OPEN ACCESS

Comparative effectiveness of exercise, antidepressants and their combination in treating non-severe depression: a systematic review and network meta-analysis of randomised controlled trials

Francesco Recchia,[1] Chit K Leung,[1] Edwin C Chin,[1] Daniel Y Fong,[2] David Montero,[1] Calvin P Cheng,[3] Suk Yu Yau,[4] Parco M Siu [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjsports-2022-105964).

[1]Division of Kinesiology, School of Public Health, The University of Hong Kong, Hong Kong, Hong Kong
[2]School of Nursing, The University of Hong Kong, Hong Kong, Hong Kong
[3]Department of Psychiatry, The University of Hong Kong, Hong Kong, Hong Kong
[4]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong, Hong Kong

Correspondence to
Dr Parco M Siu, The University of Hong Kong, Hong Kong, 999077, Hong Kong; pmsiu@hku.hk

Accepted 1 September 2022
Published Online First 16 September 2022

To cite: Recchia F, Leung CK, Chin EC, *et al*. *Br J Sports Med* 2022;**56**:1375–1380.

ABSTRACT

Objective To assess the comparative effectiveness of exercise, antidepressants and their combination for alleviating depressive symptoms in adults with non-severe depression.

Design Systematic review and network meta-analysis.

Data sources Embase, MEDLINE, PsycINFO, Cochrane Library, Web of Science, Scopus and SportDiscus.

Eligibility criteria Randomised controlled trials (1990–present) that examined the effectiveness of an exercise, antidepressant or combination intervention against either treatment alone or a control/placebo condition in adults with non-severe depression.

Study selection and analysis Risk of bias, indirectness and the overall confidence in the network were assessed by two independent investigators. A frequentist network meta-analysis was performed to examine postintervention differences in depressive symptom severity between groups. Intervention drop-out was assessed as a measure of treatment acceptability.

Results Twenty-one randomised controlled trials (n=2551) with 25 comparisons were included in the network. There were no differences in treatment effectiveness among the three main interventions (exercise vs antidepressants: standardised mean differences, SMD, −0.12; 95% CI −0.33 to 0.10, combination versus exercise: SMD, 0.00; 95% CI −0.33 to 0.33, combination vs antidepressants: SMD, −0.12; 95% CI −0.40 to 0.16), although all treatments were more beneficial than controls. Exercise interventions had higher drop-out rates than antidepressant interventions (risk ratio 1.31; 95% CI 1.09 to 1.57). Heterogeneity in the network was moderate (τ^2=0.03; I^2=46%).

Conclusions The results suggest no difference between exercise and pharmacological interventions in reducing depressive symptoms in adults with non-severe depression. These findings support the adoption of exercise as an alternative or adjuvant treatment for non-severe depression in adults.

Systematic review registration PROSPERO CRD4202122656.

WHAT ARE THE FINDINGS?

⇒ Exercise alleviates symptoms of depression to a similar extent as antidepressant treatments alone or in combination with exercise.
⇒ The drop-out rates of exercise studies was higher than that of antidepressant studies.

HOW MIGHT IT IMPACT ON CLINICAL PRACTICE IN THE FUTURE?

⇒ These results suggest that exercise may be used as an alternative treatment approach for the management of non-severe depression in adults.
⇒ This study adds to the body of evidence for the benefits of exercise in managing depression and will inform future mental health treatment guidelines regarding the protective role of exercise for non-severe depression.

INTRODUCTION

Depression is a leading cause of disability worldwide and is estimated to affect over 320 million people.[1] The burden of depression negatively affects role functioning and quality of life,[2] and is estimated to cost over US$920 billion due to lost productivity alone.[3] Depression has a lifetime prevalence of up to 19% and is highly associated with the onset of other somatic and psychiatric disorders.[4 5]

Currently, second-generation antidepressant medications are one of the first-line treatments for depression.[6] However, the evidence on their effectiveness remains controversial because the immediate and short-term benefits may be small and the long-term balance between benefit and harm is poorly understood.[7] Individual-level meta-analyses have found a direct relationship between the magnitude of depressive symptoms and the effectiveness of antidepressants.[8–10] Thus, the benefits of antidepressants in non-severe depression have been argued to be minimal.[8 11] This is concerning considering that most patients with depression report symptoms below the threshold for severe depression.[12 13] In addition, high costs, fear of addiction and possible adverse effects limit the applicability of antidepressants in some real-life settings.[14] Reluctance to use antidepressants may also be found in patients with non-severe symptoms due to low perceived need or effectiveness of the medication and/or social stigmatisation.[15] Although there is evidence that antidepressants have some beneficial effects on milder forms of depression compared with placebo,[16] concerns over the risk-to-benefit ratio and the availability of alternative treatments

raise questions about the appropriateness of pharmacological treatments for non-severe depression.

Recently, lifestyle interventional strategies incorporating diet, sleep and physical activity have been recognised as protective treatments for depression.[17 18] Specifically, the use of exercise as an alternative treatment for non-severe depression is endorsed by several treatment guidelines (EPA in Europe, CANMAT in Canada, NICE in the UK and RANZCP in Australia).[19–22] In contrast, the clinical practice guidelines provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) support exercise therapy only when antidepressants or psychotherapy treatments are ineffective or unacceptable.[6] Moreover, the DSM-5 guidelines state that there is a lack of evidence to recommend exercise as an official treatment. This contradicts the report by the European Psychiatric Association that states that there is sufficient data supporting exercise for the management of mild-to-moderate depression.[19] The contrasting statements conveyed by international treatment guidelines preclude drawing definitive conclusions regarding the role of exercise as a treatment for non-severe depression.

Comparing the effects of exercise and antidepressants is essential to elucidate whether exercise is a suitable non-pharmacological treatment approach to manage non-severe depression, and to inform current international treatment guidelines about the protective role of exercise in depression. We therefore conducted a systematic review and network meta-analysis to determine the comparative effectiveness of exercise and antidepressants on depressive symptoms in adults with non-severe depression. In addition, we examined the effect of combination treatment versus either treatment alone to explore the potential synergistic action of exercise and antidepressants. We also set to compare the drop-out rates of participants among interventions as a measure of treatment acceptance.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension guidelines for network meta-analyses[23] and was registered in PROSPERO (identifier CRD42021226561).

Search strategy and selection criteria

We searched seven electronic databases (Embase, MEDLINE (PubMed), PsycINFO, Cochrane Library, Web of Science, Scopus and SportDiscus) from January 1990 to January 2022 for relevant articles published in any language. A detailed description of the search strategy is provided in online supplemental eappendix 1. We handsearched references of previous meta-analyses and articles of interest to identify further eligible studies. Two independent researchers performed the search using pre-established criteria. In case of disagreement, a third author was consulted, and the disagreement was resolved by consensus.

We included randomised controlled trials investigating the effect of (1) exercise versus antidepressants, (2) either exercise or antidepressants versus a control condition and (3) exercise combined with antidepressants versus either treatment alone, during an initial treatment attempt in adults with non-severe depression. Non-severe depression was defined as a diagnosis of major depressive disorder with mild-to-moderate symptoms. We included studies that recruited participants with a clinical diagnosis of depression assessed using standard diagnostic criteria and determined to have mild-to-moderate symptoms using a psychiatric interview or the cut-off score of a validated rating scale. If studies did not specify the severity of depression for recruitment, they were included if (1) mild symptoms were reported as minimum inclusion criteria and (2) mean baseline depression scores were of moderate severity or lower.

We defined exercise according to the American College of Sports Medicine guideline as 'planned, structured and repetitive bodily movement aimed to improve and/or maintain one or more components of physical fitness'.[24] Studies were excluded if they involved mind-body practices such as yoga or Tai Chi, as these comprise a number of behavioural techniques that might confound the effect of physical exercise. Studies on antidepressants were included if they assessed the effectiveness of a second-generation antidepressant that was approved by the Food and Drug Administration (FDA) and that was administered in doses within the standard therapeutic range.[25] To ensure homogeneity among participant and trial characteristics, studies where all participants had treatment-resistant depression or a primary comorbidity, as well as studies where exercise or antidepressants were added to another treatment (eg, psychotherapy), were excluded. Studies with the intervention lasting less than 4 weeks were also excluded.

Outcomes

The primary outcome was depressive symptoms severity, defined as the score on a depression scale at the primary endpoint. When multiple scales were used, we applied a hierarchical protocol based on the most frequently employed scale. The secondary outcome was treatment acceptability, defined as the number of participants who withdrew from the study before the end of the intervention. We used overall drop-out as a measure of acceptability, as this encompasses all possible reasons for discontinuation, including tolerance and satisfaction to the intervention.

Data extraction

Two authors independently extracted sample sizes, postintervention mean scores of depressive symptoms, SD and number of drop-outs in each study. Disagreements were resolved by consensus. When SD were missing, we calculated them using previously validated methods.[26 27] If SD could not be computed from the available data and the authors were unreachable, these were imputed. Sensitivity analyses were performed for studies where SD were imputed. If dichotomous data for the number of drop-outs was not clearly reported, we computed the drop-outs based on the difference between participants randomised at baseline and those who completed the intervention. If data were missing, the authors were directly contacted to request additional information. If the authors were unresponsive or unreachable the study was excluded.

We extracted information on participants (ie, mean age, sex and baseline symptoms severity) and trial characteristics (ie, first author, publication date, type of intervention, type of control, outcome assessment and intervention duration) using a data extraction form embedded in an Excel spreadsheet.

We assessed risk of bias using the Cochrane risk of bias assessment tool (RoB-2).[28] We used the Confidence in Network Meta-Analysis (CINeMA) model to assess the confidence of the entire network.[29] Additional information regarding RoB-2 and CINeMA can be found in online supplemental eappendix 2.

Data analysis

We conducted a network meta-analysis with a frequentist framework using the *netmeta* package in the statistical software R (V.4.0.3). We designed a network including (1) exercise, (2) antidepressants and (3) exercise plus antidepressants as direct

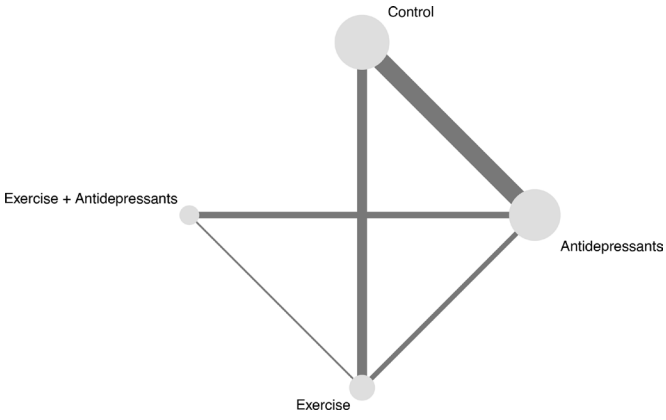


Figure 1 Geometry of the network. The size of the node represents the number of participants in each intervention. The thickness of the edges represents the number of studies in each treatment comparison.

comparisons. If studies included control interventions, these were grouped together and added as a further comparison. We performed random effects pairwise meta-analyses with the Hartung-Knapp-Sidik-Jonkman method[30] for direct comparisons to estimate standardised mean differences (SMD) from continuous outcomes and risk ratios (RR) from dichotomous outcomes. Indirect evidence was assessed using the whole network. The random effects *netmeta* model was used to control for the effect of multiarm trials.

Results from the primary outcome (depressive symptoms severity) were expressed as SMD, and results from the secondary outcome (acceptability) were expressed as RR. The 95% CI were provided whenever possible.

We used the Cochran's Q statistic to determine the pairwise between-study heterogeneity. In addition, τ^2 was calculated to determine the level of variance between studies. We used I^2 to evaluate the percentage of variance caused by between-study heterogeneity. It was assumed that heterogeneity was common across the entire network.

We assessed the transitivity in the network by a visual inspection of study characteristics: mode participant age (≥60 or <60), mode proportion of women (≥50% or <50%), mean intervention duration and mode depression scale used.[31 32] We performed meta-regression analyses within comparisons to assess the potential influence of the study characteristics on the effect sizes.[31] We measured inconsistency in the network with local and global approaches using *netsplit* and *decomp.design* functions, respectively. The former was used to assess inconsistency between direct and indirect evidence within each comparison; the latter was used to assess inconsistency between comparisons. We presumed that every participant fitting our eligibility criteria could potentially be randomised to any of the treatments compared. We used the P-score proposed by Rücker and Schwarzer to rank the treatments within the network.[33]

Owing to an insufficient number of studies in each comparison group, subgroup and meta-regression analyses, as well as the assessment of publication bias, could not be performed to explore potential sources of heterogeneity across the network. Sensitivity analyses were performed by excluding studies with high indirectness and risk of bias, studies with participants older than 60, studies with interventions longer than 12 weeks and studies that used an attention/active or passive control comparison.

RESULTS

The literature search identified 23 209 potential studies. After exclusion of studies by title and abstract, 329 full-text records were screened and 21 were included in the main analysis (online supplemental material efigure 1). All studies were written in English.

