

Aerobic Exercise Supplementation on Medication Improves Depression Scores: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background

Neuroendocrine disruption is an important mechanism in the development of depression and the modulation of neuroendocrine disruption by aerobic exercise suggests a potential antidepressant effect. Therefore, the aim of this study was to quantitatively assess the effect of aerobic exercise on depression on the basis of pharmacological treatment alone.

Methods

We conducted a randomized trial with a meta-analysis of 8 RCT studies to assess the effect of aerobic exercise on depression based on pharmacotherapy.

Results

On the basis of medication, we found a positive overall effect of aerobic exercise supplementation. This effect was seen in both moderate depression (-1.13 [$-1.56, -0.71$], $I^2 = 0\%$, $P = 0.803$) and major depression (-0.72 [$-0.89, -0.55$], $I^2 = 33\%$, $P = 0.144$), with a relatively better effect for moderate depression. In addition, a 12-week course of adjunctive aerobic exercise was the most effective in improving depression in the included clinical studies by cumulative meta-analysis.

Conclusion

The meta-analysis provides recommendations for adjunctive aerobic exercise treatment on top of medication alone. The outcome data demonstrate the better efficacy of aerobic exercise as an adjunct to antidepressants versus medication alone. Additional clinical trials are necessary in the future to develop optimal exercise parameters for different populations.

1. Introduction

Depression is one of the common psychiatric disorders with an unknown etiology and is associated with complex symptoms such as persistent low mood, loss of interest and a high rate of suicide. It is also associated with anxiety [1], cardiovascular disease [2] and pain [3]. Co-morbidities exist that severely affect patients' life quality and are a growing public health problem. COVID-19 has triggered widespread anxiety and depression across the world and global mental health resources were scarce during the epidemic. The 2022 WHO World Mental Health Report showed that 280 million people suffered from depression (including major depressive disorder and dysthymia) in 2019, with 5.8% of those aged 50–69

and a higher proportion of women overall [4]. Depression not only affects life quality and social activities but also has serious social and economic consequences.

Drug treatments such as ketamine [5] and psychological interventions [6] have some efficacy, but one third of depressed patients remain unresponsive to treatment [7]. Some patients with major depression do not remit after two or more treatments with first-line antidepressants [8], while conventional medication has toxic side effects [9]. The side effects and high cost of chemically synthesized drugs are not suitable for long-term treatment [10]. Psychological therapies have long cycles and a financial burden and poor adherence. Some people with depression do not even seek treatment [11]. Psychotherapy also fails to address the physical co-morbidities associated with depression. The effectiveness of medication and psychotherapy in curing depression is still lacking, therefore, finding a therapy to improve depression is a priority.

In recent years, it has been shown that disorders of the hypothalamic-pituitary-adrenocortical axis (HPA axis) play a key role in the pathogenesis of depression [12], including life quality and suicidal behaviour, etc. HPA dysregulation may cause various physiological responses in the sympathetic nervous system through activation and cascade effects. Excessive levels of cortisol can reduce hippocampal 5-hydroxytryptamine system function, decrease the expression of various neurotrophic factors, which in turn can lead to hippocampal neuronal degeneration and ultimately depression [13]. In addition, HPA dysregulation can also contribute to depression through glucocorticoid resistance [14] and increased circulating inflammatory cytokines [15]. Animal models of HPA dysfunction suggest that sustained increases in glucocorticoid cycling (human cortisol) produce a range of neurotoxic effects in prefrontal and hippocampal regions, including desensitisation of relevant cell receptors, microglia activation, cell death and a reduction in neurogenesis and BDNF cycling [16]. Exercise has significant effects on the neuroendocrine system and HPA activity. Prolonged elevations in HPA hyperactivity and cortisol levels likely contributing to the pathophysiology of depression, which can be partially counteracted by exercise. Exercise could reduce neuroendocrine stress hormones (adrenal and cortisol), modulating dopamine, serotonin levels [17] and regulating HPA axis activity. Meanwhile, it also reduce systemic circulating inflammatory cytokines [18]. These processes affect the development of new neurons and increase synaptic connections between neurons. Considering that exercise and antidepressants may affect depression through overlapping molecular pathways, they may also affect overlapping neural systems. Therefore, we hypothesize that adjunctive aerobic exercise may be an effective therapy to improve depression by modulating neuroendocrine disruption.

Exercise therapy has been on the rise in recent years and the ACSM Guidelines for Exercise Testing and Exercise Prescription (10th edition) [19] developed by the American College of Sports Medicine provides clearer guidance on exercise prescription in terms of exercise testing and recommendations. There are clinical studies suggesting that aerobic exercise or stretching as a supplement to inpatient treatment for depression has similar antidepressant effects on depressive symptoms, while aerobic exercise alone has been shown to have a greater effect on working memory [20]. However, it has also been shown that aerobic exercise appears to have a less pronounced effect as an adjunct to pharmacotherapy for

depression [21]. Although most studies currently suggest a positive effect of adjunctive aerobic exercise, relevant data remain scarce and data sources are variable. To date, no relevant meta-analyses have yielded positive and consistent conclusions. Therefore, we use meta-analysis to provide quantitative results on the effect of aerobic exercise assisted medication on depression scores in subjects.

2. Methods

We have prospectively registered this topic in the INPLASY database (registration number: INPLASY202270115, doi: 10.37766/inplasy2022.7.0115). In this article, we present the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 27-item checklist, an expanded checklist that details reporting recommendations for each item, the PRISMA 2020 abstract checklist, and the revised flow diagrams for original and updated reviews. [22]

2.1 Eligibility Criteria

All of the studies included from the initial search strictly met the criteria of the Population, Intervention, Comparison, Outcome and Study design (PICOS) framework. Inclusion criteria: (1) Population: All adults aged over 18 years with a diagnosis of depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV) and International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria or patients with above-threshold depressive symptoms determined by validated screening measures (such as Hamilton Depression Inventory (HAM-D), Beck Depression Inventory (BDI or BDI-II)), or by a medical professional who has revised the scale to confirm depression. Patients with depressive disorders other than MDD, such as dysphoria, were included. (2) Intervention: Aerobic exercise of any duration, including walking, running or similar continuous activities. (3) Comparison: Absolute pharmaco-therapy rather than usual-care, wait-list control conditions or other social activities. (4) Outcome: Validated depression rating scales (HAM-D, BDI, etc.), measuring depression scores before and after intervention or reporting mean change and standard deviation (SD) using validated measures. (5) Study: RCTs. Excluded criteria: (1) Trials that included other exercise intervention (such as stretching, low-dose exercise, free weight training, machine resistance exercise, body weight or similar forms of exercise or combined interventions where both aerobic and non-aerobic exercise were performed) for comparison as well as other structured active treatment comparisons (such as electroconvulsive therapy (ECT) or psychotherapy) were excluded. Studies using yoga, tai chi or qigong were excluded as these activities also included a core set of behavioural techniques. (2) Non-RCTs such as quasi-experiment, reviews, qualitative researches and so on. (3) Animal experiments. (4) Literature in language types other than English. (5) Literature with incomplete data or full text loss. (6) Clinical trial design.

2.2 Literature Search Strategy

A systematic literature search was conducted to identify studies of the effects of aerobic exercise assisted medication on depression scores. Four databases (Cochrane Library, PubMed, Embase and Web of Science) were searched, using medical subject headings (MeSH) and the free terms “aerobic exercise”,

“Depression”, “Depressive Symptoms” or “Emotional Depression”. The full search strategy is given in Supporting Information 1.

2.3 Literature Screening

We first excluded duplicates and secondary studies, then two independent reviewers (XH, HC) read the titles and abstracts for screening and initially identified articles that met the inclusion criteria. Once the full text was available, the independent reviewers applied the eligibility criteria and referred divergent articles to a third independent reviewer (YH) for discussion and reached a consensus to generate a final list of included articles.

2.4 Risk-of-Bias and Quality Assessment

We assessed studies at high, low or unclear risk of bias using the Cochrane Collaboration's Risk of Bias Assessment Tool [23], assessing risk of bias by the following factors: random allocation, allocation concealment, blinding of subjects, investigators and assessors, integrity of outcome data, selective reporting or other. For each indicator, we use “low risk of bias”, “uncertain risk of bias” or “high risk of bias”. Assessments were conducted by two investigators (XH, BY), with a third investigator (HC) intervening when disagreements arose, leading to consensus.

2.5 Summary of Outcome

The outcome indicator we chose was the post-experimental depression score, and if studies reported changes in depression scores before and after the intervention at the same time, the post-intervention depression score was preferred to ensure consistency of outcome data. If a study reported more than one post-treatment depression score (e.g. measures from different periods of the total course of treatment), data from each period were included separately. If a study reported depression scores for multiple outcome indicators, only the most clinically relevant depression indicator was used.

2.6 Data Extraction

Study characteristics and outcome statistics were extracted and checked for accuracy by two researchers (XH, JH) using a data extraction form and discrepancies were resolved by consensus with a third researcher (HC). For studies without direct data, we asked authors to provide unpublished data when specific data were not available or only graphs were available. If we were unable to obtain these data, we used software to extract data (GetData Graph Digitizer). An image of the graph was taken and the data points on the graph were then digitized using the axes and proportions set by the data extractor. For data that could not be used directly, we applied statistical methods to synthesize the available data to produce the final post-intervention data.

2.7 Statistical Analysis

Statistics included mean (M), standard deviation (SD) and sample size (n) cause the scale scores were continuous type data, with SMD selected. As for predictable sources of heterogeneity the study had, by convention, SMD was assessed using Hedges' g as a measure of effect size, 0.2–0.5 was interpreted as

small, 0.5–0.8 as medium and above 0.8 as large. We used Stata software version 17.0 for statistical analysis (see Supporting material 2 for the specific program code). 95% confidence intervals (CIs), which are equivalent to the hypothesis of using 0.05 as the test level are recorded, with *P* values < 0.05 being considered statistically significant. In addition, *P* values in the graphs and tables are heterogeneous *P* values. Publication bias was assessed using funnel plots with Egger and Begg tests.

