), but in both results were statistically significant in therapeutic efficacy. MDD results from a complex interaction of vulnerability genes and environmental factors that act cumulatively throughout the life of the individual (Lopizzo et al., 2015). Stressful life experiences, especially when they occur early in life, have been suggested as having a common crucial impact on brain development, leading to permanent functional changes that can contribute to mental health risks. For Albert (2015), women had greater sensitivity to interpersonal relationships, while men had greater sensitivity to external career and objectively oriented factors. The authors concluded that what could contribute to a higher female prevalence are the diseases related to depression: premenstrual

dysphoric disorder, postpartum depression, and postpartum anxiety menopause, which are associated with changes in ovarian hormones (female hormonal fluctuations may be a trigger during puberty, before menstruation, or after pregnancy, or in perimenopause). Considering gender differences in relation to the disease, according to L. Zhao et al. (2020) the evidence of genetic heterogeneity in men and women with major depression is insufficient. In addition to these issues, we consider important to reflect on age groups that may be sensitive to the disease, but first we would like to make it clear that this pathology has no contraindication related to physical exercise. Our review analyzes PE interventions performed in people aged 18 years old or more. Most of the studies intervened in the ages of 18 to 65 years, presenting significant results in favor of the group that combined exercise and medication as treatment. Through this meta-analysis, we could not observe significant effects, from the ages above 50 years. This data makes us alert about how the RCT was developed, since this interval begins to coincide with the predominant age of depression in both sexes (over 55 years). When the age of the participants was not defined, the results were significant in favor of exercise therapy and medication, which allowed us to focus on this pathology in other age groups. Recently, an investigation found that recent rates of severe psychological distress (suicidal ideation, plans, attempts, and deaths by suicide) increased in adolescents aged 12 to 17 years and in young adults aged 18 to 25 years between 2000 and 2017, with smaller and less consistent increases among adults aged 26 years or older, identifying the use of technology and sleep disorders as the main causes of mood disorders and relation to suicide (Twenge, Cooper, Joiner, Duffy, & Binau, 2019). In this perspective, Wang et al. (2022), recommended secondary schools to activate disease screenings with health tests for students and effective implementation of strategies to reduce depressive symptoms in adolescents. Another possible strategy could involve the application of a program focused on associating movement with pleasure, encouraging positive and non-competitive interactions between participants, with low-to-moderate intensity (Philippot et al., 2019).

7. Recommendations

It would be interesting if the next studies focuses on adolescents and young people, given that, according to the World Health Organization (2021), annually, more than 700 thousand people die by suicide, becoming the fourth leading cause of death among young people from 15 to 29 years. Although the depression is especially prevalent on females, they have a longer life span and the highest rates of suicide/addictive behaviours concern men (Shi et al., 2021). For the authors, women are more likely to report mild to moderate depressive symptoms and more severe/suicide reports are more evident in men. Thus, it would be interesting if there were more research particularizing males because it is also in this population that depression is often not recognized or treated (Roche et al., 2016). In addition, as during adolescence, the number of depressive symptoms has increased (Bertha & Balazs, 2013), it would be important for new studies to address this age group in a detailed and extensive way. We also consider that it would be a good step in research, to consider exercise interventions for people over 50 years old since they are entering the most prevalent phase of the disease. For the various populations, we highlight the importance of applying a greater aerobic component and other types of exercise (such as TCC and stretching), not necessarily having to separate them since combined training seems to be a good option. We also consider it important that new articles intervene with strength training programs and exercise at vigorous intensities, since there is evidence suggesting blood lactate as a biomarker to correlate with depressive symptoms (Pereira, Picoli, Valenti, & Shiguemoto, 2022). When produced during exercise, lactate regulates brain function and induces an antidepressant effect (Chen et al., 2022). Pedersen and Saltin (2015), concluded that resistance and mixed training may be more effective than AE. It would be important to define, legally, health rules so that this special population is trained by a professional specialized in exercise and health/physiologist of clinical exercise, to combat the strategy of combating the lack of adherence to exercise. We suggest that, preferably, professionals streamline small work groups, as a way to improve social aspects related to illness and to particularize

the most correct dose of exercise for each person. We recommend that investigations focus on the dose of medication, as a constant update of the dose/type of drug is critical for effectiveness of treatment. Finally, future research should be perfectionist and take into account the preferences of participants, according to gender (Busch et al., 2016) and/or body composition (Reading & LaRose, 2022), regarding the type and intensity zone of the training, in order to counter low adherence to such programmes. For treatment to be pointed in a more correct direction, there is still a scientific need to clarify the pathophysiological mechanism of depression, given the heterogeneity of existing hypotheses.

8. Conclusion

In conclusion, data from this meta-analysis suggest that PE is an option that should be seen as an adjunct to depression medication, since many people are resistant to treatments. Thus, we suggest that the dose and/ or the type of exercise and medication should be always well adjusted, by qualified professionals in their respective areas, according to the particularities of each person. We consider the where and with whom the exercise is performed, preponderant and differential factors when it comes to intervening with this population that often shows resistance when adhering to exercise and medication intervention programs. The practice of PA has been pointed out as a weapon to prevent depression, so it is important that the dualism between PE and PA is well differentiated. Finally, it was concluded that it is increasingly important to implement strategies to encourage the practice of PA from earlier ages (for example through schools), in order to reduce the prevalence of the disease at these ages and especially the risk of developing it at an advanced age.

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