Study characteristics

Overall, 2551 participants in 25 pairwise comparisons were assigned to one of the three treatments and control groups (figure 1). The comparison studies included: antidepressants versus controls (n=11), exercise versus controls (n=6), combined treatments versus antidepressants (n=4) and combined treatments versus exercise (n=1). Three studies provided direct evidence on the comparative effects of antidepressants and exercise. Control interventions included placebo (n=11), attention control (n=2), stretching (n=2), no intervention (n=1) and wait-list (n=1). We visually assessed the distribution of study characteristics across direct comparisons (table 1, online supplemental material etable 1). Participant age, the proportion of women and the outcome measure used were balanced across comparisons. The duration of the intervention differed among comparisons, with the exercise versus antidepressants comparison having the mean longest intervention (19 weeks), and the antidepressants versus control comparison having the shortest (9 weeks). Nonetheless, meta-regression analyses suggest that none of the study characteristics influenced the treatment effect (online supplemental material etable 2). Overall, we considered the assumption of transitivity to be valid.

Risk of bias was determined to be low in 5 studies, moderate in 15 studies and high in 1 study (online supplemental material etable 3). Most of the network evidence relied on moderate risk of bias and low-moderate indirectness (online supplemental material efigure 2, 3 and online supplemental material etable 4). The confidence in the network was moderate-to-high for all comparisons of interest (online supplemental material etable 5).

Depressive symptoms severity

At the end of the interventions, exercise (SMD, −0.45; 95% CI −0.67 to −0.23), antidepressants (SMD, −0.33; 95% CI −0.48 to −0.19) and combined treatments (SMD, −0.45; 95% CI −0.76 to −0.14) were superior in reducing depressive symptoms compared with controls (table 2). There were no differences among the main treatments. Exercise had a similar beneficial effect to that of antidepressants (SMD, −0.12; 95% CI −0.33 to 0.10), and the effect of combined treatments was similar to the effect of exercise (SMD, 0.00; 95% CI −0.33 to 0.33) and antidepressants (SMD, −0.12; 95% CI −0.40 to 0.16) alone. The ranking of treatments based on the P-score is reported in online supplemental material etable 6.

The network meta-analysis showed that there was moderate heterogeneity (τ^2=0.03; I^2=46.2%), which was mostly caused by the comparison of exercise versus control (Q=15.80; df=4; p=0.003). All other comparisons showed no evidence of heterogeneity. Inconsistency was assessed both within and between comparisons. There was no evidence of inconsistency within any of the comparisons of interest (online supplemental material etable 7). Similarly, no inconsistency between comparisons was observed (Q=5.62, df=5, p=0.34).

The pairwise meta-analysis supported the findings of the network meta-analysis, with both exercise (SMD, −0.58; 95% CI −1.14 to −0.01) and antidepressants (SMD, −0.33;

Table 1 Characteristics of the included studies

Study	Mean age (SD)	Gender (M/F)	Baseline score (SD)	Depression scale	Intervention	Duration (weeks)
Bjerkenstedt, 2005*	50 (12)	23M 86F	24.5 (4)	HAM-D	Fluoxetine Placebo	4
Blumenthal *et al.* 1999† ‡ §	57 (7)	43M 113F	17.9 (7.2)	HAM-D	Exercise Sertraline Aerobic exercise + sertraline	16
Blumenthal *et al.* 2007* ¶ †	52 (8)	35M 114F	17 (4)	HAM-D	Exercise Sertraline Placebo	16
Danielsson, 2014‡	46 (14)	10M 32F	24 (4.6)	MADRS	Exercise + antidepressants Antidepressants + advice	10
Detke, 2002*	41 (14)	83M 184F	20.4 (3.4)	HAM-D	Duloxetine Placebo	9
Detke, 2004*	45 (12)	47M 139F	20.1 (3.5)	HAM-D	Duloxetine Placebo	8
Dunn, 2005¶	34 (7)	9M 21F	19.8 (2.1)	HAM-D	Exercise Stretching	12
Fava, 2005*	37 (11)	37M 53F	19.7 (3.2)	HAM-D	Fluoxetine Placebo	12
Gastpar, 2006*	49 (12)	80M 177F	21.9 (1.2)	HAM-D	Citalopram Placebo	6
Goldstein, 2004*	41 (13)	67M 113F	17.6 (4.9)	HAM-D	Duloxetine Placebo	8
Hemat-Far, 2012¶	18–25	20F	24.4 (5)	BDI	Exercise No-treatment	8
Hidalgo *et al.* 2021†	> 65	67M 246F	15.5 (4.3)	MADRS	Exercise Antidepressants	24
Krogh, 2012¶	42 (11)	38M 77F	18.9 (4.4)	HAM-D	Exercise Stretching	12
Mao, 2015*	44 (15)	19M 18F	15 (3)	HAM-D	Sertraline Placebo	12
Mather, 2002‡	65 (NA)	27M 59F	17.2 (6.5)	HAM-D	Exercise + antidepressants Antidepressants + attention control	10
McNeil, 1991¶	NA	20 M/F	15.9 (2.8)	BDI	Exercise Wait-list	6
Moreno, 2006*	41 (11)	8M 38F	16.1 (4.8)	HAM-D	Fluoxetine Placebo	8
Perahia, 2006*	45 (11)	60 142F	21 (4.1)	HAM-D	Duloxetine Placebo	8
Philipp, 1999*	46 (12)	40M 117F	22.5 (4.1)	HAM-D	Imipramine Placebo	8
Sadeghi, 2016¶	21 (1)	24M 6F	22.9 (4.2)	BDI-II	Exercise Attention control	8
Siqueira, 2016‡	39 (11)	16M 41F	19.8 (3.1)	HAM-D	Exercise + sertraline Sertraline	4

*Included in the antidepressants versus control pairwise comparison.
†Included in the exercise versus antidepressants comparison.
‡Included in the exercise plus antidepressants versus antidepressants comparison.
§Included in the exercise plus antidepressants versus exercise comparison.
¶Included in the exercise versus control pairwise comparison.
BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not applicable.

Table 2 Results on the comparative effectiveness of the interventions from the network and pairwise meta-analyses

Combination	0.18 (−0.20 to 0.55) (N=1; I^2=NA*)	−0.13 (−0.63 to 0.36) (N=4, I^2=41%)	NA†
−0.00 (−0.33 to 0.33) (N=21; I^2=46%)	**Exercise**	−0.08 (−0.29 to 0.12) (N=3; I^2=0%)	−0.58 (−1.14 to −0.01) (N=6; I^2=69%)
−0.12 (−0.40 to 0.16) (N=21; I^2=46%)	−0.12 (−0.33 to 0.10) (N=21; I^2=46%)	**Antidepressants**	−0.33 (−0.49 to −0.16) (N=11; I^2=38%)
−0.45 (−0.76 to −0.14) (N=21; I^2=46%)	−0.45 (−0.67 to −0.23) (N=21; I^2=46%)	−0.33 (−0.48 to −0.19) (N=21; I^2=46%)	**Control**

Results of the network meta-analyses are presented in grey and results of the pairwise meta-analyses are presented in white. Estimates are displayed as column versus row for the network meta-analyses and row versus column for the pairwise meta-analyses. Results are expressed as standardised mean differences (SMD). A negative SMD indicates a superiority of the first treatment over the comparison treatment.
*No evidence on I^2 is available as there was only one study for that comparison.
†No studies compared combination treatment versus no treatment.
N, number of studies in the comparison; NA, not available.

95% CI −0.49 to −0.16) showing greater improvements over the controls. The comparison of exercise and antidepressants showed no evidence of the superiority of one treatment over the other (SMD, −0.08; 95% CI −0.29 to 0.12). Similarly, there was no evidence of the superiority of combined treatments over exercise (SMD, 0.18; 95% CI −0.20 to 0.55) and antidepressants (SMD, −0.13; 95% CI −0.63 to 0.36) alone (online supplemental eappendix 3).

Sensitivity analyses confirmed the robustness of the results (online supplemental material etable 8).

Acceptability

Four studies were excluded from the secondary outcome analyses as they failed to report the drop-out rate in the intervention groups and data could not be extracted from the text or

Table 3 Results on the comparative acceptability of the interventions from the network and pairwise meta-analyses

Combination	0.76 (0.38 to 1.52) (N=1; I^2=NA*)	1.03 (0.40 to 2.65) (N=3, I^2=0%)	NA†
0.75 (0.47 to 1.21) (N=17; I^2=0%)	**Exercise**	1.40 (1.13 to 1.72) (N=3; I^2=0%)	0.84 (0.27 to 2.58) (N=3; I^2=14%)
0.99 (0.62 to 1.57) (N=17; I^2=0%)	1.31 (1.09 to 1.57) (N=17; I^2=0%)	**Antidepressants**	0.97 (0.84 to 1.13) (N=11; I^2=0%)
0.97 (0.60 to 1.58) (N=17; I^2=0%)	1.29 (1.03 to 1.61) (N=17; I^2=0%)	0.98 (0.84 to 1.15) (N=17; I^2=0%)	**Control**

Results of the network meta-analyses are presented in grey and results of the pairwise meta-analyses are presented in white. Estimates are displayed as column versus row for the network meta-analyses and row versus column for the pairwise meta-analyses. Results are expressed as risk ratios (RRs). RRs that are smaller than one indicate a superiority of the first treatment over the comparison treatment.
*No evidence on I^2 is available as there was only one study for that comparison.
†No studies compared combination treatment versus no treatment.
N, number of studies in the comparison; NA, not available.

there were no drop-outs in any of the interventions of interest. Drop-out rates in the exercise group were greater than in the antidepressant group (RR 1.31; 95% CI 1.09 to 1.57) and control group (RR 1.29; 95% CI 1.03 to 1.61) across all studies (table 3). No other differences were observed among the interventions.

The pairwise meta-analyses were in line with the results of the network analysis, as the drop-out rates were higher in the exercise group than in the antidepressant group (RR 1.40; 95% CI 1.13 to 1.72). There was no evidence of heterogeneity among pairwise comparisons (table 3, online supplemental eappendix 3).

DISCUSSION

This is the first network meta-analysis to comparatively assess the effectiveness of exercise, antidepressants and combined treatments on depressive symptoms in adults with non-severe depression. Results showed that all treatments had similar beneficial effects on depressive symptoms when compared with the controls, but no treatment was superior to another. Assessment of acceptability showed that antidepressant treatments induced fewer intervention drop-outs than exercise.

Our findings align with the recommendations provided by European, Canadian, Australian and UK treatment guidelines supporting the use of exercise as an alternative treatment for non-severe depression.[19–22] These guidelines recommend exercise programmes consisting of 30–60 min sessions at moderate intensity performed 2–3 times weekly for 9–12 weeks, and delivered in groups by a competent practitioner. This is in contrast with the DSM-5 guidelines, which only suggest exercise therapy to people who are unresponsive to antidepressant or psychotherapy treatment, but not as a first-line option.[6] Importantly, they do not categorise depression by severity of symptoms, but rather offer treatment advice based on several reviews that met quality criteria. All the included reviews used in their assessment, except one, exclusively focused on psychotherapy or pharmacotherapy treatments. Gartlehner *et al*[34] compared pharmacological versus non-pharmacological treatments, but only direct evidence was analysed. This resulted in the inclusion of two exercise studies and with the conclusion that there was insufficient evidence to promote exercise as a depression treatment. In this study, we gathered direct and indirect evidence and found no differences in treatment effectiveness between exercise and antidepressants.

Combination treatment did not demonstrate greater beneficial effects on depressive symptoms compared with either treatment alone, probably due to the limited number of studies included in our analyses. The effects of the combination of exercise and pharmacotherapy on depression remains largely unclear. Although some studies have attempted to explain the possible synergism between the two interventions,[35] evidence of their combined effectiveness against pharmacological treatment alone is still inconclusive.[36 37] Our findings do not support the synergistic effects of exercise and antidepressants; however, considering the various health benefits of physical exercise, using exercise as an adjunctive treatment to pharmacotherapy may counterbalance the side effects that are often associated with antidepressant use and promote a faster recovery.

Exercise interventions induced greater drop-outs than antidepressant treatments, although only one study reported a substantial difference in drop-out rates between the two interventions. In this study, 58% and 40% of participants withdrew from the exercise and antidepressant groups, respectively.[38] This is considerably higher than what reported in the two other trials directly comparing exercise and antidepressants, where drop-out rates ranged from 14% to 26%.[39 40] Despite the greater drop-out rates in the exercise group, the proportion of participants with adverse events was greater in the antidepressant group, with 22% reporting adverse events compared with 9% in the exercise group. In our study, we used overall drop-out as a measure of treatment acceptability. It is possible that an analysis of drop-out due to adverse events alone would have led to different results. Clearly, both interventions have limitations in securing treatment adherence. Exercise is physically demanding and harder to implement in comparison to standard pharmacological treatments. On the other hand, antidepressant treatments are associated with greater adverse effects, higher costs and social stigma.[14] Although both interventions can effectively alleviate depressive symptoms, different strategies must be adopted to enhance treatment adherence in depressed individuals. Further research needs to address this topic, possibly differentiating between treatment satisfaction, adverse events and overall study withdrawal.