Meta-analysis results were analyzed using Cochrane's Q test and the I^2 statistic. I^2 values of 25%- 50%, 50%-75% and $\geq 75\%$ indicated low, moderate and high heterogeneity, respectively [24]. Heterogeneity was considered when the *P* value for heterogeneity was less than 0.1. To find possible sources of heterogeneity, sensitivity analyses were performed. In addition, six subgroup analyses were performed based on the PICOS criteria to explore potential sources of heterogeneity.

3. Results

3.1 Search Result

A total of 2446 records were retrieved: 238 from PubMed, 1404 from Cochrane Library, 346 from Embase, 452 from Web of Science and 6 from other sources. After removing duplicate records (*n* = 778) and excluding secondary and animal studies using keywords (review, meta-analysis, case study, etc.), the remaining 1602 documents were screened by two independent researchers (XH, HC) through reading the titles and abstracts with 89% consistency. The 183 resulting documents were further screened by reading the full text. Ultimately, 9 studies were included. Reasons for exclusion are as follows: implausible study design (aerobic exercise was not used as an adjunct or the control group was not treated with medication alone but in combination with other physiotherapy, etc.), conference papers, non-English literature, missing data, not strictly RCTs and contradictory points before and after study. Disagreements arising from the screening process were negotiated by a third investigator (YH) who intervened and eventually reached an agreement. The PRISMA flow chart for the study selection is shown in Fig. 1. 9 trials involved a total of 624 subjects, with 322 and 302 in the aerobic exercise assisted treatment and control groups respectively.

3.2 Risk of Bias and Quality Assessment

The overall quality of the literature was fair, all 9 papers used random allocation, but nearly half of the literature did not describe specific methods [25–29]. When evaluating allocation concealment, for studies without direct mention, we inferred allocation concealment from analyses of subject-blinded studies in the literature and from subjects' propensity to choose during the experiment ([21, 30]). As for blind method, half of the studies could only achieve single blindness of the evaluator, unable to achieve the double blindness of the subjects and researchers. A study didn't mention the blind method [31]. This may be related to the topic of our study, as it is difficult to be blinded when regarding aerobic exercise as a supplementary intervention. In terms of data integrity, more than half of the studies specifically indicated number and reasons for withdrawal, only a small part did not specify. All literature performed well in

selective study reporting and was assessed as low risk, a few literature had a small sample size bias [27, 31]. Other sources of bias mainly based on small sample sizes, baseline characteristics differences and potential conflicts of interest. Studies with low risk of bias must include adequate allocation concealment, intention-to-treat principles, and must be blinded to outcome assessors. (See Fig. 2,3 for results)

3.3 Characteristics of Studies

The general characteristics of these 9 studies are described in Table 1. Data from a total of 624 participants (322 from treatment groups and 302 from control group) across 9 studies were included in the meta-analysis. In addition to general items such as publication time, region, we also extracted potential factors relevant to the study, such as depression degree, type of antidepressant, main inclusion criteria, exercise parameters (frequency, intensity, duration, mode, social participation - group or individual exercise). Of the 9 studies, one study had imperfect baseline data on gender and general body mass (BMI) [29], two studies had an older mean age [29, 30] while the rest were young to middle-aged. There were some differences in the degree of depression (including moderate to major depression) and type of antidepressant (mostly sertraline and SSRIs) among the subjects in the studies. The scales used to measure outcome indicators included HAMD, HRSD, BDI and BDI-II. In addition, we extracted secondary data such as adherence, shedding rate and loss of follow-up to examine the precision of the data. We found low adherence in one study [29] and one study did not mention adherence [25]. See Table 1 for details.

3.4 Meta-Analysis

Meta-analyses were conducted on 9 studies and a random effects model was chosen, but sensitivity analysis revealed that one of the included studies [32] had very variable results that deviated significantly from the overall confidence interval, and we found its experimental design to be deficient, with the study starting with inclusion of patients with major depressive disorder recruited through the media and mental health agency letters. Subjects who appeared to meet the inclusion criteria were recruited to participate in an initial screening interview, and were included if they met DSM-IV criteria. However, the presence of mild to moderate patients was subsequently identified, suggesting a large initial screening error. The post-intervention depression scores were different fitted curves according to the depression degree, and there were inconsistencies before and after the intervention to conclude the effect of aerobic exercise assisted treatment on major depression, and the unstable results of this study had a significant overall impact, so the team members decided to exclude it after a comprehensive quality assessment consultation and discussion. The results of the sensitivity analysis are shown in Fig. 5. Meta-analysis of the results of the quality assessment of the eight studies showed a random effects model with an overall effect size of $(-0.78 [-0.98, -0.58], I^2 = 50.4\%, P = 0.000$ Fig. 4) and moderate heterogeneity. We inferred that adjunctive aerobic exercise treatment had a greater ameliorative effect on depression.

3.5 Subgroup Analysis

To explore the effect of potential factors on outcomes, subgroup analyses were conducted for six variables: depression degree, duration of aerobic exercise, frequency and duration per session, type of antidepressant, scale and exercise pattern. Table 2 summarizes the results of these subgroup analyses and details the differences between them.

3.5.1 Scales

Divided into 4 groups according to the different scale types of HAMD, HRSD, BDI and BDI-II, our forest plots show that the outcome indicator results measured using the HAMD and BDI scales showed a moderate effect (-0.66 [$-0.89, -0.43$], $I^2 = 73.9\%$, $P = 0.009$, -0.77 [$-1.04, -0.5$], $I^2 = 76.0\%$, $P = 0.006$), with group results using HRSD and BDI-II scale suggesting a significant effect (-0.80 [$-1.02, -0.58$], $I^2 = 0.0\%$, $P = 0.929$, -1.07 [$-1.72, -0.43$], $I^2 = 0.0\%$, $P = 0.894$). (Fig. 6)

3.5.2 Depression Degree

Subjects can be classified as moderately and severely depressed depending on their level of depression, and forest plots show a significant effect of assisted aerobic exercise for moderate depression (-1.13 [$-1.56, -0.71$], $I^2 = 0.0\%$, $P = 0.803$) and a moderate effect for severe depression (-0.72 [$-0.89, -0.55$], $I^2 = 33\%$, $P = 0.144$). One study [28] did not mention the specific depression of the study participants and there was extreme within-group heterogeneity (-0.70 [$-0.96, -0.44$], $I^2 = 89.2\%$, $P = 0.002$). (Fig. 7)

3.5.3 Types of Antidepressants

We divided the study into 4 groups according to the type of antidepressant, including sertraline alone, fluoxetine alone, SSRIs antidepressants and SSRIs combined with other antidepressants such as SNRIs and milnacipran. Our forest plots show that for the group using sertraline alone, adjunctive aerobic exercise had a moderate improvement in depression (-0.65 [$-0.83, -0.47$], $I^2 = 6.2\%$, $P = 0.380$), the group using fluoxetine alone showed a larger effect (-1.16 [$-1.63, -0.69$], $I^2 = 0.0\%$, $P =$). The group of SSRIs and combined use of SSRIs with other medications showed a more significant effect (-1.02 [$-1.99, -0.06$], $I^2 = 0.0\%$, $P =$, -1.26 [$-1.75, -0.76$], $I^2 = 0.0\%$, $P = 0.379$). (Fig. 8)

3.5.4 Duration

Cumulative meta-analysis showed that the adjuvant aerobic exercise group had a higher ameliorative effect on depression than the drug-only group. Effect values and 95% CIs stabilized as time progressed. According to our results, the aerobic exercise session was 12 weeks when the improvement in depression was had the best effect (-1.73 [$-2.64, -0.83$]). (Fig. 9)

3.5.5 Frequency and duration per session

The results showed a more significant reduction in depression scores for 5 times a week (-1.32 [$-1.93, -0.72$], $I^2 = 44\%$, $P = 0.181$) and a relatively smaller reduction for 3 times a week (-0.77 [$-0.92, -0.63$], $I^2 = 44.6\%$, $P = 0.071$) according to the different exercise frequencies. Duration was grouped using a 45min

cut-off which showed little difference in effect size, both being moderate ($-0.82 [-1.14, -0.5]$, $I^2 = 57.1\%$, $P = 0.072$, $-0.87 [-1.07, -0.68]$, $I^2 = 0.0\%$, $P = 0.788$). In addition, two studies [21] and [28] did not specify specific exercise duration and had an overall smaller effect on depression improvement ($-0.58 [-0.80, -0.35]$, $I^2 = 76.6\%$, $P = 0.005$). (Fig. 10)

3.5.6 Exercise Pattern

The results of the three exercise modes including group exercise, individual exercise and combined group and individual exercise showed little overall difference in the improvement of depression, but group exercise ($-0.81 [-1.03, -0.59]$, $I^2 = 0.0\%$, $P = 0.957$) had a greater effect size relative to individual exercise ($-0.6 [-0.96, -0.25]$, $I^2 = 71.0\%$, $P = 0.016$) and combined patterns ($-0.74 [-0.94, -0.54]$, $I^2 = 77.9\%$, $P = 0.004$) with larger effect sizes. (Fig. 11)

3.6 Publication Bias

The funnel plots for each subgroup were symmetrical and showed no evidence of significant asymmetry, suggesting a small publication bias. The P values of Begg and Egger's tests were both greater than 0.05. The funnel plots for subgroups grouped by aerobic exercise duration had a tendency for missing corners. However, as the number of studies was too small to make absolute conclusions, the possibility of unpublished negative results was considered.

4. Discussion

The included studies were all randomized controlled trials, which further enhances the rigour and credibility of the studies. Based on our findings, we found a positive overall effect of aerobic exercise assisted medication on depression. This effect was seen in both moderate depression ($-1.13 [-1.56, -0.71]$, $I^2 = 0\%$, $P = 0.803$) and major depression ($-0.72 [-0.89, -0.55]$, $I^2 = 33\%$, $P = 0.144$). Aerobic exercise as a daily exercise routine is low cost and has few side effects [33]. Therefore, we hypothesized that adjunctive aerobic exercise would be an effective treatment for depression.