In the current review, evidence from studies that compared exercise and/or antidepressants to each other or to a control comparison was gathered. To our own surprise, only 6 and 11 studies comparing exercise and antidepressants to control were found, respectively. Several exercise studies were excluded because they did not include participants with a clinical diagnosis of depression, or because some but not all of participants randomised were taking antidepressants, thereby confounding the true effect of exercise. Most of the antidepressant studies were excluded because participants reported levels of depression that are indicative of moderate-to-severe depression. This was also reflected in a comprehensive network meta-analysis by Cipriani *et al*,[41] who analysed over 500 antidepressant studies and found that 89% only recruited participants with moderate-to-severe symptoms (mean Hamilton Rating Scale score of 25.7). Compared with Cipriani *et al*, our study had tighter inclusion criteria to ensure that the transitivity assumption was not violated. This led to the exclusion of several antidepressant studies in mild-to-moderate depression. Overall, there is an imbalance between the proportion of studies assessing treatment effectiveness in mild-to-moderate depression and those focusing on severe depression. This imbalance has been suggested to be partly caused by the inclusion criteria used for FDA-funded trials, where higher cut-off scores are imposed at baseline to increase the sensitivity of the antidepressant versus placebo comparison.[8] We hope that the current study will contribute to highlight the clinical importance of non-severe depression, and that more clinical trials on non-severe depression can be conducted in the future.

Limitations

There were some limitations in this study. First, the overall low number of studies available for each comparison precluded us to explore potential sources of heterogeneity and publication bias,

and may have generated inaccurate estimates of between-study heterogeneity. This limited the interpretation of our findings, which need to be corroborated by further research. Second, the control groups in all comparisons were combined into a single node. While all antidepressant studies used a placebo comparison, exercise studies used various types of control. This might have contributed to the heterogeneity detected in the exercise-control comparison. Although our sensitivity analyses found no considerable changes in study effects after excluding studies with an active or passive control comparison, the effect of exercise might have been overestimated and needs to be validated by additional high-quality studies. Similarly, we combined exercise, antidepressant and combination treatments into their respective nodes without accounting for differences within interventions. This method was chosen because previous network meta-analyses showed little heterogeneity among antidepressant[41] and exercise[42] interventions. Yet, antidepressant studies can vary by type, dose and duration of antidepressant used, whereas exercise studies can vary by type, frequency, intensity and duration of the training sessions. These differences might have affected the overall heterogeneity of the network. Third, this study examined the comparative effectiveness of exercise and antidepressants in mild-to-moderate depression, but did not explore the potential benefits of exercise in individuals with more severe symptoms. This limited the interpretation of our findings, which cannot be extended to all depressed patients.

CONCLUSION

The meta-analytical evidence gathered through direct and indirect comparisons found no differences in treatment effectiveness between exercise, antidepressants and their combination. These findings support the use of exercise interventions as an alternative treatment option for non-severe depression. Results were corroborated through stringent sensitivity analyses that accounted for the quality of studies as well as types of participants and interventions. Further trials directly comparing the individual and synergistic action of exercise and antidepressants are warranted to corroborate the findings of this study.

Correction notice This article has been corrected since it published Online First. The footnotes in tables 2 and 3 have been amended.

Contributors All authors had full access to the data in the study and agreed to the decision to submit for publication. FR, CL and PS accessed and verified the data in this study. FR, CL and EC conducted the database search and data extraction. FR, DM and CPWC conducted the data analysis. All authors interpreted the data and wrote and edited the manuscript.

Funding This work was supported by Health and Medical Research Fund (17182461) of Food and Health Bureau, Hong Kong SAR Government and the Seed Fund for Basic Research of The University of Hong Kong.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Parco M Siu http://orcid.org/0000-0002-3548-5058

REFERENCES

1 World Health Organization. *Depression and other common mental disorders: global health estimates*. Geneva: World Health Organization, 2017.
2 Kessler RC. The costs of depression. *Psychiatr Clin North Am* 2012;35:1–14.
3 Chisholm D, Sweeny K, Sheehan P, *et al*. Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry* 2016;3:415–24.
4 Hasin DS, Sarvet AL, Meyers JL, *et al*. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 2018;75:336–46.
5 Weissman MM, Bland RC, Canino GJ, *et al*. Cross-national epidemiology of major depression and bipolar disorder. *JAMA* 1996;276:293–9.
6 American Psychological Association. Clinical practice guideline for the treatment of depression across three age cohorts. Guideline development panel for the treatment of depressive disorders, 2019. Available: https://www.apa.org/depression-guideline/guideline.pdf
7 Ioannidis JPA. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? *Philos Ethics Humanit Med* 2008;3:14.
8 Fournier JC, DeRubeis RJ, Hollon SD, *et al*. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 2010;303:47–53.
9 Kirsch I, Deacon BJ, Huedo-Medina TB, *et al*. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the food and drug administration. *PLoS Med* 2008;5:e45.
10 Khan A, Leventhal RM, Khan SR, *et al*. Severity of depression and response to antidepressants and placebo: an analysis of the food and drug administration database. *J Clin Psychopharmacol* 2002;22:40–5.
11 Jakobsen JC, Gluud C, Kirsch I. Should antidepressants be used for major depressive disorder? *BMJ Evid Based Med* 2020;25:130.
12 Shim RS, Baltrus P, Ye J, *et al*. Prevalence, treatment, and control of depressive symptoms in the United States: results from the National health and nutrition examination survey (NHANES), 2005-2008. *J Am Board Fam Med* 2011;24:33–8.
13 Zimmerman M, Posternak MA, Chelminski I. Symptom severity and exclusion from antidepressant efficacy trials. *J Clin Psychopharmacol* 2002;22:610–4.
14 Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? *Innov Clin Neurosci* 2012;9:41–6.
15 Andrade LH, Alonso J, Mneimneh Z, *et al*. Barriers to mental health treatment: results from the who world mental health surveys. *Psychol Med* 2014;44:1–15.
16 Cipriani A, Barbui C, Butler R, *et al*. Depression in adults: drug and physical treatments. *BMJ Clin Evid* 2011;2011:1003.
17 Opie RS, Jacka FN, Marx W, *et al*. Designing lifestyle interventions for common mental disorders: what can we learn from diabetes prevention programs? *Nutrients* 2021;13. doi:10.3390/nu13113766. [Epub ahead of print: 25 Oct 2021].
18 Sarris J, O'Neil A, Coulson CE, *et al*. Lifestyle medicine for depression. *BMC Psychiatry* 2014;14:107.
19 Stubbs B, Vancampfort D, Hallgren M, *et al*. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and position statement from the European psychiatric association (EPA), supported by the International organization of physical therapists in mental health (IOPTMH). *Eur Psychiatry* 2018;54:124–44.
20 Ravindran AV, Balneaves LG, Faulkner G, *et al*. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 5. complementary and alternative medicine treatments. *Can J Psychiatry* 2016;61:576–87.
21 Malhi GS, Bassett D, Boyce P, *et al*. Royal Australian and New Zealand college of psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* 2015;49:1087–206.
22 National Institute for Health and Clinical Excellence. Depression in adults: treatment and management NICE; 2022.
23 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
24 American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*. Lippincott Williams & Wilkins, 2000.
25 Gartlehner GHR, Reichenpfader U, Kaminski A. Drug class review: second-generation antidepressants. update 5; 2011.
26 Higgins JPT TJ, Chandler J, Cumpston M, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020)*, 2020.
27 Furukawa TA, Barbui C, Cipriani A, *et al*. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006;59:7–10.
28 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

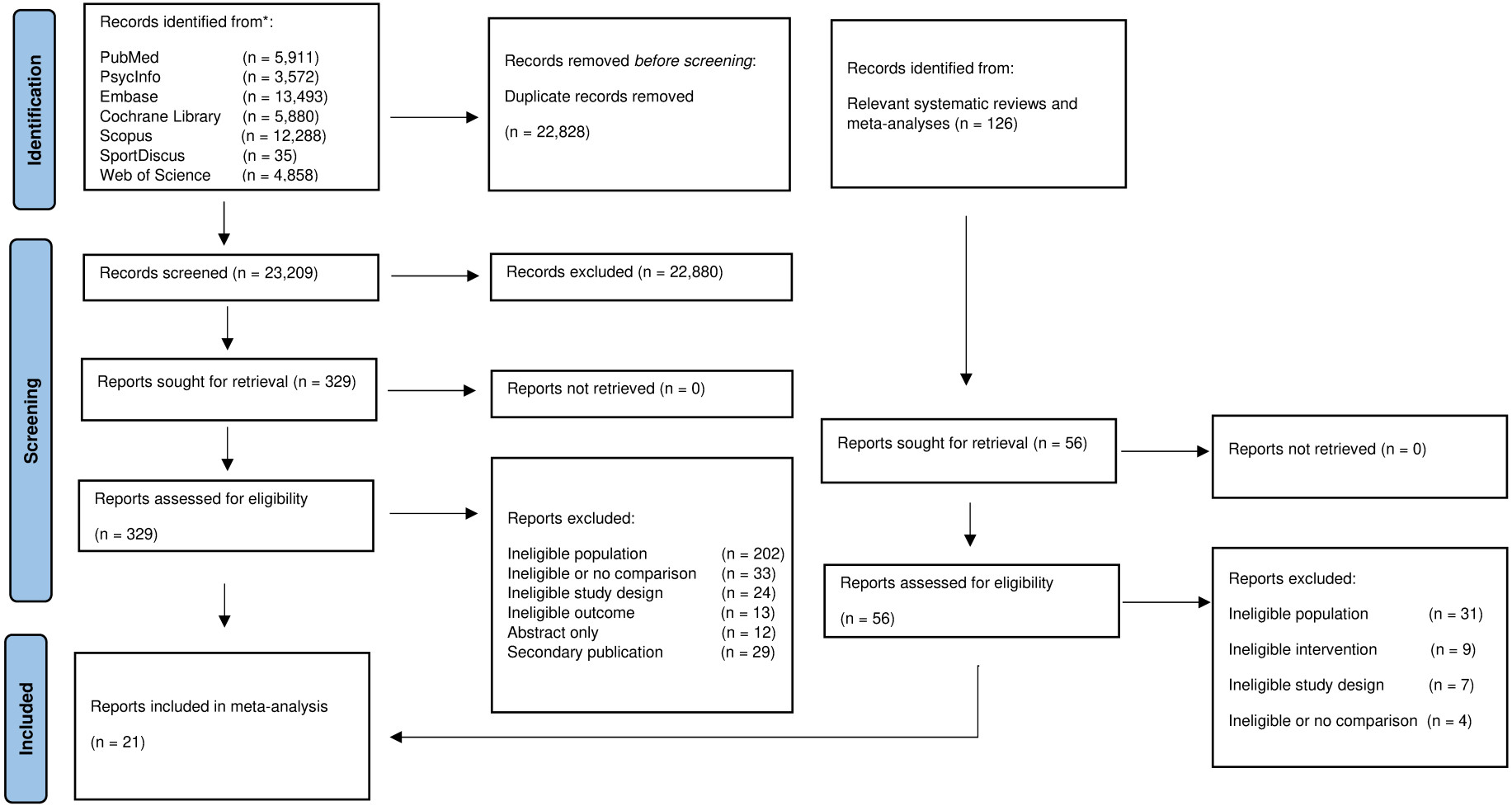
29 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.
30 IntHout J, Ioannidis JPA, Borm GF. The hartung-knapp-sidik-jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-laird method. *BMC Med Res Methodol* 2014;14:25.
31 Ho EK-Y, Chen L, Simic M, *et al*. Psychological interventions for chronic, non-specific low back pain: systematic review with network meta-analysis. *BMJ* 2022;376:e067718.
32 Watt JA, Goodarzi Z, Veroniki AA, *et al*. Comparative efficacy of interventions for reducing symptoms of depression in people with dementia: systematic review and network meta-analysis. *BMJ* 2021;372:n532.
33 Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;15:58.
34 Gartlehner G, Gaynes BN, Amick HR, *et al*. Comparative benefits and harms of antidepressant, psychological, complementary, and exercise treatments for major depression: an evidence report for a clinical practice guideline from the American College of physicians. *Ann Intern Med* 2016;164:331–41.
35 Guerrera CS, Furneri G, Grasso M, *et al*. Antidepressant drugs and physical activity: a possible synergism in the treatment of major depression? *Front Psychol* 2020;11:857.
36 Mura G, Moro MF, Patten SB, *et al*. Exercise as an add-on strategy for the treatment of major depressive disorder: a systematic review. *CNS Spectr* 2014;19:496–508.
37 Kvam S, Kleppe CL, Nordhus IH, *et al*. Exercise as a treatment for depression: a meta-analysis. *J Affect Disord* 2016;202:67–86.
38 Hidalgo JL-T, Sotos JR, DEP-EXERCISE Group. Effectiveness of physical exercise in older adults with mild to moderate depression. *Ann Fam Med* 2021;19:302–9.
39 Blumenthal JA, Babyak MA, Doraiswamy PM, *et al*. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med* 2007;69:587–96.
40 Blumenthal JA, Babyak MA, Moore KA, *et al*. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;159:2349–56.
41 Cipriani A, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet* 2018;391:1357–66.
42 Brupbacher G, Gerger H, Zander-Schellenberg T, *et al*. The effects of exercise on sleep in unipolar depression: a systematic review and network meta-analysis. *Sleep Med Rev* 2021;59:101452.