Despite the paucity of evidence for the effects of assisted aerobic exercise on depression, the link between the HPA axis (hypothalamic-pituitary-adrenal axis) and depression has been well studied. The HPA axis is one of the most important neuroendocrine systems in the body and is the regulatory nerve centre that controls the release of the stress hormones ACTH and COR, mediating neuroplasticity and regulating neurotransmitters through neuroendocrine mechanisms. The mechanisms of aerobic exercise are mainly explained through these two aspects. In mediating neuroplasticity, stress stimulation activates the HPA axis, initiating a cascade effect that promotes the release of hormones such as CRH, ACTH and COR, causing various physiological responses in the sympathetic nervous system. This response is terminated by a negative feedback loop when the stressor disappears. Prolonged exposure to glucocorticoids is neurotoxic and preclinical studies have shown that hippocampal granule cells are more sensitive to these effects [34]. Mature neurons express GR, and exposure to glucocorticoids leads to a decrease in glucocorticoid receptor (GR) responses in hippocampal granule cells, resulting in de-inhibition

of the HPA axis and a further increase in corticosteroid stimulation, a sustained hyperactivity of the HPA axis. Sustained increase in circulating glucocorticoids producing a range of neurotoxic effects in the prefrontal and hippocampal regions, including desensitisation of relevant cell receptors, microglia activation, cell death, decreased neurogenesis and BDNF cycling [16]. BDNF is a key neurotrophin that plays a critical role in hippocampal neuronal growth, survival and plasticity. It is also required for many brain functions such as cognition in adults [35]. Aerobic exercise increases the circulation of several neurotrophic factors. Most notably, it increases the concentration of BDNF in human serum or plasma samples [36, 37]. Animal studies have also shown that exercise increases the circulation of vascular endothelial growth factor (VEGF) [38], an important growth factor for angiogenesis that also mediates neurogenesis and synaptic plasticity [39]. Exercise also induces several other cellular and molecular changes that contribute to neuroplasticity, such as synaptic plasticity [40] and the release of insulin growth factor 1 (IGF-1) as well as fibroblast growth factor (FGF) [41]. Exercise stimulates a range of cellular mechanisms through the induction of neurotrophic factor release, resulting in structural and functional changes in several brain regions, including the hippocampus [42]. In regulating neurotransmitters, CRH receptors are abundantly expressed in extrahypothalamic regions such as nucleus raphe and locus coeruleus, which respectively constitute the serotonin (5-HT) and norepinephrine (NA) systems' major cell bodies [43, 44]. Glucocorticoids stimulate the 5-HT and NA systems via MR and GR [45], both 5-HT and NA are monoamine neurotransmitters. Low function of monoaminergic neurotransmitters in the nervous system can lead to depression [46]. As mentioned above, dysregulation of the HPA axis causes persistently high levels of GC. The hippocampal 5-HT system subsequently becomes less functional due to excessive cortisol levels while aerobic exercise increases 5-HT levels [47]. Exercise leads to an initial elevation in cortisol cycling while habitual exercise leads to a diminished cortisol response, which may respond to increased HPA resilience [48]. Although limited, the available evidence suggests that exercise may be a positive stressor for certain neuroendocrine pathways and that regular exercise suppresses HPA activity and cortisol sensitivity.

- Although mechanisms have been associated to explain the antidepressant effects of aerobic exercise and antidepressant medication, few studies have explored the putative mechanisms for their combined efficacy. Nevertheless, there are several lines of evidence suggesting that exercise may enhance drug efficacy through complementary and overlapping mechanisms. Aerobic exercise has many health benefits, which may complement the effects of medication. A large body of evidence supports the positive effects of exercise on the physical health of people with depression, such as cardiorespiratory fitness and cardiovascular risk factors [49, 50]. Furthermore, exercise has beneficial effects on many psychosocial health outcomes, such as life quality and daily functioning, which are often compromised by depression [51]. Preliminary findings also suggest that exercise can improve some cognitive outcomes in people with depression. For example, Greer and colleagues found that 12 weeks of exercise improved aspects of cognitive functioning (attention, working memory, etc.) in depressed patients who were under-responsive to antidepressant medication [52], and importantly, these pro-cognitive effects are thought to possibly represent the behavioural consequences of exercise-induced neuroplasticity [35]. We hypothesize that this is the main premise

behind the mechanisms about overlap between exercise and antidepressant. For example, in animal models of depression, the combination of antidepressants and exercise has been shown to increase hippocampal brain-derived neurotrophic factor (BDNF) and reduce depression-like behaviours more than antidepressants alone [53, 54]. With these possible mechanisms, it is reasonable to assume that aerobic exercise and antidepressant medication will lead to greater therapeutic benefits for depression. Several researchers have suggested that exercise and standard antidepressant treatment may have a synergist meaning that their combined effect is greater than the sum of each individual effect [55, 56]. Given the lack of evidence, it is unclear whether these potential mechanisms underline the combined treatment effects. Furthermore, neurobiological effects are difficult to measure in humans and are often assessed indirectly in the periphery, reverse translation in animal models of depression may contribute to these studies and in the future we hope to see more studies demonstrating the mechanisms of effects from such combinations.

In a combined subgroup analysis we found that aerobic exercise assisted treatment showed superior efficacy to medication alone for different levels of depression, with a higher reduction for moderate depression (-1.13 [-1.56, -0.71], $\hat{P} = 0\%$, $P = 0.803$) and a relatively lower improvement for patients with major depression (-0.72 [-0.89, -0.55], $\hat{P} = 33\%$, $P = 0.144$). Patients with MDD often have cognitive dysfunction in areas such as attention, executive function [57]. Due to their physiological and psychological reasons, patients have low tolerance and compliance with aerobic exercise. Meanwhile, current antidepressant medications only result in complete remission in approximately one third of patients with MDD [58]. Many people with MDD experience relapses and severe functional impairment are unable to respond to conventional therapies [59]. Uncertainty about efficacy can, to some extent, cause patients to lose confidence in treatment, bringing about negative psychological cues and leading to relatively small effect sizes.

With regard to the type of antidepressant, the use of SSRIs is more effective than sertraline alone. As a variant 5-hydroxytryptamine reuptake inhibitor that differs from the classical SSRIs, escitalopram is currently the preferred choice for efficacy and tolerability compared to sertraline, which has moderate drug interaction problems [60]. Diarrhoea is another possible cause. In an early study in which 659 patients were randomly assigned to treatment with sertraline and 592 patients to treatment with other SSRIs (paroxetine, fluoxetine or fluvoxamine), the incidence of other adverse events was similar for all four drugs, but the incidence of diarrhoea was higher for sertraline (14%) than for the other SSRIs (6.8%) [61]. We hypothesize that there are differences in safety and tolerability between the SSRIs and that the high diarrhoea rate of sertraline compared to the other SSRIs may affect compliance with aerobic exercise and to some extent its efficacy. However, due to the small sample size and the variety of drugs included in the study, higher quality studies are needed to explore the efficacy of different drug classes alone or in combination.

Regarding the choice of aerobic exercise duration, the cumulative meta-analysis showed that adjunctive aerobic exercise significantly improved depression scores. The magnitude of improvement in depression scores fluctuated but gradually stabilized. A 12-week adjunctive aerobic exercise duration was most

effective in improving depression according to our results. However, due to limitations in the range of durations included, it was not possible to determine whether precise effect values emerged. In the 2016 Canadian Network for Mood and Anxiety Treatment (CANMAT) guidelines [62], the guidelines recommend exercise as a treatment for mild-moderate depression. The guideline recommends supervised moderate-intensity exercise at least 3 times per week for at least 9 weeks. This differs somewhat from our conclusions, and we speculate that there is individual variation in subjects, coupled with differences in the type of exercise. In the meantime, some studies [25] using low-intensity exercise and others [31] using moderate intensity, so it is difficult to draw uniform conclusions about the optimal duration of treatment for the time being, therefore, further researches are needed to investigate the type and intensity of exercise to find the optimal duration for each type of aerobic exercise.

In addition, studies have explored the role of physiological adaptations and exercise intensity in interval training [63], but the interaction between intensity, duration and frequency has not been thoroughly explored. Based on the results of frequency, five times a week is more effective compared to three times a week, which is somewhat different from the CANMAT guidelines. We hypothesize that this is related to subject compliance. Higher frequency may associate with negative effects of exercise, coupled with individual differences in physiological conditions and habits. Exercise performed at a personally preferred frequency will produce higher compliance rates. Studies conducted in rodents have shown that increase of duration [64] and frequency [65] can enhance mitochondrial adaptation to aerobic exercise and maintain increased maximal oxygen uptake (VO_{2max}). However, there are insufficient data to fully determine the role of these variables in modulating mitochondrial adaptation to exercise in humans. Therefore, there is a need to develop a series of continuous interventions in which one exercise program variable is manipulated at a time to control for variables such as exercise session, frequency, intensity and duration. More high-quality researches are needed to investigate the mechanisms of exercise adaptation in humans.

One study [21] showed that physical activity did not show an advantage in terms of antidepressant improvement, but improved VO_{2max} parameters. According to their data, none of the changes in HAM-D or BDI scores were associated with changes in VO_{2max} , HR_{max} , O₂ pulse or VO_{2-VT2} . VO_{2max} remained stable during the study period in the control group ($p = 0.803$), but increased significantly in the exercise group ($p < 0.001$). O₂ pulse was also significantly higher than baseline values in the exercise group ($p = 0.008$) and the difference between the two groups in terms of final O₂ pulse was also significant ($p = 0.05$). In addition, VO_{2-VT2} was significantly increased in the exercise group ($p = 0.01$), but this was not the case in the control group ($p = 0.297$). Aerobic exercise significantly improved several parameters related to cardiorespiratory capacity in depressed patients, which may be another possible mechanism for its antidepressant efficacy. This approach also reduced the need for higher doses of antidepressants to achieve antidepressant effects and is therefore a valuable adjunctive treatment during depressive episodes.

Despite the significant overall effect, the modest heterogeneity of these studies is also of concern. Therefore, we divided all included data into smaller units for subgroup analyses based on different

clinical heterogeneity and methodological heterogeneity of the studies. We first used different levels of depression to examine sources of heterogeneity, and we found a significant effect of assisted aerobic exercise for moderate depression (-1.13 [-1.56, -0.71], $I^2 = 0.0\%$, $P = 0.803$) and a relatively moderate effect for major depression (-0.72 [-0.89, -0.55], $I^2 = 33\%$, $P = 0.144$), we then categorized the heterogeneity according to aerobic exercise duration. From our results it appears that aerobic exercise efficacy fluctuated but gradually stabilized, with the best results at 12 weeks. Finally we categorized aerobic exercise frequency and antidepressants to examine sources of heterogeneity, 5 times a week (-1.32 [-1.93, -0.72], $I^2 = 44\%$, $P = 0.181$), 3 times a week (-0.77 [-0.92, -0.63], $I^2 = 44.6\%$, $P = 0.071$), sertraline group (-0.65 [-0.83, -0.47], $I^2 = 6.2\%$, $P = 0.380$), fluoxetine group (-1.16 [-1.63, -0.69], $I^2 = 0.0\%$, $P =$), SSRIs group and SSRIs with other antidepressants group (-1.02 [-1.99, -0.06], $I^2 = 0.0\%$, $P =$, -1.26 [-1.75, -0.76], $I^2 = 0.0\%$, $P = 0.379$). Results mentioned above showed that heterogeneity was reduced to low heterogeneity (excluding the two groups of exercise frequency being slightly higher). We infer that the moderate heterogeneity in overall effect size arised from different depression degree, durations and types of antidepressants. The results of screening for sources of heterogeneity in terms of exercise duration per session and frequency, scale type and whether it was a team sport were not favourable and were therefore not considered as potential sources of heterogeneity for the time being.

The main strength of our study is that it is the first meta-analysis in the field to quantify the effects of assisted aerobic exercise on different levels of depression. Furthermore, subgroup analysis and cumulative meta-analysis provide recommendations for the implementation of assisted aerobic exercise for psychiatric related health professionals namely 1) it can be applied for both moderate and major depression 2) a 12-week aerobic exercise course is more effective in clinical settings 3) on this basis, clinically depressed patients can choose their preferred type of exercise to achieve optimal compliance. Nevertheless, several limitations of the meta-analysis must be considered. Firstly, in some studies we used data extraction software to obtain data, which may be subject to some error with the original data. Secondly, subject blinding is currently imperfect due to the specificity of the intervention. Thirdly, differences arising from limitations in subject recruitment and inconsistencies in some of the depression assessment criteria make the results less convincing.

5. Conclusion

Our meta-analysis showed that aerobic exercise supplemented with medication has a positive overall effect on depression and that aerobic exercise is a low-cost and effective treatment. A subgroup analysis found that aerobic exercise was effective for both moderate and severe depression, with a more significant effect for moderate depression; a cumulative meta-analysis showed that a 12-week course of adjunctive aerobic exercise was best for depression, but more high-quality RCTs are needed to investigate a more precise course. Due to differences in subjects' physiological conditions and tolerances, we tend to support tailored exercise programmes for different individuals to improve depression and achieve a healthy state. Therefore, we recommend adjunctive aerobic training and determination of exercise duration and frequency for depressed patients with appropriate follow-up. Further high-quality studies

should be conducted to understand the detailed effects and mechanisms of different aerobic exercise types, frequency, duration per session and intensity and to select the most appropriate programme.

Tables

Table 1

Baseline characteristics of included studies See the attachment for details

Table 2

Results of subgroup analysis.

Subgroup	Meta-analysis			Heterogeneity		Number of RCTs (n)
	SMD	Estimate Mean (95% CI)		Cochrane Q	I ²	
Scale						
HAMD	-0.66	-0.89	-0.43	0.009	73.90%	4
BDI	-0.77	-1.04	-0.5	0.006	76.00%	4
HRSD	-0.8	-1.02	-0.58	0.929	0%	4
BDI-II	-1.07	-1.72	-0.43	0.894	0%	2
Degree of Depression						
MDD	-0.72	-0.89	-0.55	0.144	33%	10
Moderate depression	-1.13	-1.56	-0.71	0.803	0%	2
NR	-0.7	-0.96	-0.44	0.002	89.20%	2
Duration						
4 weeks	-0.41	-0.64	-0.18	0.373	4%	4
8 weeks	-1.01	-1.26	-0.77	0.283	20.70%	3
16 weeks	-0.59	-0.98	-0.21	0.339	0%	2
24 weeks	-0.9	-1.35	-0.45	-	0%	1
12 weeks	-1.02	-1.38	-0.66	0.189	39.90%	3
10 days	-1.11	-1.99	-0.24	-	0%	1
Exercise Pattern						
Seperate	-0.6	-0.96	-0.25	0.016	71%	4
Group	-0.81	-1.03	-0.59	0.957	0%	5
Seperate&group	-1.11	-1.99	-0.24	-	0%	1
NR	-0.74	-0.94	-0.54	0.004	77.90%	4
Type of antidepressant						
Sertraline	-0.65	-0.83	-0.47	0.38	6.20%	7
Fluoxetine	-1.16	-1.63	-0.69	-	0%	1
SSRIs	-1.02	-1.99	-0.06	-	0%	1
SSRIs with other antidepressants	-1.26	-1.75	-0.76	0.379	0%	3
NR	-0.70	-0.96	-0.44	0.002	89.20%	2
Exercise Frequency						
3 times per week	-0.77	-0.92	-0.63	0.071	44.60%	9
5 days per week	-1.32	-1.93	-0.72	0.181	44.00%	2
NR	-0.4	-0.79	0	0.195	38.90%	3
Duration per Session						
<=45min	-0.82	-1.14	-0.5	0.072	57.10%	4
>45min	-0.87	-1.07	-0.68	0.788	0%	6
NR	-0.58	-0.8	-0.35	0.005	76.60%	4

Declarations

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Authors'Contributions

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Quality Assessment and Information Extraction: Bei Yu, Jingxuan Hao. Check Information: Mengfei Wang. Statistical analysis and graphing: Yue Huang, Chenxi Ma. Manuscript Drafting: Yue Huang.

Critical revision of the manuscript for important intellectual content: Xinyi Hu, Huijie Cen. All authors have read and approved the final manuscript.

Data availability

All relevant data will be freely available to any scientist wishing to use them for non-commercial purposes, upon a reasonable written request from the corresponding author (AJ).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors reviewed the manuscript and are agree to the publication NA (Not Applicable). No identifying human images or data were used in the study.

Competing interests

The authors declare no competing interests.

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Figures

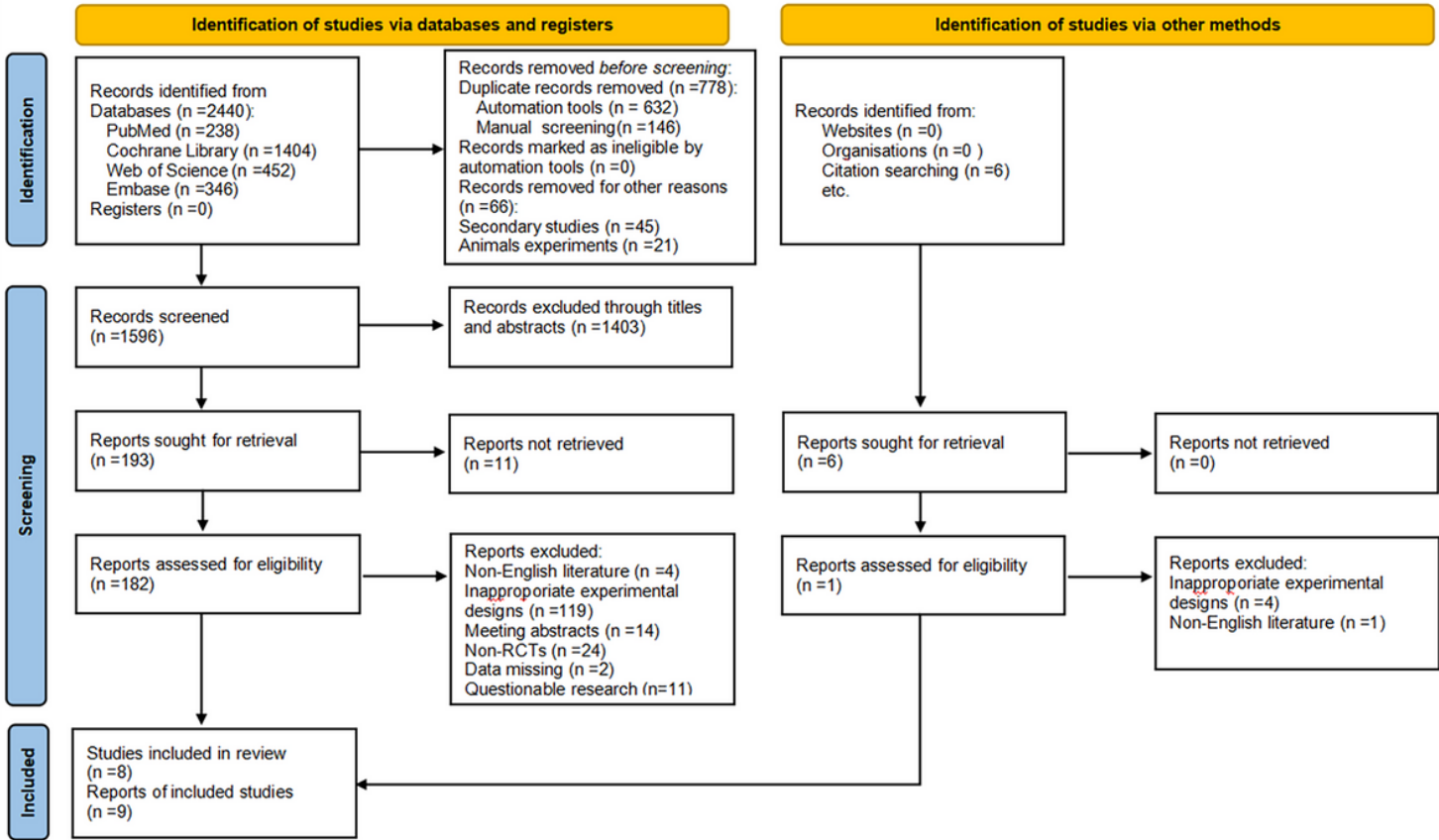


Figure 1

Selection process for trials included in the meta-analysis.