Comparative effectiveness of exercise, antidepressants, and their combination in treating non-severe depression: A systematic review and network meta-analysis of randomized controlled trials

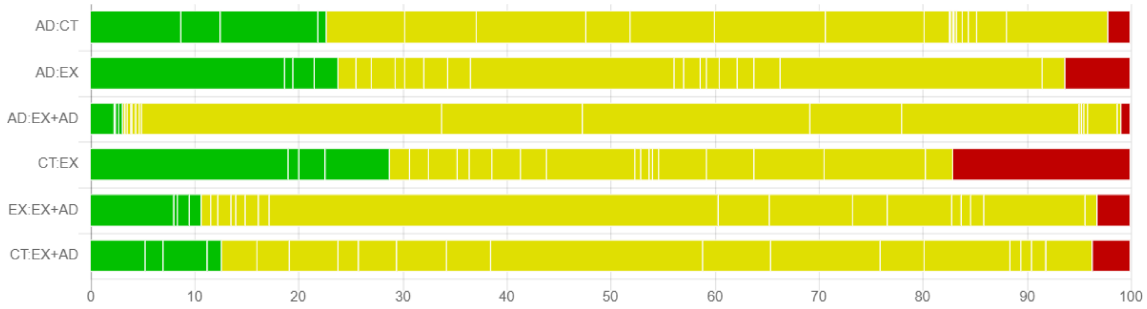
Supplementary Online Content

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

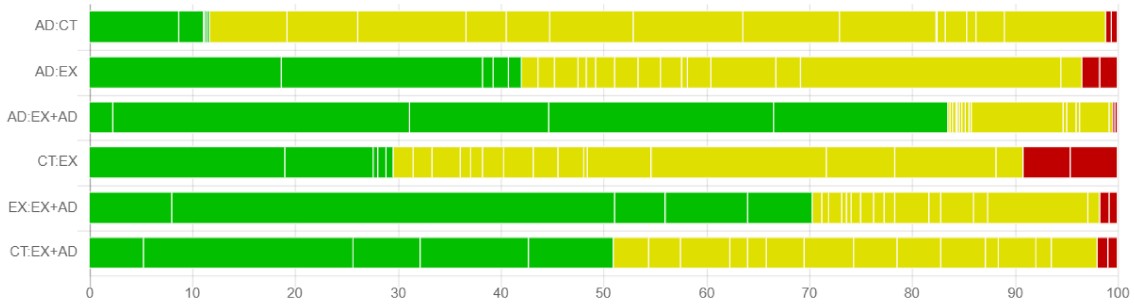
eFigure 1. PRISMA flow chart



eFigure 2. Risk of bias contributions



eFigure 3. Indirectness contributions



eTable 1. Distribution of study characteristics

Comparison	N studies	Participant age (years)	Sex (% women)	Intervention duration (weeks)	Outcome measure
EX:AD	3	< 60	≥ 50%	19	HAM-D
AD:CT	11	< 60	≥ 50%	9	HAM-D
EX:CT	6	< 60	≥ 50%	10	HAM-D
EX+AD:AD	4	< 60	≥ 50%	11	HAM-D
EX+AD:EX	1	< 60	≥ 50%	16	HAM-D

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

eTable 2. Meta-regression for direct comparisons

Comparison[a]	N	Coefficient [95% CI]	SE	P value
EX:AD	3			
- Mean age		-0.00 [-0.16 to 0.16]	0.01	0.94
- Mean duration		-0.01 [-0.21 to 0.20]	0.02	0.75
- Proportion of women		-0.02 [-0.39 to 0.36]	0.03	0.67
- Outcome measure		-0.05 [-1.68 to 1.58]	0.13	0.75
AD:CT	11			
- Mean age		0.01 [-0.03 to 0.05]	0.02	0.70
- Mean duration		0.02 [-0.03 to 0.08]	0.02	0.35
- Proportion of women		-0.01 [-0.03 to 0.01]	0.01	0.40
- Outcome measure[b]		NA	NA	NA
EX:CT	6			
- Mean age		0.03 [-0.03 to 0.08]	0.02	0.20
- Mean duration		0.08 [-0.08 to 0.25]	0.06	0.22
- Proportion of women		0.00 [-0.04 to 0.04]	0.01	0.92
- Outcome measure		0.63 [-0.48 to 1.74]	0.40	0.19
EX+AD:AD	4			
- Mean age		0.01 [-0.06 to 0.09]	0.02	0.54
- Mean duration		0.04 [-0.09 to 0.18]	0.03	0.28
- Proportion of women		-0.05 [-0.36 to 0.27]	0.07	0.58
- Outcome measure		-0.49 [-2.03 to 1.06]	0.36	0.31

[a]Meta-regression for the EX+AD:EX comparison could not be performed because only one study was available for that comparison

[b]Meta-regression for this categorical outcome could not be performed because all studies within this comparison used the same outcome measure

eTable 3. Risk of bias for all studies

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	RoB
Bjerkenstedt et al., 2004	Low	Low	Low	Low	Some concerns	Some concerns
Blumenthal et al., 1999	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Blumenthal et al., 2007	Low	Low	Low	Low	Low	Low
Danielsson et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Detke et al., 2002	Some concerns	Low	Low	Low	Low	Some concerns
Detke et al., 2004	Some concerns	Low	Low	Low	Low	Some concerns
Dunn et al., 2005	Low	Low	Low	Low	Low	Low
Fava et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gastpar et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Goldstein et al., 2004	Low	Low	Low	Low	Low	Low
Hemat-Far et al., 2012	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Hidalgo et al., 2021	Some concerns	Low	Low	Some concerns	Low	Some concerns
Krogh et al., 2012	Some concerns	High	Low	Low	Low	High
Mao et al., 2015	Low	Low	Low	Low	Low	Low
Mather et al., 2002	Low	Some concerns	Low	Low	Some concerns	Some concerns
McNeil et al., 1991	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Moreno et al., 2005	Low	Low	Low	Low	Low	Low
Perahia et al., 2006	Some concerns	Low	Low	Low	Low	Some concerns
Philipp et al., 1999	Some concerns	Low	Low	Low	Some concerns	Some concerns
Sadeghi et al., 2016	Some concerns	Low	Some concerns	Low	Low	Some concerns
Siqueira et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns

eTable 4. Indirectness for all studies

Author	Population		Intervention		Outcome		Comparisons	Indirectness
Bjerkenstedt et al., 2005	Low		Low		Low		High	Moderate
Blumenthal et al., 1999	Low		Low		Low		Low	Low
Blumenthal et al., 2007	Low		Low		Low		Low	Low
Danielsson et al., 2014	Low		Low		Low		Low	Low
Detke et al., 2002	Low		Low		Low		High	Moderate
Detke et al., 2004	Low		Low		Low		High	Moderate
Dunn et al., 2005	Low		Low		Low		High	Moderate
Fava et al., 2005	Low		Low		Low		High	Moderate
Gastpar et al., 2006	Low		Low		Low		High	Moderate
Goldstein et al., 2004	Low		Low		Low		High	Moderate
Hemat-Far et al., 2012	High	Female students	Low		Moderate	Self-reported questionnaire	High	High
Hidalgo et al. 2021	High	Elderly	Low		Low		Low	Moderate
Krogh et al., 2012	Low		Low		Low		High	Moderate
Mao et al., 2015	Low		Low		Low		High	Moderate
Mather et al., 2002	Low		Low		Low		Low	Low
McNeil et al., 1991	High	Elderly	Moderate	Somewhat different	Moderate	Self-reported questionnaire	High	High
Moreno et al., 2006	Low		Low		Low		High	Moderate
Perahia et al., 2006	Low		Low		Low		High	Moderate
Philipp et al., 1999	Low		Low		Low		High	Moderate
Sadeghi et al., 2016	Low		Low		Moderate	Self-reported questionnaire	High	Moderate
Siqueira et al., 2016	Low		Low		Low		Low	Low

eTable 5. Confidence in Network Meta-analysis (CINeMA) final report

Comparison	N	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AD:CT	10	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
AD:EX	2	Some concerns	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Moderate
EX+AD:AD	5	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	High
EX:CT	6	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
EX+AD:EX	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
EX+AD:CT	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	High

eTable 6. Treatment ranking based on the P-score

Treatment	P-score
EX	0.7865
EX+AD	0.7639
AD	0.4489
CT	0.0008

eTable 7. Assessment of inconsistency within comparisons

Comparison	k	Direct	Indirect	Difference	z	P-value
AD:CT	11	-0.33	-0.38	0.05	0.22	0.83
AD:EX	3	0.07	0.19	-0.12	-0.52	0.60
EX+AD:AD	4	0.12	0.09	0.03	0.06	0.95
EX:CT	6	-0.43	-0.48	0.05	0.21	0.83
EX+AD:CT	0	NA	-0.45	NA	NA	NA
EX+AD:EX	1	-0.18	0.12	-0.30	-0.89	0.38

AD: Antidepressants; CT: Control; EX: Exercise; NA: Not available

eTable 8. Sensitivity analyses

Reasons for exclusion	N	EX-AD	Comb-AD	Comb-EX	Comb-CT	EX-CT	AD-CT	I^2
All included	21	-.12 (-.33 to .10)	-.12 (-.40 to .16)	-.00 (-.33 to .33)	-.45 (-.76 to -.14)	-.45 (-.67 to -.23)	-.33 (-.48 to -.19)	46.2%
Participants older than 60	19	-.10 (-.37 to .16)	-.12 (-.41 to .17)	-.02 (-.37 to .34)	-.44 (-.76 to -.12)	-.43 (-.69 to -.17)	-.33 (-.48 to -.18)	49.0%
High Risk of Bias	20	-.20 (-.40 to .00)	-.13 (-.38 to .13)	.07 (-.23 to .37)	-.48 (-.77 to -.20)	-.56 (-.77 to -.34)	-.36 (-.49 to -.23)	31.0%
High Indirectness	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%
Intervention longer than 12 weeks	18	-.18 (-.58 to .21)	-.29 (-.67 to .09)	-.11 (-.65 to .44)	-.63 (-1.05 to -.22)	-.53 (-.88 to -.17)	-.35 (-.52 to -.17)	52.5%
SD imputed	16	-.17 (-.42 to .09)	-.14 (-.45 to .18)	-.03 (-.34 to .40)	-.41 (-.78 to -.04)	-.44 (-.70 to 0.19)	-.28 (-.50 to .05)	50.4%
Attention/active control comparison	17	-.14 (-.35 to .07)	-.09 (-.39 to .21)	-.05 (-.28 to .38)	-.44 (-.76 to -.11)	-.48 (-.71 to -.25)	-.34 (-.47 to -.22)	32.6%
Passive control comparison	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

eAppendix 1. Search strategy

PubMed

Search	Query
#1	Bupropion[MeSH Terms] OR bupropion[Title/Abstract] OR 34911-55-2[EC/RN Number]
#2	Citalopram[MeSH Terms] OR citalopram[Title/Abstract] OR 59729-33-8[EC/RN Number]
#3	escitalopram[Title/Abstract] OR 128196-01-0[EC/RN Number]
#4	desvenlafaxine[Title/Abstract] OR 386750-22-7[EC/RN Number]
#5	Fluoxetine[MeSH Terms] OR fluoxetine[Title/Abstract] OR 54910-89-3[EC/RN Number]
#6	Fluvoxamine[MeSH Terms] OR fluvoxamine[Title/Abstract] OR 54739-18-3[EC/RN Number]
#7	Milnacipran[Supplementary Concept] OR milnacipran[Title/Abstract] OR levomilnacipran[Title/Abstract]
#8	Mirtazapine[Supplementary Concept] OR mirtazapine[Title/Abstract] OR 4685R51V7M[EC/RN Number]
#9	Nefazodone[Supplementary Concept] OR nefazodone[Title/Abstract]
#10	Paroxetine[MeSH Terms] OR paroxetine[Title/Abstract] OR 61869-08-7[EC/RN Number]
#11	Sertraline[MeSH Terms] OR sertraline[Title/Abstract] OR 79617-96-2[EC/RN Number]
#12	Trazodone[MeSH Terms] OR trazodone[Title/Abstract] OR 19794-93-5[EC/RN Number]
#13	venlafaxine[Title/Abstract] OR 99300-78-4[EC/RN Number]
#14	vilazodone[Title/Abstract] OR 163521-08-2[EC/RN Number]
#15	Vortioxetine[Supplementary Concept] OR vortioxetine[Title/Abstract] OR TKS641KOAY[EC/RN Number]
#16	duloxetine[Title/Abstract] OR 116539-58-3[EC/RN Number]
#17	Antidepressive Agents, Second Generation[MeSH Terms] OR Antidepressive Agents, Second-Generation[Pharmacological Action] OR antidepress*[Title/Abstract]
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	Depression, unipolar[MeSH Terms] OR Depressive disorders[MeSH Terms] OR depress*[Title/Abstract]
#20	Randomized controlled trial[MeSH Terms] OR Random allocation[MeSH Terms] OR (random*[Title/Abstract] AND (control*[Title/Abstract] OR placebo[Title/Abstract]))
#21	#18 AND #19 AND #20
#22	Exercise[MeSH Terms] OR exercise[Title/Abstract] OR "physical activity"[Title/Abstract] OR aerobic[Title/Abstract] OR training[Title/Abstract] OR lift*[Title/Abstract] OR running[Title/Abstract] OR walk*[Title/Abstract] OR jogging[Title/Abstract] OR swim*[Title/Abstract] OR cycl*[Title/Abstract]
#23	#19 AND #20 AND #22
#24	Adults[MeSH Terms] OR adult*[Title/Abstract]
#25	#21 AND #24
#26	#23 AND #24
#27	#25 OR #26
#28	Filters: Chinese, English, Italian, from 1990 - 3000/12/12

PsycInfo

Search	Query
S1	SU(bupropion) OR AB(bupropion) OR TI(bupropion)

S2	SU(citalopram) OR AB(citalopram) OR TI(citalopram)
S3	SU(escitalopram) OR AB(escitalopram) OR TI(escitalopram)
S4	SU(Desvenlafaxine) OR AB(Desvenlafaxine) OR TI(Desvenlafaxine)
S5	SU(Fluoxetine) OR AB(Fluoxetine) OR TI(Fluoxetine)
S6	SU(Fluvoxamine) OR AB(Fluvoxamine) OR TI(Fluvoxamine)
S7	SU(Levomilnacipran) OR AB(Levomilnacipran) OR TI(Levomilnacipran)
S8	SU(mirtazapine) OR AB(mirtazapine) OR TI(mirtazapine)
S9	SU(Nefazodone) OR AB(Nefazodone) OR TI(Nefazodone)
S10	SU(Paroxetine) OR AB(Paroxetine) OR TI(Paroxetine)
S11	SU(Sertraline) OR AB(Sertraline) OR TI(Sertraline)
S12	SU(Trazodone) OR AB(Trazodone) OR TI(Trazodone)
S13	SU(Venlafaxine) OR AB(Venlafaxine) OR TI(Venlafaxine)
S14	SU(vilazodone) OR AB(vilazodone) OR TI(vilazodone)
S15	SU(vortioxetine) OR AB(vortioxetine) OR TI(vortioxetine)
S16	SU(duloxetine) OR AB(duloxetine) OR TI(duloxetine)
S17	SU(Antidepressive Drugs, Second-Generation) OR TI(antidepress*) OR AB(antidepress*)
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S19	SU(depression) OR SU(depressive disorder) OR TI(depress*) OR AB(depress*)
S20	SU(randomized controlled trial) OR SU(randomized clinical trial) OR SU(random allocation) OR TI(random* AND control*) OR AB(random* AND control*) OR TI(random* AND placebo) OR AB(random* AND placebo)
S21	S18 AND S19 AND S20
S22	SU(adults) OR TI(adult*) OR AB(adult*)
S23	S21 AND S22
S24	SU(exercise) OR TI(exercise) OR AB(exercise) OR SU(physical activity) OR TI(aerobic) OR AB(aerobic) OR TI(training) OR AB(training) OR TI(lift*) OR AB(lift*) OR SU(running) OR TI(running) OR AB(running) OR TI(jogging) OR AB(jogging) OR TI(walk*) OR AB(walk*) OR TI(swim*) OR AB(swim*) OR TI(cycl*) OR AB(cycl*)
S25	S19 AND S20 AND S24
S26	S22 AND S25
S27	S23 AND S26
S28	#27 Limit date range 1990-2021 AND Limit language: English, Chinese, Italian

Cochrane Library

ID	**Search**
#1	bupropion:ti,ab,kw OR [mh bupropion]
#2	citalopram:ti,ab,kw OR [mh citalopram]
#3	escitalopram:ti,ab,kw OR [mh escitalopram]
#4	desvenlafaxine:ti,ab,kw OR [mh desvenlafaxine]
#5	duloxetine:ti,ab,kw OR [mh duloxetine]
#6	fluoxetine:ti,ab,kw OR [mh fluoxetine]
#7	fluvoxamine:ti,ab,kw OR [mh fluvoxamine]
#8	Levomilnacipran:ti,ab,kw OR [mh levomilnacipran]
#9	mirtazapine:ti,ab,kw OR [mh mirtazapine]
#10	nefazodone:ti,ab,kw OR [mh nefazodone]
#11	Paroxetine:ti,ab,kw OR [mh paroxetine]
#12	sertraline:ti,ab,kw OR [mh sertraline]
#13	Trazodone:ti,ab,kw OR [mh trazodone]
#14	venlafaxine:ti,ab OR [mh venlafaxine]
#15	vilazodone:ti,ab,kw OR [mh vilazodone]
#16	vortioxetine:ti,ab,kw OR [mh duloxetine]

#17	[mh Antidepressive Agents, Second-Generation] OR antidepress*:ti,ab,kw
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR 11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	[mh Depression] OR [mh Depressive Disorder, Major] OR depress*:ti,ab,kw
#20	[mh Randomized Controlled Trials as Topic] OR [mh Randomized Controlled Trial] OR [mh Random Allocation] OR ("randomized controlled"):ti,ab,kw OR ("controlled clinical"):ti,ab,kw
#21	#18 AND #19 AND #20
#22	[mh Adults] OR adults:ti,ab,kw
#23	#21 AND #22
#24	[mh Exercise] OR [mh "physical activity"] OR exercise:ti,ab,kw OR training:ti,ab,kw OR lift*:ti,ab,kw OR aerobic:ti,ab,kw OR running:ti,ab,kw OR walk*:ti,ab,kw OR jogging:ti,ab,kw OR swim*:ti,ab,kw OR cycl*:ti,ab,kw
#25	#19 AND #20 AND #24
#26	#25 AND #22
#27	#23 OR #26 with Publication Year from 1990 to 2021 AND language: English, Chinese, Italian

Embase

#	Searches
1	exp bupropion/ or bupropion.tn,ab,ti. or 34911 55 2.rn.
2	exp citalopram/ or citalopram.tn,ab,ti. or 59729 33 .rn.
3	exp escitalopram/ or escitalopram.tn,ab,ti. or 128196 01 0.rn.
4	exp desvenlafaxine/ or desvenlafaxine.tn,ab,ti. or 93413 62 8.rn.
5	exp fluoxetine/ or fluoxetine.tn,ab,ti. or 54910 89 3.rn.
6	exp fluvoxamine/ or fluvoxamine.tn,ab,ti. or 54739 18 3.rn.
7	exp milnacipran/ or levomilnacipran.tn,ab,ti. or 96847 54 0.rn.
8	exp mirtazapine/ or mirtazapine.tn,ab,ti. or 85650 52 8.rn.
9	exp nefazodone/ or nefazodone.tn,ab,ti. or 82752 99 6.rn.
10	exp paroxetine/ or paroxetine.tn,ab,ti. or 61869 08 7.rn.
11	exp sertraline/ or sertraline.tn,ab,ti. or 79617 96 2.rn.
12	exp trazodone/ or trazodone.tn,ab,ti. or 19794 93 5.rn.
13	exp venlafaxine/ or venlafaxine.tn,ab,ti. or 93413 69 5.rn.
14	exp vilazodone/ or vilazodone.tn,ab,ti. or 163521 12 8.rn.
15	exp vortioxetine/ or vortioxetine.tn,ab,ti. or 508233 74 7.rn.
16	exp duloxetine/ or duloxetine.tn,ab,ti. or 116539 59 4.rn.
17	exp antidepressant agent/ or antidepress*.ti,ab.
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	exp depression/ or exp major depression/ or depress*.ab,ti,kw.
20	exp randomized controlled trial/ or randomized controlled trial.ab,ti,pt. or randomized placebo trial.ti,ab. or exp randomization/
21	18 and 19 and 20
22	exp exercise/ or exercise.ti,ab. or aerobic.ti,ab. or training.ti,ab. or lift*.ti,ab. or running.ti,ab. or jogging.ti,ab. or walk*.ti,ab. or swim*.ti,ab. or cycl*.ti,ab.
23	19 and 20 and 22
24	exp adults/ or adult*.ti,ab.
25	21 and 24
26	23 and 24
27	25 or 26
28	Limit 27 to yr=1990-Current, English, Chinese, Italian language

Scopus

#	Query
#1	TITLE-ABS-KEY(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR

	paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TITLE-ABS-KEY(depress*)
#3	TITLE-ABS-KEY(randomized controlled trial)
#4	TITLE-ABS-KEY(adult*)
#5	#1 AND #2 AND #3 AND #4
#6	TITLE-ABS-KEY(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#7	#2 AND #3 AND #4 AND #6
#8	#5 OR #7

SportDiscus

Search	Query
S1	(TI(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (AB(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (SU(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*))
S2	SU(depression or depressive disorder or depressive symptoms or major depressive disorder) OR TI depress* OR AB depress*
S3	SU(randomized controlled trials or rtc or randomised control trials) OR TI(random* AND control*) OR AB (random* AND control*)
S4	SU(adults or adult) OR TI adult* OR AB adult*
S5	S1 AND S2 AND S3 AND S4
S6	SU(exercise or physical activity) OR TI(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*) OR AB(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
S7	S2 AND S3 AND S4 AND S6
S8	S5 OR S7

Web of Science

#	Query
#1	TS=(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TS=(depress*)
#3	TS=(random* AND (control* OR placebo))
#4	TS=(adult*)
#5	TS=(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#6	#1 AND #2 AND #3 AND #4
#7	#2 AND #3 AND #4 AND #5
#8	#6 OR #7

eAppendix 2. Additional methodology information

Risk of bias

The Cochrane risk of bias assessment tool (RoB-2) was used to determine the quality of the individual studies.[1] Bias was assessed in the following domains: 1) randomization process, 2) deviations from the intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported results. Each domain was assessed as having either low risk of bias, some concerns, or high risk of bias.

To implement RoB-2, we utilized the Excel template provided in the "Cochrane Handbook for Systematic Reviews of Interventions",[2] which includes "signalling questions" that can be used to assess bias in each domain. Each domain is automatically evaluated by an algorithm based on the signalling questions, as well as subjectively by the author. To avoid the influence of personal bias, the assessment of each domain was strictly based on the output of the algorithm.

1. Bias due to the randomization process was rated "low" if the study allocation sequence was reported as random and there was evidence that the allocation sequence was concealed. Allocation concealment was considered adequate if the allocation was carried out by investigators that were external to the project, or if authors used a form of remote or centrally administered method that ensured allocation concealment (e.g., sealed opaque envelopes). If the strategy for allocation concealment was not clearly reported, the domain was rated as having "some concerns". If both categories were deemed to be inadequately described, the domain was rated "high".

2. Bias due to deviations from the intended interventions was based on whether participants and/or study personnel were blinded to participants' assigned intervention, whether there were deviations from the intervention due to the trial context, and whether an appropriate analysis was used to estimate the effect of the intervention. Bias was rated "low" if all categories were rated as low. Following the Cochrane algorithm, if participants or study personnel were aware of participants' allocated intervention but all other categories were considered as low, the domain was still rated as "low". If there were deviations from the interventions that were suspected to affect the outcome, and if these were not balanced between groups, or if an inappropriate statistical analysis was used that was suspected to substantially impact the outcome, the domain was rated "high". Any other combination was rated as having "some concerns".

3. Bias due to missing outcome data was rated "low" if data were available for all, or nearly all, participants randomized. If there was the possibility that missingness in the outcome was influenced by its true value, the domain was rated "some concerns". If missingness in the outcome was likely influenced by its true value, the domain was rated "high".

4. Bias in measurement of the outcome was rated "high" if the method for measuring the outcome was inappropriate, if it differed between groups, or if it was likely that the assessment was influenced by knowledge of the intervention. It was rated "some concerns" if outcome assessors were aware of the intervention received by participants, but it was not likely that assignment was influenced by knowledge of the intervention. Bias in measurement of the outcome was rated "low" if all categories were considered as low.

5. Bias in selection of the reported result was rated "low" if it was unlikely that the results were selected from multiple measurements or analyses, and data were analysed in accordance with a pre-specified plan. If no pre-specified plan was available but it was unlikely that results were selected from multiple measurements or analyses, the domain was rated "some concerns". If it was suspected that results were selected from multiple measurements or analyses, the domain was rated "high".

Overall risk of bias was rated "low" if all domains were rated "low", it was rated "some concerns" if the study was judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain, and it was was rated "high" if at least one domain was considered as "high".

Confidence of Network Meta-analysis (CINeMA) rating

We used the CINeMA framework to assess the overall credibility of the results.[3] CINeMA is based on the following domains: 1) within-study bias, 2) reporting bias, 3) indirectness, 4) imprecision, 5) heterogeneity, and 6) incoherence. Within-study bias was evaluated using the RoB-2 tool. Reporting bias for each comparison was coded as "suspected" or "undetected" based on the completeness of the research and availability of published data. Indirectness was assessed as described below. To assess imprecision, heterogeneity, and incoherence, we set the clinically significant effect size to 0.35.[4]

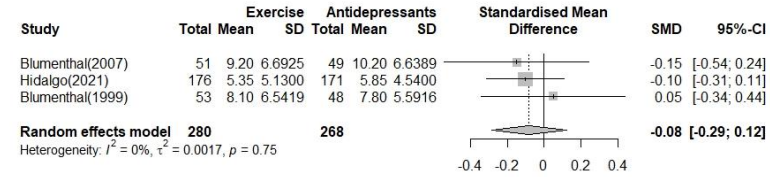
Indirectness

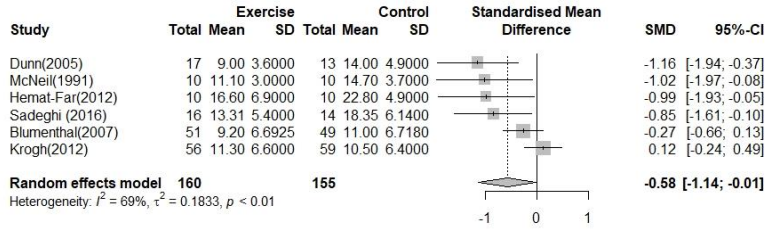
Indirectness was assessed based on recommended guidelines.[5] We evaluated whether studies differed in relation to 1) population, 2) intervention, 3) outcome, and 4) whether a study showed direct evidence for at least one comparison of interest. Study indirectness was coded as "low" if three or more outcomes were considered to be "low" and no more than one was "unclear", and coded as "high" if two or more outcomes were considered to be "high", whereas any other combination was coded as "moderate".