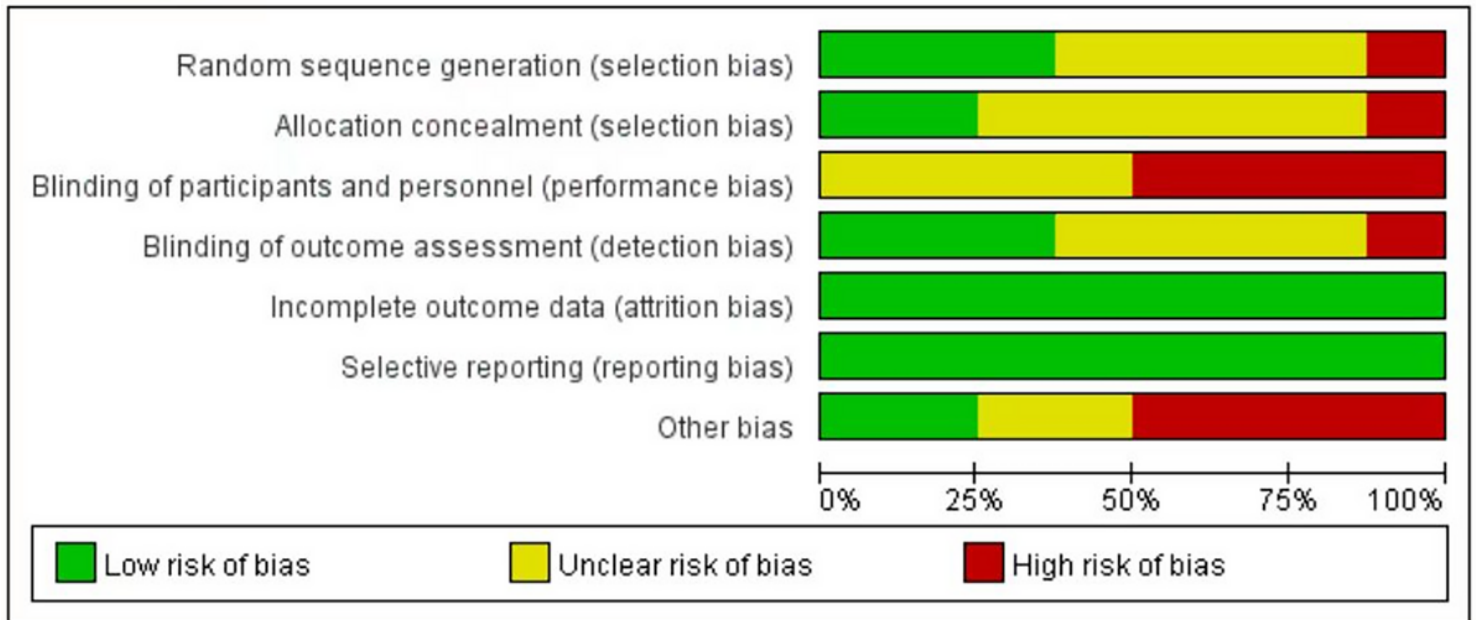


Figure 2

Risk-of-bias assessments of the included studies (domains from the Cochrane Handbook for Systematic Reviews of Interventions).

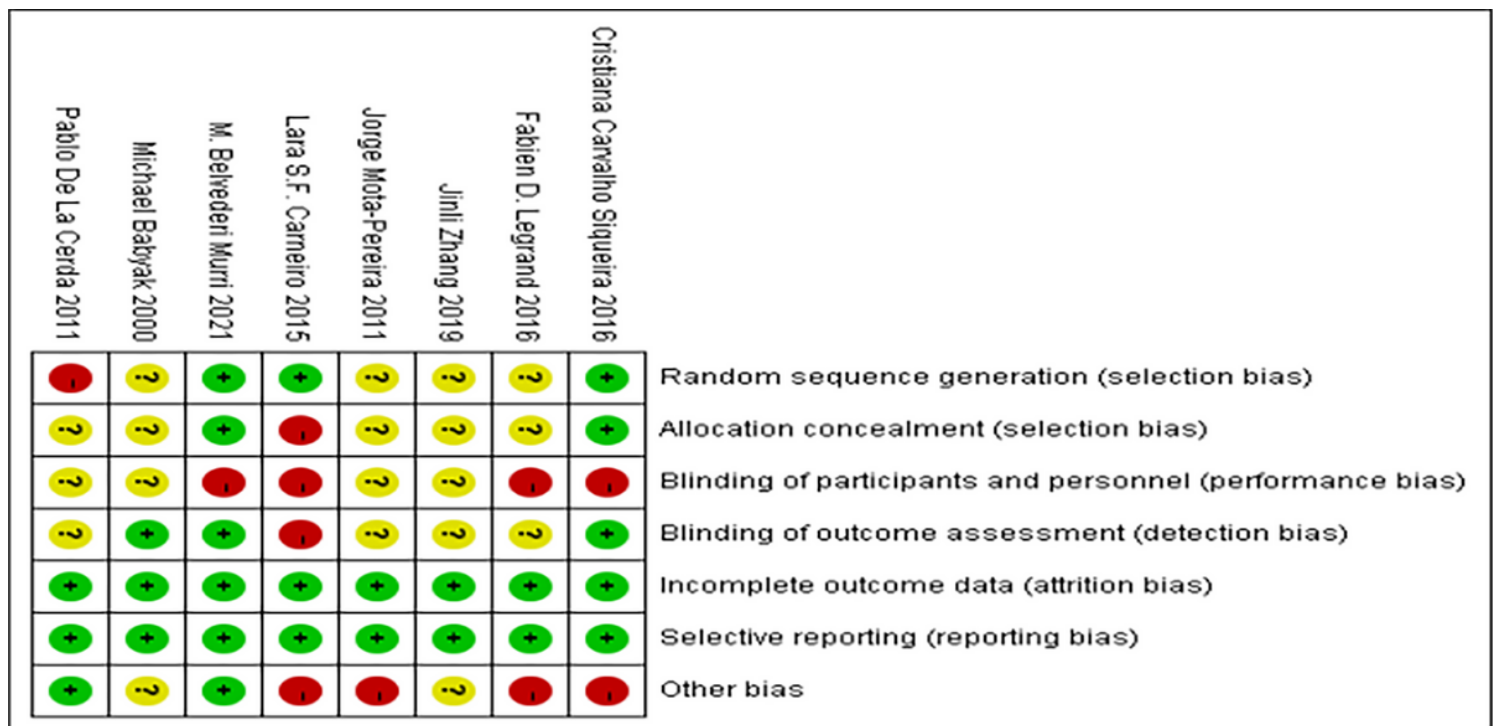


Figure 3

Risk-of-bias assessments of the included studies summary (domains from the Cochrane Handbook for Systematic Reviews of Interventions).

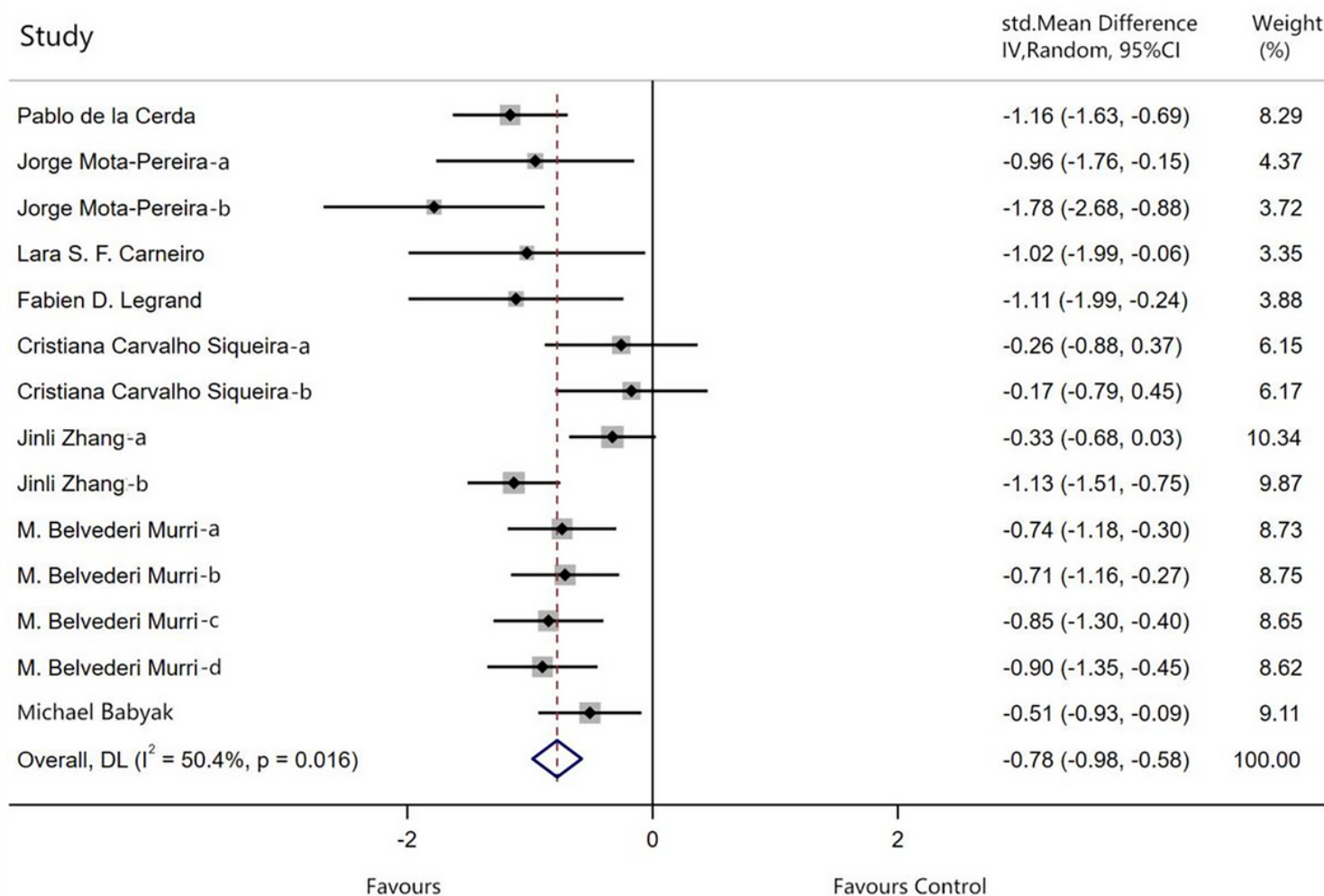


Figure 4

Forest plot of random-effects model meta-analysis of the overall effect of auxiliary aerobic exercise on depression. CI, confidence interval; p was heterogeneity p-value.