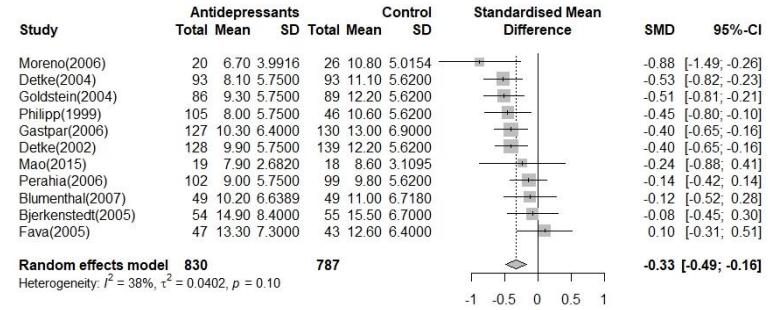
1. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
2. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
3. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine.* 2020;17(4):e1003082.
4. Kroenke K, Stump TE, Chen CX, et al. Minimally important differences and severity thresholds are estimated for the PROMIS depression scales from three randomized clinical trials. *Journal of affective disorders*. 2020;266:100-108. doi:10.1016/j.jad.2020.01.101
5. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology*. 2011;64(12):1303-1310.

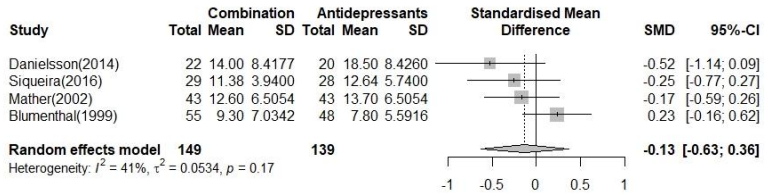
eAppendix 3. Pairwise meta-analyses

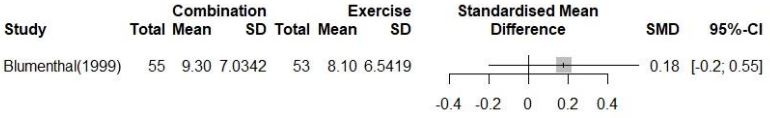
Comparative effectiveness on depressive symptoms from pairwise meta-analyses



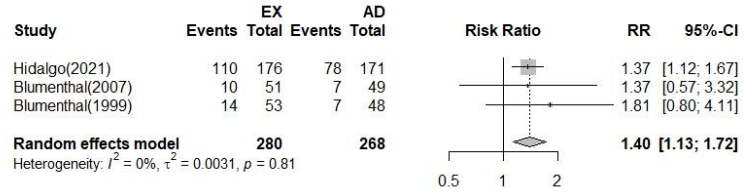


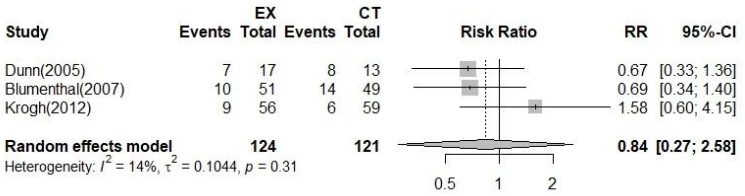


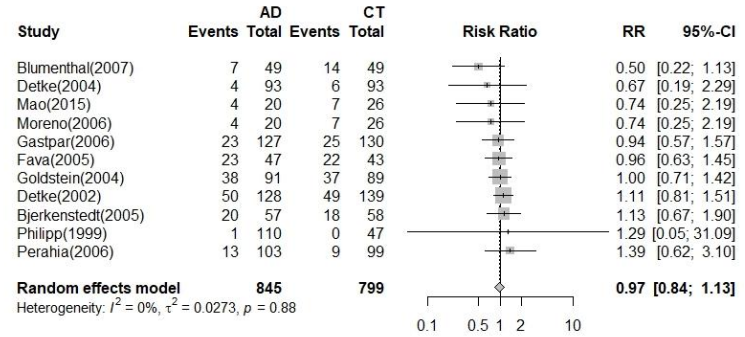


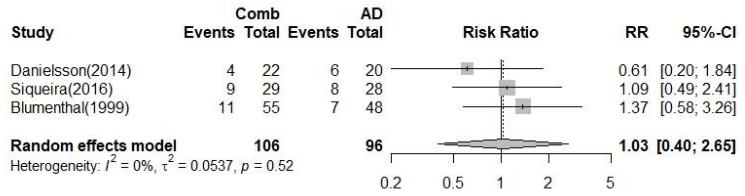


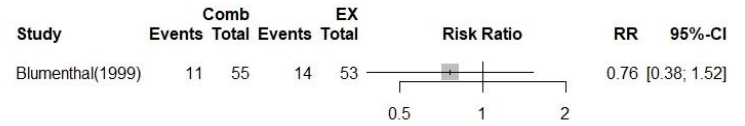
Comparative effectiveness on acceptability from pairwise meta-analyses











eAppendix 4. References

Bjerkenstedt L, Edman GV, Alken RG, Mannel M. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. *European archives of psychiatry and clinical neuroscience*. Feb 2005;255(1):40-7. doi:10.1007/s00406-004-0532-z

Blumenthal J, Babyak M, Moore K, et al. Effects of Exercise Training on Older Patients With Major Depression. *Archives of internal medicine*. 10/01 1999;159:2349-56. doi:10.1001/archinte.159.19.2349

Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. Sep-Oct 2007;69(7):587-96. doi:10.1097/PSY.0b013e318148c19a

Danielsson L, Papoulias I, Petersson EL, Carlsson J, Waern M. Exercise or basic body awareness therapy as add-on treatment for major depression: a controlled study. *Journal of affective disorders*. Oct 2014;168:98-106. doi:10.1016/j.jad.2014.06.049

Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *Journal of psychiatric research*. Nov-Dec 2002;36(6):383-90. doi:10.1016/s0022-3956(02)00060-2

Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. Dec 2004;14(6):457-70. doi:10.1016/j.euroneuro.2004.01.002

Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: Efficacy and dose response. *American journal of preventive medicine*. January 2005;28(1):1-8

Fava M, Alpert J, Nierenberg AA, et al. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *Journal of clinical psychopharmacology*. Oct 2005;25(5):441-7. doi:10.1097/01.jcp.0000178416.60426.29

Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: A double-blind, randomised, multicentre, placebo-controlled study. *Pharmacopsychiatry*. March 2006;39(2):66-75

Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of clinical psychopharmacology*. Aug 2004;24(4):389-99. doi:10.1097/01.jcp.0000132448.65972.d9

Hemat-Far A, Shahsavari A, Mousavi SR. Effects of selected aerobic exercises on the depression and concentrations of plasma serotonin in the depressed female students aged 18 to 25. *Journal of Applied Research*. 2012;12(1):47-52

Hidalgo JL-T, Sotos JR, Group D-E. Effectiveness of Physical Exercise in Older Adults With Mild to Moderate Depression. *The Annals of Family Medicine*. 2021;19(4):302-309. doi:10.1370/afm.2670

Krogh J, Videbech P, Thomsen C, Gluud C, Nordentoft M. DEMO-II Trial. Aerobic Exercise versus Stretching Exercise in Patients with Major Depression-A Randomised Clinical Trial. *PLoS One*. 31 Oct 2012;7 (10) (e48316)

Mao JJ, Xie SX, Zee J, et al. Rhodiola rosea versus sertraline for major depressive disorder: A randomized placebo-controlled trial. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. Mar 15 2015;22(3):394-9. doi:10.1016/j.phymed.2015.01.010

Mather AS, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo MET. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder. *British Journal of Psychiatry*. 2002;180(MAY):411-415

McNeil JK, LeBlanc EM, Joyner M. The effect of exercise on depressive symptoms in the moderately depressed elderly. *Psychology and aging*. Sep 1991;6(3):487-8. doi:10.1037//0882-7974.6.3.487

Moreno RA, Teng CT, Almeida KM, Tavares Junior H. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. Mar 2006;28(1):29-32. doi:10.1590/s1516-44462006000100007

Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European psychiatry : the journal of the Association of European Psychiatrists*. Sep 2006;21(6):367-78. doi:10.1016/j.eurpsy.2006.03.004

Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: Randomised multicentre study of treatment for eight weeks. *British Medical Journal*. 11 Dec 1999;319(7224):1534-1538

Sadeghi K, Ahmadi SM, Ahmadi SM, et al. A Comparative Study of the Efficacy of Cognitive Group Therapy and Aerobic Exercise in the Treatment of Depression among the Students. *Global journal of health science*. Oct 1 2016;8(10):54171. doi:10.5539/gjhs.v8n10p1

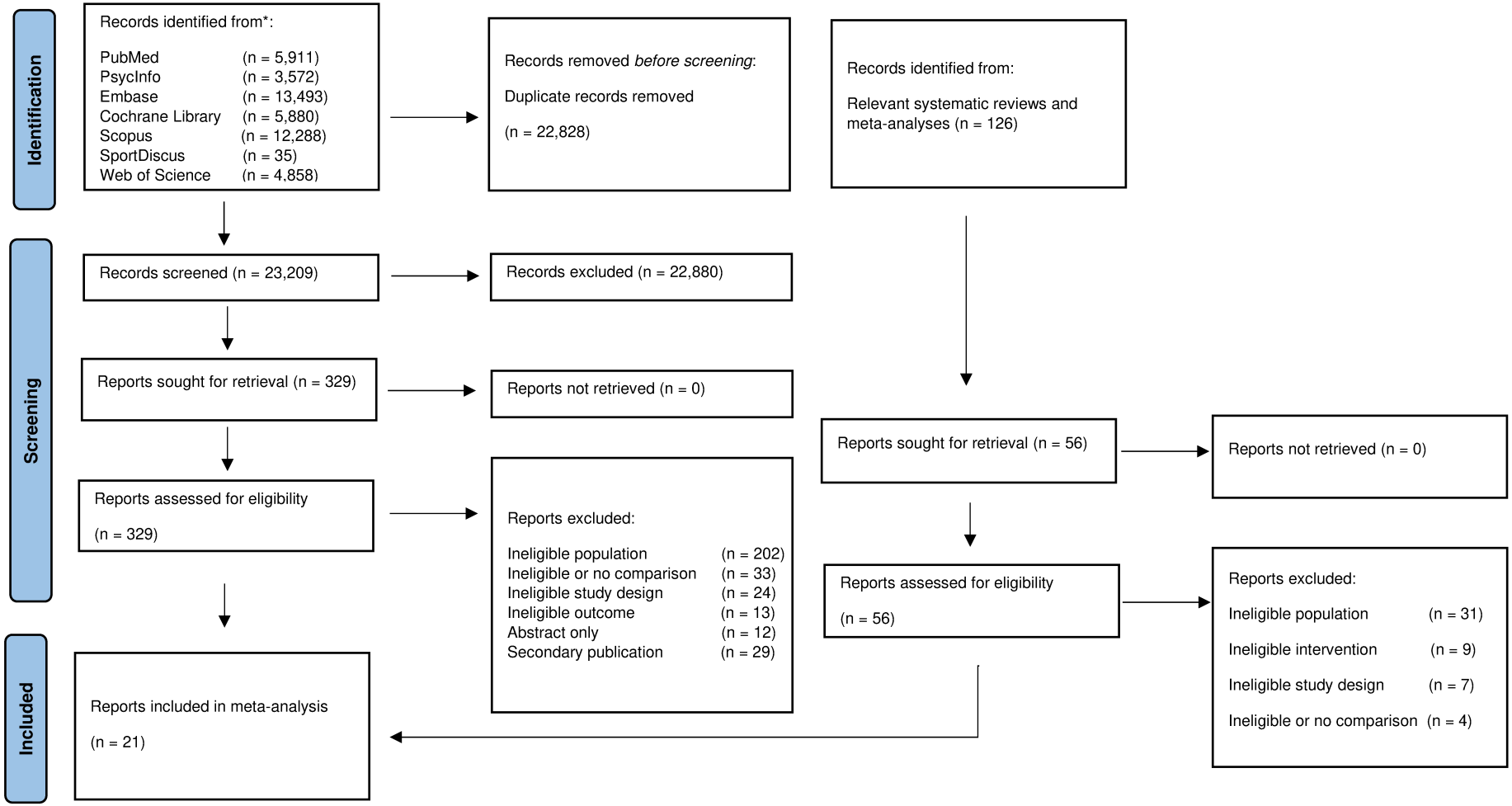
Siqueira CC, Valiengo LL, Carvalho AF, et al. Antidepressant Efficacy of Adjunctive Aerobic Activity and Associated Biomarkers in Major Depression: A 4-Week, Randomized, Single-Blind, Controlled Clinical Trial. *PLoS One*. 2016;11(5):e0154195 doi:10.1371/journal.pone.0154195

Comparative effectiveness of exercise, antidepressants, and their combination in treating non-severe depression: A systematic review and network meta-analysis of randomized controlled trials

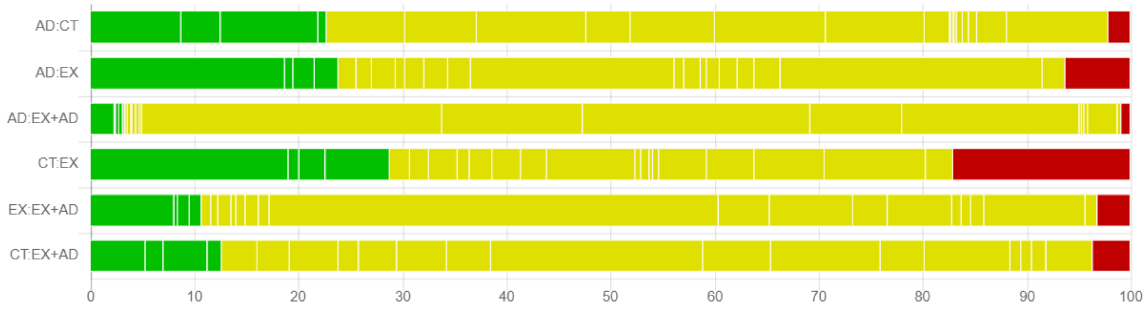
Supplementary Online Content

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

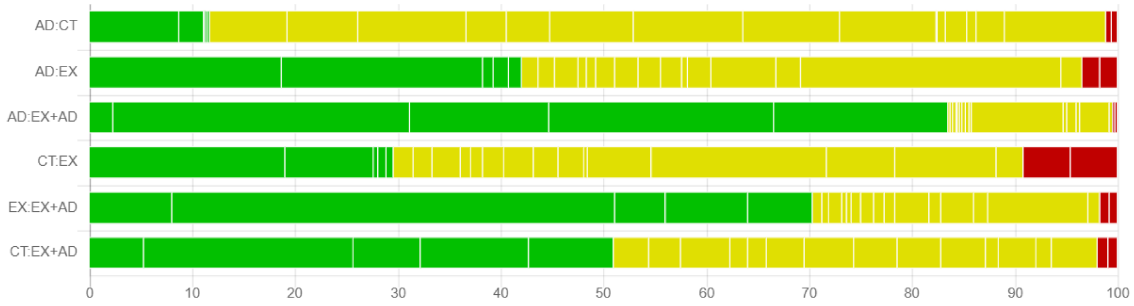
eFigure 1. PRISMA flow chart



eFigure 2. Risk of bias contributions



eFigure 3. Indirectness contributions



eTable 1. Distribution of study characteristics

Comparison	N studies	Participant age (years)	Sex (% women)	Intervention duration (weeks)	Outcome measure
EX:AD	3	< 60	≥ 50%	19	HAM-D
AD:CT	11	< 60	≥ 50%	9	HAM-D
EX:CT	6	< 60	≥ 50%	10	HAM-D
EX+AD:AD	4	< 60	≥ 50%	11	HAM-D
EX+AD:EX	1	< 60	≥ 50%	16	HAM-D

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

eTable 2. Meta-regression for direct comparisons

Comparison[a]	N	Coefficient [95% CI]	SE	P value
EX:AD	3			
- Mean age		-0.00 [-0.16 to 0.16]	0.01	0.94
- Mean duration		-0.01 [-0.21 to 0.20]	0.02	0.75
- Proportion of women		-0.02 [-0.39 to 0.36]	0.03	0.67
- Outcome measure		-0.05 [-1.68 to 1.58]	0.13	0.75
AD:CT	11			
- Mean age		0.01 [-0.03 to 0.05]	0.02	0.70
- Mean duration		0.02 [-0.03 to 0.08]	0.02	0.35
- Proportion of women		-0.01 [-0.03 to 0.01]	0.01	0.40
- Outcome measure[b]		NA	NA	NA
EX:CT	6			
- Mean age		0.03 [-0.03 to 0.08]	0.02	0.20
- Mean duration		0.08 [-0.08 to 0.25]	0.06	0.22
- Proportion of women		0.00 [-0.04 to 0.04]	0.01	0.92
- Outcome measure		0.63 [-0.48 to 1.74]	0.40	0.19
EX+AD:AD	4			
- Mean age		0.01 [-0.06 to 0.09]	0.02	0.54
- Mean duration		0.04 [-0.09 to 0.18]	0.03	0.28
- Proportion of women		-0.05 [-0.36 to 0.27]	0.07	0.58
- Outcome measure		-0.49 [-2.03 to 1.06]	0.36	0.31

[a]Meta-regression for the EX+AD:EX comparison could not be performed because only one study was available for that comparison

[b]Meta-regression for this categorical outcome could not be performed because all studies within this comparison used the same outcome measure

eTable 3. Risk of bias for all studies

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	RoB
Bjerkenstedt et al., 2004	Low	Low	Low	Low	Some concerns	Some concerns
Blumenthal et al., 1999	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Blumenthal et al., 2007	Low	Low	Low	Low	Low	Low
Danielsson et al., 2014	Low	Low	Low	Low	Some concerns	Some concerns
Detke et al., 2002	Some concerns	Low	Low	Low	Low	Some concerns
Detke et al., 2004	Some concerns	Low	Low	Low	Low	Some concerns
Dunn et al., 2005	Low	Low	Low	Low	Low	Low
Fava et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Gastpar et al., 2005	Some concerns	Low	Low	Low	Some concerns	Some concerns
Goldstein et al., 2004	Low	Low	Low	Low	Low	Low
Hemat-Far et al., 2012	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Hidalgo et al., 2021	Some concerns	Low	Low	Some concerns	Low	Some concerns
Krogh et al., 2012	Some concerns	High	Low	Low	Low	High
Mao et al., 2015	Low	Low	Low	Low	Low	Low
Mather et al., 2002	Low	Some concerns	Low	Low	Some concerns	Some concerns
McNeil et al., 1991	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Moreno et al., 2005	Low	Low	Low	Low	Low	Low
Perahia et al., 2006	Some concerns	Low	Low	Low	Low	Some concerns
Philipp et al., 1999	Some concerns	Low	Low	Low	Some concerns	Some concerns
Sadeghi et al., 2016	Some concerns	Low	Some concerns	Low	Low	Some concerns
Siqueira et al., 2016	Some concerns	Low	Low	Low	Low	Some concerns

eTable 4. Indirectness for all studies

Author	Population		Intervention		Outcome		Comparisons	Indirectness
Bjerkenstedt et al., 2005	Low		Low		Low		High	Moderate
Blumenthal et al., 1999	Low		Low		Low		Low	Low
Blumenthal et al., 2007	Low		Low		Low		Low	Low
Danielsson et al., 2014	Low		Low		Low		Low	Low
Detke et al., 2002	Low		Low		Low		High	Moderate
Detke et al., 2004	Low		Low		Low		High	Moderate
Dunn et al., 2005	Low		Low		Low		High	Moderate
Fava et al., 2005	Low		Low		Low		High	Moderate
Gastpar et al., 2006	Low		Low		Low		High	Moderate
Goldstein et al., 2004	Low		Low		Low		High	Moderate
Hemat-Far et al., 2012	High	Female students	Low		Moderate	Self-reported questionnaire	High	High
Hidalgo et al. 2021	High	Elderly	Low		Low		Low	Moderate
Krogh et al., 2012	Low		Low		Low		High	Moderate
Mao et al., 2015	Low		Low		Low		High	Moderate
Mather et al., 2002	Low		Low		Low		Low	Low
McNeil et al., 1991	High	Elderly	Moderate	Somewhat different	Moderate	Self-reported questionnaire	High	High
Moreno et al., 2006	Low		Low		Low		High	Moderate
Perahia et al., 2006	Low		Low		Low		High	Moderate
Philipp et al., 1999	Low		Low		Low		High	Moderate
Sadeghi et al., 2016	Low		Low		Moderate	Self-reported questionnaire	High	Moderate
Siqueira et al., 2016	Low		Low		Low		Low	Low

eTable 5. Confidence in Network Meta-analysis (CINeMA) final report

Comparison	N	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
AD:CT	10	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
AD:EX	2	Some concerns	Some concerns	Some concerns	Some concerns	No concerns	No concerns	Moderate
EX+AD:AD	5	Some concerns	Some concerns	No concerns	Some concerns	No concerns	No concerns	High
EX:CT	6	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Moderate
EX+AD:EX	1	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Moderate
EX+AD:CT	0	Some concerns	Some concerns	Some concerns	No concerns	No concerns	No concerns	High

eTable 6. Treatment ranking based on the P-score

Treatment	P-score
EX	0.7865
EX+AD	0.7639
AD	0.4489
CT	0.0008

eTable 7. Assessment of inconsistency within comparisons

Comparison	k	Direct	Indirect	Difference	z	P-value
AD:CT	11	-0.33	-0.38	0.05	0.22	0.83
AD:EX	3	0.07	0.19	-0.12	-0.52	0.60
EX+AD:AD	4	0.12	0.09	0.03	0.06	0.95
EX:CT	6	-0.43	-0.48	0.05	0.21	0.83
EX+AD:CT	0	NA	-0.45	NA	NA	NA
EX+AD:EX	1	-0.18	0.12	-0.30	-0.89	0.38

AD: Antidepressants; CT: Control; EX: Exercise; NA: Not available

eTable 8. Sensitivity analyses

Reasons for exclusion	N	EX-AD	Comb-AD	Comb-EX	Comb-CT	EX-CT	AD-CT	I^2
All included	21	-.12 (-.33 to .10)	-.12 (-.40 to .16)	-.00 (-.33 to .33)	-.45 (-.76 to -.14)	-.45 (-.67 to -.23)	-.33 (-.48 to -.19)	46.2%
Participants older than 60	19	-.10 (-.37 to .16)	-.12 (-.41 to .17)	-.02 (-.37 to .34)	-.44 (-.76 to -.12)	-.43 (-.69 to -.17)	-.33 (-.48 to -.18)	49.0%
High Risk of Bias	20	-.20 (-.40 to .00)	-.13 (-.38 to .13)	.07 (-.23 to .37)	-.48 (-.77 to -.20)	-.56 (-.77 to -.34)	-.36 (-.49 to -.23)	31.0%
High Indirectness	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%
Intervention longer than 12 weeks	18	-.18 (-.58 to .21)	-.29 (-.67 to .09)	-.11 (-.65 to .44)	-.63 (-1.05 to -.22)	-.53 (-.88 to -.17)	-.35 (-.52 to -.17)	52.5%
SD imputed	16	-.17 (-.42 to .09)	-.14 (-.45 to .18)	-.03 (-.34 to .40)	-.41 (-.78 to -.04)	-.44 (-.70 to 0.19)	-.28 (-.50 to .05)	50.4%
Attention/active control comparison	17	-.14 (-.35 to .07)	-.09 (-.39 to .21)	-.05 (-.28 to .38)	-.44 (-.76 to -.11)	-.48 (-.71 to -.25)	-.34 (-.47 to -.22)	32.6%
Passive control comparison	19	-.07 (-.29 to .15)	-.11 (-.39 to .17)	-.04 (-.36 to .29)	-.43 (-.74 to -.12)	-.39 (-.62 to -.16)	-.32 (-.46 to -.18)	46.9%