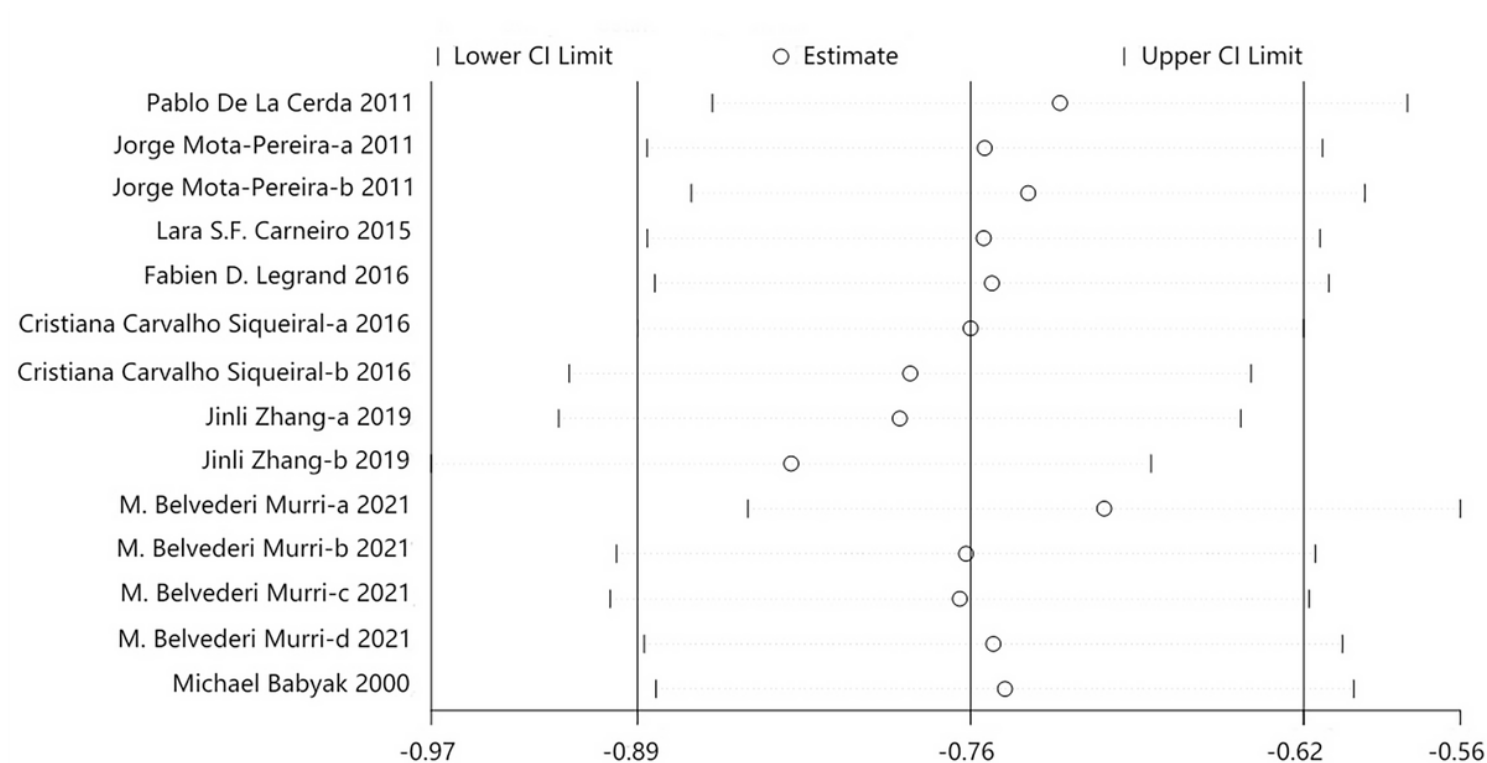


Figure 5

Result of sensitivity analysis

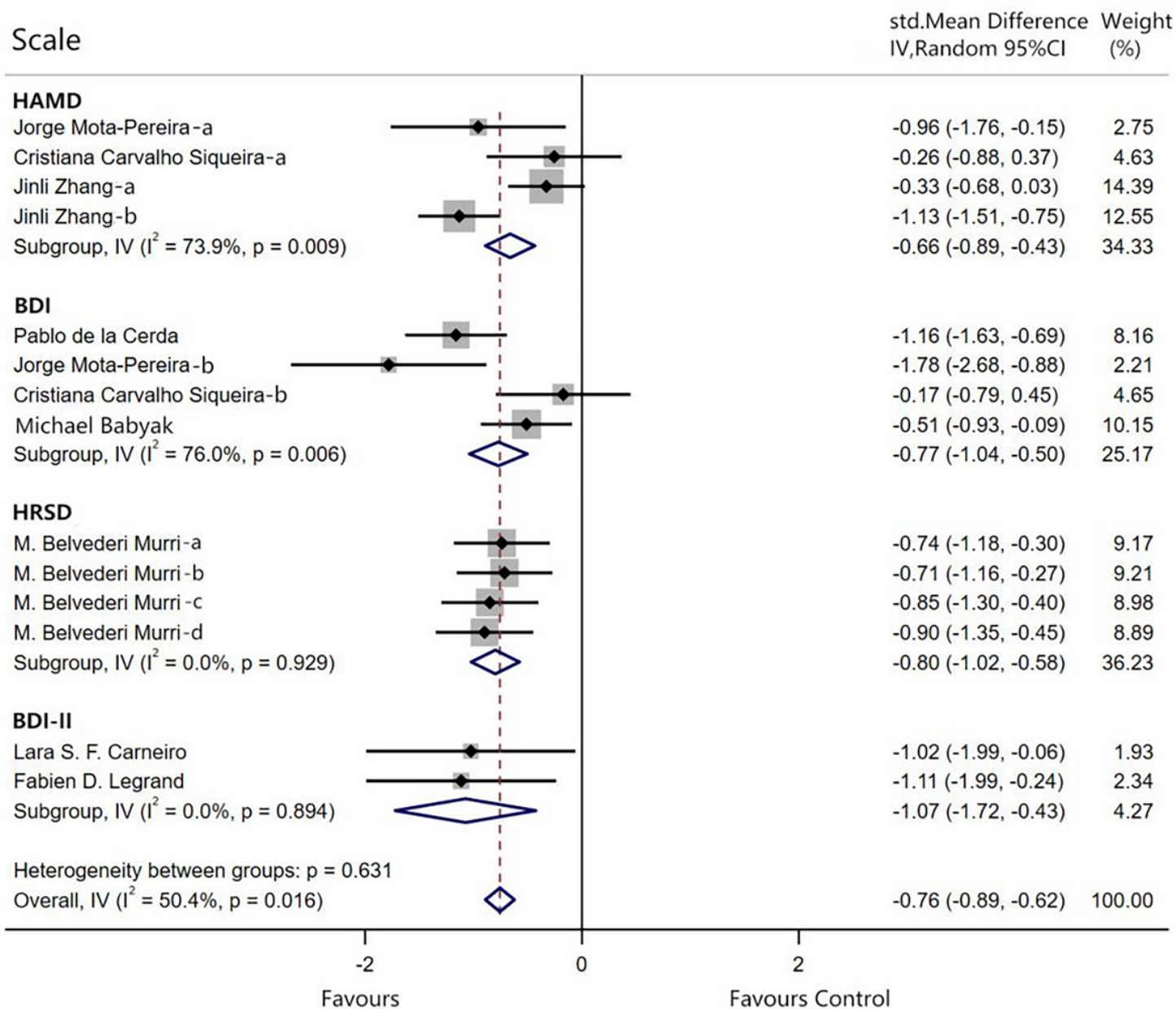


Figure 6

Forest plot of random-effects model subgroup analysis according to scale.

CI, confidence interval; p was heterogeneity p-value.

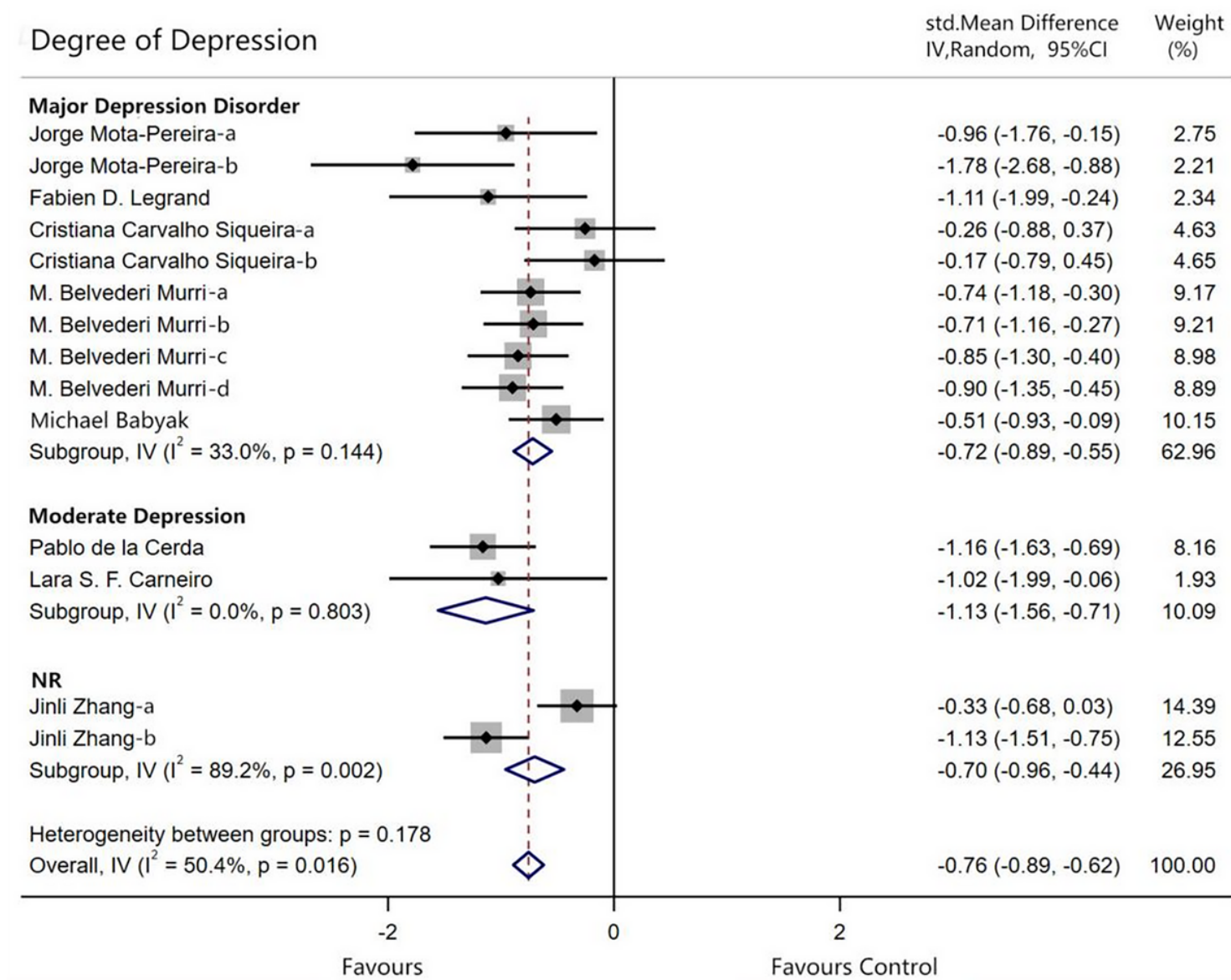


Figure 7

Forest plot of random-effects model subgroup analysis according to degree of depression .

CI, confidence interval; p was heterogeneity p-value.

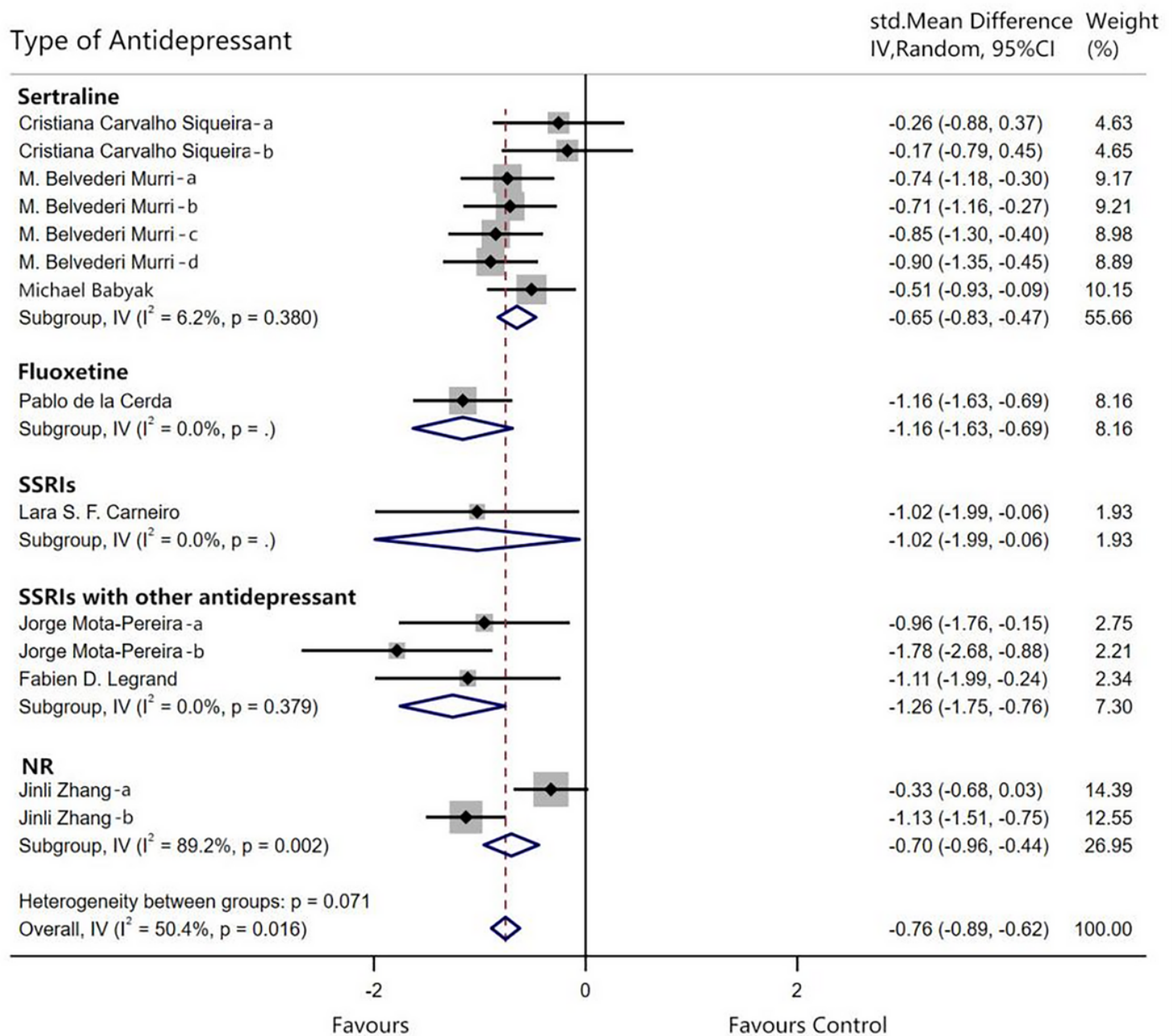


Figure 8

Forest plot of random-effects model subgroup analysis according to Type of antidepressant .

CI, confidence interval; p was heterogeneity p-value.

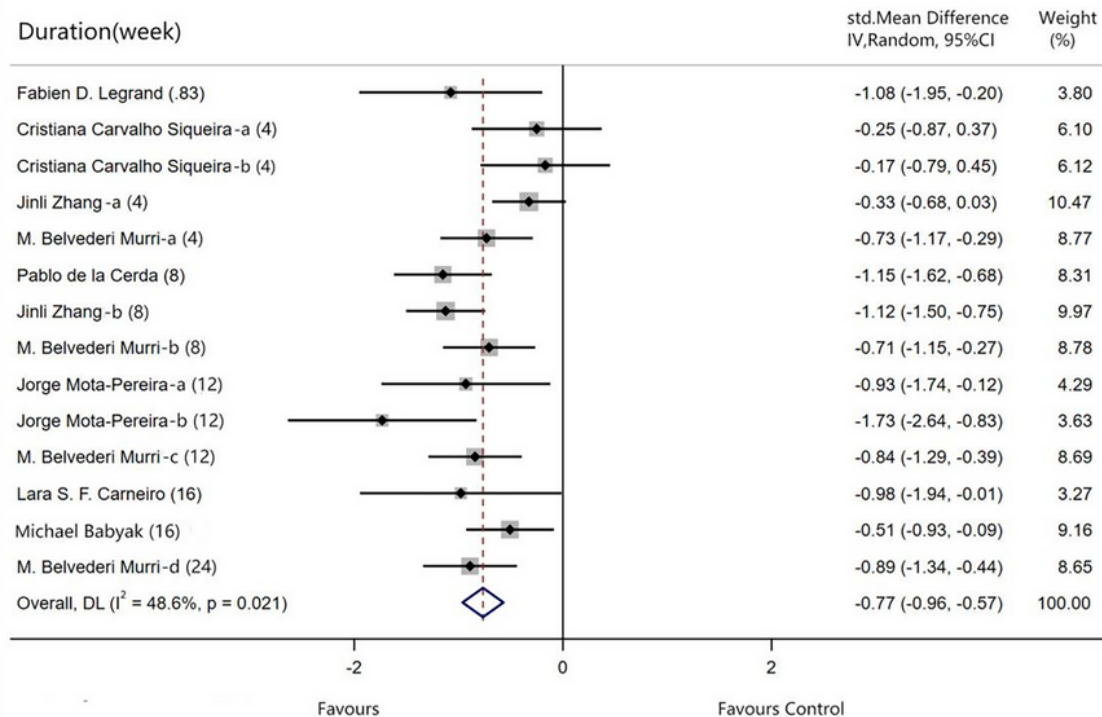
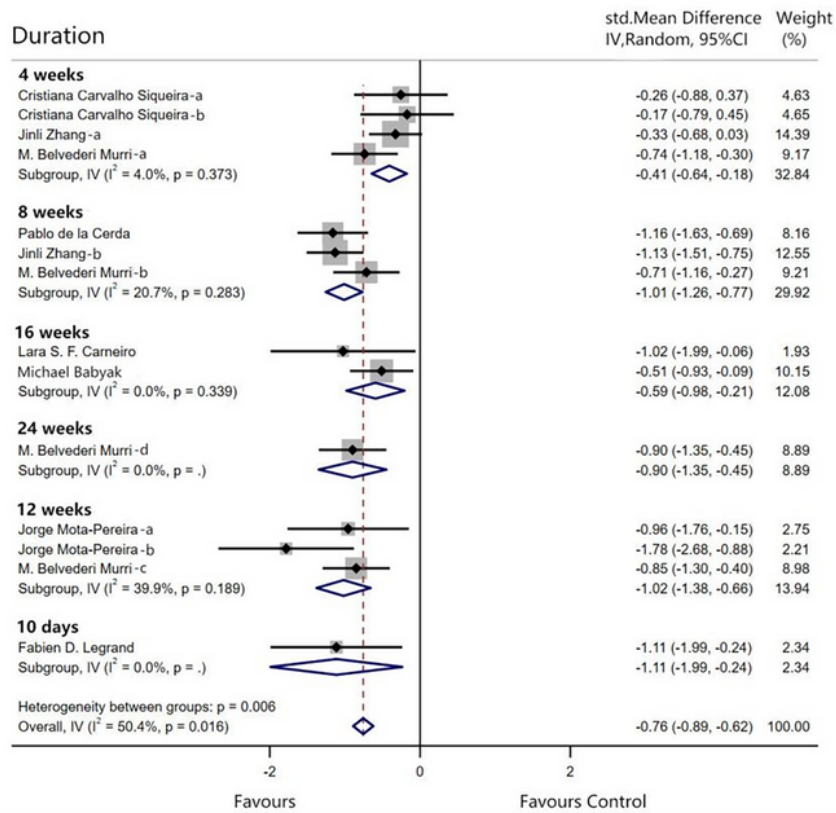


Figure 9

Forest plot of random-effects model subgroup analysis and cumulative meta-analysis according to duration .

CI, confidence interval; p was heterogeneity p-value.

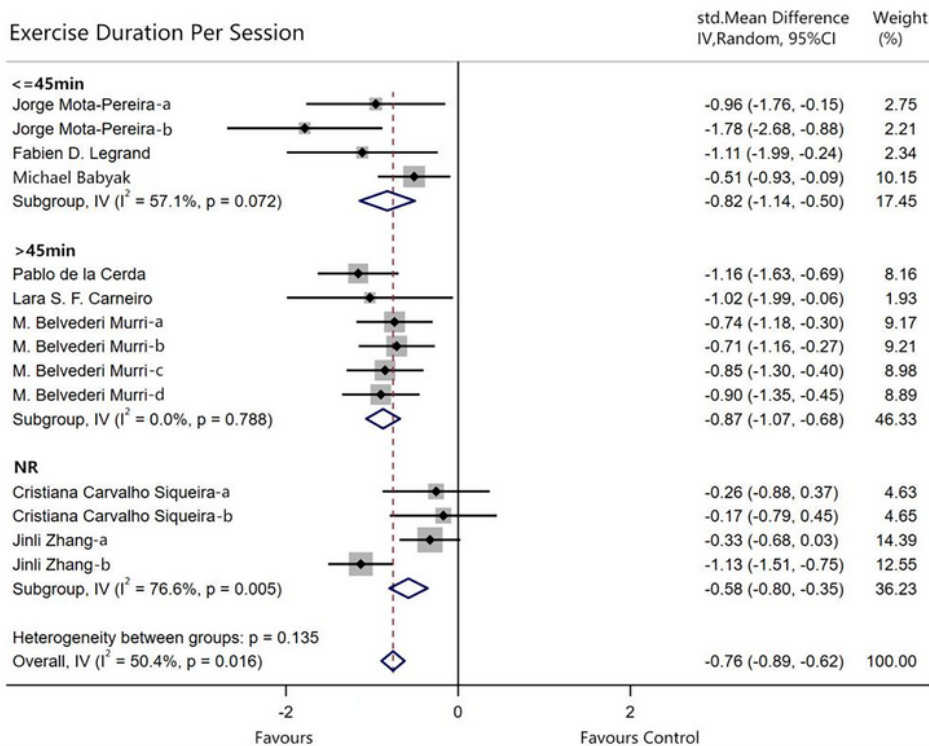
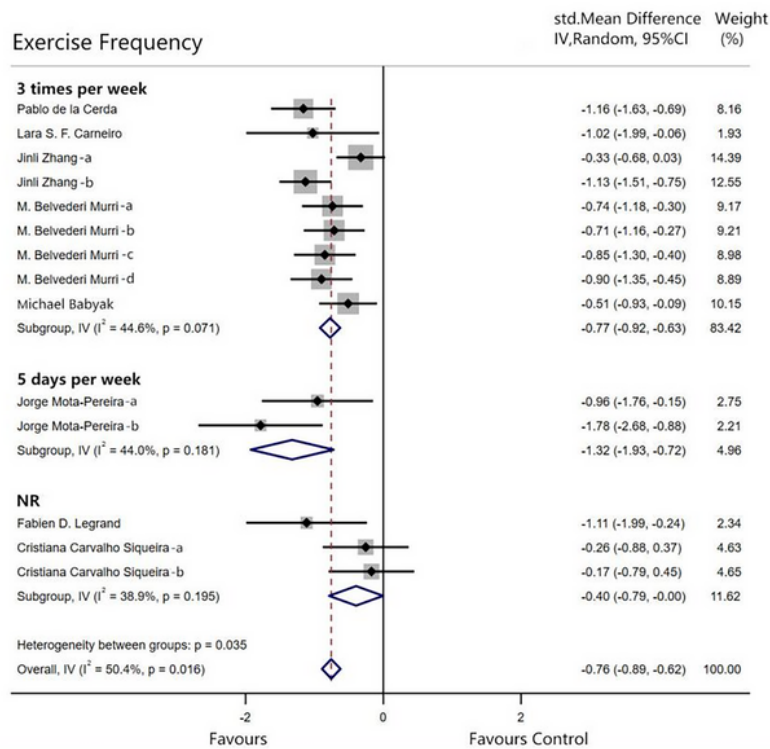


Figure 10

Forest plot of random-effects model subgroup analysis according to exercise frequency and duration per session. CI, confidence interval; p was heterogeneity p-value.

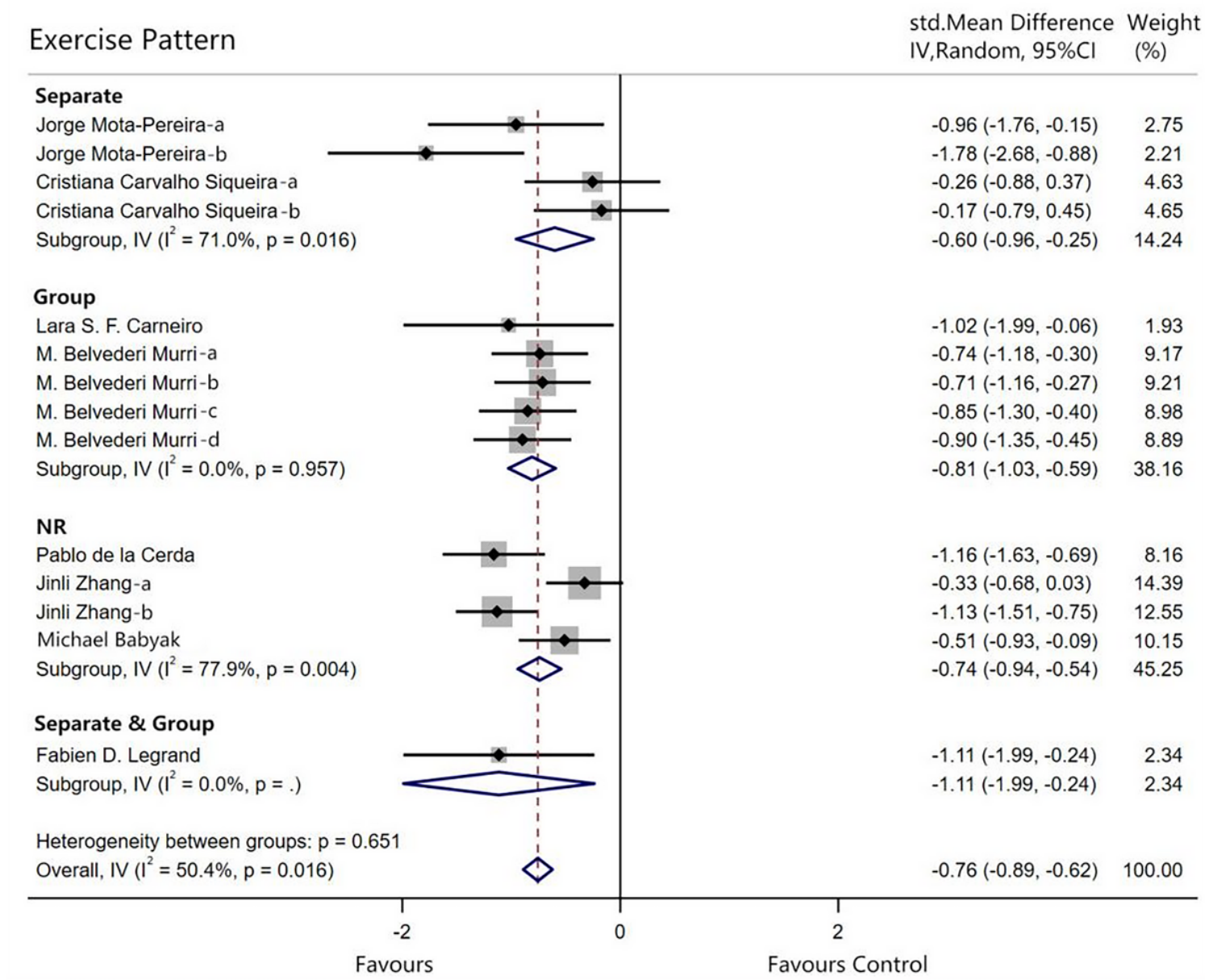


Figure 11

Forest plot of random-effects model subgroup analysis according to exercise pattern (group or individual). CI, confidence interval; p was heterogeneity p-value.

Supplementary Files

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- [Table2.png](#)
- [SupportingInformation1Fullsearchstrategy.docx](#)
- [Supportingmaterial2statacode.txt](#)
- [Supportingmaterial3Table1baselinedata.xlsx](#)