Recchia F, *et al. Br J Sports Med* 2022;0:1–7. doi: 10.1136/bjsports-2022-105964

eAppendix 1. Search strategy

PubMed

Search	Query
#1	Bupropion[MeSH Terms] OR bupropion[Title/Abstract] OR 34911-55-2[EC/RN Number]
#2	Citalopram[MeSH Terms] OR citalopram[Title/Abstract] OR 59729-33-8[EC/RN Number]
#3	escitalopram[Title/Abstract] OR 128196-01-0[EC/RN Number]
#4	desvenlafaxine[Title/Abstract] OR 386750-22-7[EC/RN Number]
#5	Fluoxetine[MeSH Terms] OR fluoxetine[Title/Abstract] OR 54910-89-3[EC/RN Number]
#6	Fluvoxamine[MeSH Terms] OR fluvoxamine[Title/Abstract] OR 54739-18-3[EC/RN Number]
#7	Milnacipran[Supplementary Concept] OR milnacipran[Title/Abstract] OR levomilnacipran[Title/Abstract]
#8	Mirtazapine[Supplementary Concept] OR mirtazapine[Title/Abstract] OR 4685R51V7M[EC/RN Number]
#9	Nefazodone[Supplementary Concept] OR nefazodone[Title/Abstract]
#10	Paroxetine[MeSH Terms] OR paroxetine[Title/Abstract] OR 61869-08-7[EC/RN Number]
#11	Sertraline[MeSH Terms] OR sertraline[Title/Abstract] OR 79617-96-2[EC/RN Number]
#12	Trazodone[MeSH Terms] OR trazodone[Title/Abstract] OR 19794-93-5[EC/RN Number]
#13	venlafaxine[Title/Abstract] OR 99300-78-4[EC/RN Number]
#14	vilazodone[Title/Abstract] OR 163521-08-2[EC/RN Number]
#15	Vortioxetine[Supplementary Concept] OR vortioxetine[Title/Abstract] OR TKS641KOAY[EC/RN Number]
#16	duloxetine[Title/Abstract] OR 116539-58-3[EC/RN Number]
#17	Antidepressive Agents, Second Generation[MeSH Terms] OR Antidepressive Agents, Second-Generation[Pharmacological Action] OR antidepress*[Title/Abstract]
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	Depression, unipolar[MeSH Terms] OR Depressive disorders[MeSH Terms] OR depress*[Title/Abstract]
#20	Randomized controlled trial[MeSH Terms] OR Random allocation[MeSH Terms] OR (random*[Title/Abstract] AND (control*[Title/Abstract] OR placebo[Title/Abstract]))
#21	#18 AND #19 AND #20
#22	Exercise[MeSH Terms] OR exercise[Title/Abstract] OR "physical activity"[Title/Abstract] OR aerobic[Title/Abstract] OR training[Title/Abstract] OR lift*[Title/Abstract] OR running[Title/Abstract] OR walk*[Title/Abstract] OR jogging[Title/Abstract] OR swim*[Title/Abstract] OR cycl*[Title/Abstract]
#23	#19 AND #20 AND #22
#24	Adults[MeSH Terms] OR adult*[Title/Abstract]
#25	#21 AND #24
#26	#23 AND #24
#27	#25 OR #26
#28	Filters: Chinese, English, Italian, from 1990 - 3000/12/12

PsycInfo

Search	Query
S1	SU(bupropion) OR AB(bupropion) OR TI(bupropion)

S2	SU(citalopram) OR AB(citalopram) OR TI(citalopram)
S3	SU(escitalopram) OR AB(escitalopram) OR TI(escitalopram)
S4	SU(Desvenlafaxine) OR AB(Desvenlafaxine) OR TI(Desvenlafaxine)
S5	SU(Fluoxetine) OR AB(Fluoxetine) OR TI(Fluoxetine)
S6	SU(Fluvoxamine) OR AB(Fluvoxamine) OR TI(Fluvoxamine)
S7	SU(Levomilnacipran) OR AB(Levomilnacipran) OR TI(Levomilnacipran)
S8	SU(mirtazapine) OR AB(mirtazapine) OR TI(mirtazapine)
S9	SU(Nefazodone) OR AB(Nefazodone) OR TI(Nefazodone)
S10	SU(Paroxetine) OR AB(Paroxetine) OR TI(Paroxetine)
S11	SU(Sertraline) OR AB(Sertraline) OR TI(Sertraline)
S12	SU(Trazodone) OR AB(Trazodone) OR TI(Trazodone)
S13	SU(Venlafaxine) OR AB(Venlafaxine) OR TI(Venlafaxine)
S14	SU(vilazodone) OR AB(vilazodone) OR TI(vilazodone)
S15	SU(vortioxetine) OR AB(vortioxetine) OR TI(vortioxetine)
S16	SU(duloxetine) OR AB(duloxetine) OR TI(duloxetine)
S17	SU(Antidepressive Drugs, Second-Generation) OR TI(antidepress*) OR AB(antidepress*)
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S19	SU(depression) OR SU(depressive disorder) OR TI(depress*) OR AB(depress*)
S20	SU(randomized controlled trial) OR SU(randomized clinical trial) OR SU(random allocation) OR TI(random* AND control*) OR AB(random* AND control*) OR TI(random* AND placebo) OR AB(random* AND placebo)
S21	S18 AND S19 AND S20
S22	SU(adults) OR TI(adult*) OR AB(adult*)
S23	S21 AND S22
S24	SU(exercise) OR TI(exercise) OR AB(exercise) OR SU(physical activity) OR TI(aerobic) OR AB(aerobic) OR TI(training) OR AB(training) OR TI(lift*) OR AB(lift*) OR SU(running) OR TI(running) OR AB(running) OR TI(jogging) OR AB(jogging) OR TI(walk*) OR AB(walk*) OR TI(swim*) OR AB(swim*) OR TI(cycl*) OR AB(cycl*)
S25	S19 AND S20 AND S24
S26	S22 AND S25
S27	S23 AND S26
S28	#27 Limit date range 1990-2021 AND Limit language: English, Chinese, Italian

Cochrane Library

ID	**Search**
#1	bupropion:ti,ab,kw OR [mh bupropion]
#2	citalopram:ti,ab,kw OR [mh citalopram]
#3	escitalopram:ti,ab,kw OR [mh escitalopram]
#4	desvenlafaxine:ti,ab,kw OR [mh desvenlafaxine]
#5	duloxetine:ti,ab,kw OR [mh duloxetine]
#6	fluoxetine:ti,ab,kw OR [mh fluoxetine]
#7	fluvoxamine:ti,ab,kw OR [mh fluvoxamine]
#8	Levomilnacipran:ti,ab,kw OR [mh levomilnacipran]
#9	mirtazapine:ti,ab,kw OR [mh mirtazapine]
#10	nefazodone:ti,ab,kw OR [mh nefazodone]
#11	Paroxetine:ti,ab,kw OR [mh paroxetine]
#12	sertraline:ti,ab,kw OR [mh sertraline]
#13	Trazodone:ti,ab,kw OR [mh trazodone]
#14	venlafaxine:ti,ab OR [mh venlafaxine]
#15	vilazodone:ti,ab,kw OR [mh vilazodone]
#16	vortioxetine:ti,ab,kw OR [mh duloxetine]

#17	[mh Antidepressive Agents, Second-Generation] OR antidepress*:ti,ab,kw
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR 11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	[mh Depression] OR [mh Depressive Disorder, Major] OR depress*:ti,ab,kw
#20	[mh Randomized Controlled Trials as Topic] OR [mh Randomized Controlled Trial] OR [mh Random Allocation] OR ("randomized controlled"):ti,ab,kw OR ("controlled clinical"):ti,ab,kw
#21	#18 AND #19 AND #20
#22	[mh Adults] OR adults:ti,ab,kw
#23	#21 AND #22
#24	[mh Exercise] OR [mh "physical activity"] OR exercise:ti,ab,kw OR training:ti,ab,kw OR lift*:ti,ab,kw OR aerobic:ti,ab,kw OR running:ti,ab,kw OR walk*:ti,ab,kw OR jogging:ti,ab,kw OR swim*:ti,ab,kw OR cycl*:ti,ab,kw
#25	#19 AND #20 AND #24
#26	#25 AND #22
#27	#23 OR #26 with Publication Year from 1990 to 2021 AND language: English, Chinese, Italian

Embase

#	Searches
1	exp bupropion/ or bupropion.tn,ab,ti. or 34911 55 2.rn.
2	exp citalopram/ or citalopram.tn,ab,ti. or 59729 33 .rn.
3	exp escitalopram/ or escitalopram.tn,ab,ti. or 128196 01 0.rn.
4	exp desvenlafaxine/ or desvenlafaxine.tn,ab,ti. or 93413 62 8.rn.
5	exp fluoxetine/ or fluoxetine.tn,ab,ti. or 54910 89 3.rn.
6	exp fluvoxamine/ or fluvoxamine.tn,ab,ti. or 54739 18 3.rn.
7	exp milnacipran/ or levomilnacipran.tn,ab,ti. or 96847 54 0.rn.
8	exp mirtazapine/ or mirtazapine.tn,ab,ti. or 85650 52 8.rn.
9	exp nefazodone/ or nefazodone.tn,ab,ti. or 82752 99 6.rn.
10	exp paroxetine/ or paroxetine.tn,ab,ti. or 61869 08 7.rn.
11	exp sertraline/ or sertraline.tn,ab,ti. or 79617 96 2.rn.
12	exp trazodone/ or trazodone.tn,ab,ti. or 19794 93 5.rn.
13	exp venlafaxine/ or venlafaxine.tn,ab,ti. or 93413 69 5.rn.
14	exp vilazodone/ or vilazodone.tn,ab,ti. or 163521 12 8.rn.
15	exp vortioxetine/ or vortioxetine.tn,ab,ti. or 508233 74 7.rn.
16	exp duloxetine/ or duloxetine.tn,ab,ti. or 116539 59 4.rn.
17	exp antidepressant agent/ or antidepress*.ti,ab.
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	exp depression/ or exp major depression/ or depress*.ab,ti,kw.
20	exp randomized controlled trial/ or randomized controlled trial.ab,ti,pt. or randomized placebo trial.ti,ab. or exp randomization/
21	18 and 19 and 20
22	exp exercise/ or exercise.ti,ab. or aerobic.ti,ab. or training.ti,ab. or lift*.ti,ab. or running.ti,ab. or jogging.ti,ab. or walk*.ti,ab. or swim*.ti,ab. or cycl*.ti,ab.
23	19 and 20 and 22
24	exp adults/ or adult*.ti,ab.
25	21 and 24
26	23 and 24
27	25 or 26
28	Limit 27 to yr=1990-Current, English, Chinese, Italian language

Scopus

#	Query
#1	TITLE-ABS-KEY(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR

	paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TITLE-ABS-KEY(depress*)
#3	TITLE-ABS-KEY(randomized controlled trial)
#4	TITLE-ABS-KEY(adult*)
#5	#1 AND #2 AND #3 AND #4
#6	TITLE-ABS-KEY(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#7	#2 AND #3 AND #4 AND #6
#8	#5 OR #7

SportDiscus

Search	Query
S1	(TI(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (AB(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)) OR (SU(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*))
S2	SU(depression or depressive disorder or depressive symptoms or major depressive disorder) OR TI depress* OR AB depress*
S3	SU(randomized controlled trials or rtc or randomised control trials) OR TI(random* AND control*) OR AB (random* AND control*)
S4	SU(adults or adult) OR TI adult* OR AB adult*
S5	S1 AND S2 AND S3 AND S4
S6	SU(exercise or physical activity) OR TI(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*) OR AB(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
S7	S2 AND S3 AND S4 AND S6
S8	S5 OR S7

Web of Science

#	Query
#1	TS=(bupropion OR citalopram OR escitalopram OR desvenlafaxine OR fluoxetine OR fluvoxamine OR milnacipran OR mirtazapine OR nefazodone OR paroxetine OR sertraline OR trazodone OR venlafaxine OR vilazodone OR vortioxetine OR duloxetine OR antidepress*)
#2	TS=(depress*)
#3	TS=(random* AND (control* OR placebo))
#4	TS=(adult*)
#5	TS=(exercise OR 'physical activity' OR aerobic OR training OR lift* OR running OR walk* OR jogging OR swim* OR cycl*)
#6	#1 AND #2 AND #3 AND #4
#7	#2 AND #3 AND #4 AND #5
#8	#6 OR #7

eAppendix 2. Additional methodology information

Risk of bias

The Cochrane risk of bias assessment tool (RoB-2) was used to determine the quality of the individual studies.[1] Bias was assessed in the following domains: 1) randomization process, 2) deviations from the intended interventions, 3) missing outcome data, 4) measurement of the outcome, and 5) selection of the reported results. Each domain was assessed as having either low risk of bias, some concerns, or high risk of bias.

To implement RoB-2, we utilized the Excel template provided in the "Cochrane Handbook for Systematic Reviews of Interventions",[2] which includes "signalling questions" that can be used to assess bias in each domain. Each domain is automatically evaluated by an algorithm based on the signalling questions, as well as subjectively by the author. To avoid the influence of personal bias, the assessment of each domain was strictly based on the output of the algorithm.

1. Bias due to the randomization process was rated "low" if the study allocation sequence was reported as random and there was evidence that the allocation sequence was concealed. Allocation concealment was considered adequate if the allocation was carried out by investigators that were external to the project, or if authors used a form of remote or centrally administered method that ensured allocation concealment (e.g., sealed opaque envelopes). If the strategy for allocation concealment was not clearly reported, the domain was rated as having "some concerns". If both categories were deemed to be inadequately described, the domain was rated "high".

2. Bias due to deviations from the intended interventions was based on whether participants and/or study personnel were blinded to participants' assigned intervention, whether there were deviations from the intervention due to the trial context, and whether an appropriate analysis was used to estimate the effect of the intervention. Bias was rated "low" if all categories were rated as low. Following the Cochrane algorithm, if participants or study personnel were aware of participants' allocated intervention but all other categories were considered as low, the domain was still rated as "low". If there were deviations from the interventions that were suspected to affect the outcome, and if these were not balanced between groups, or if an inappropriate statistical analysis was used that was suspected to substantially impact the outcome, the domain was rated "high". Any other combination was rated as having "some concerns".

3. Bias due to missing outcome data was rated "low" if data were available for all, or nearly all, participants randomized. If there was the possibility that missingness in the outcome was influenced by its true value, the domain was rated "some concerns". If missingness in the outcome was likely influenced by its true value, the domain was rated "high".

4. Bias in measurement of the outcome was rated "high" if the method for measuring the outcome was inappropriate, if it differed between groups, or if it was likely that the assessment was influenced by knowledge of the intervention. It was rated "some concerns" if outcome assessors were aware of the intervention received by participants, but it was not likely that assignment was influenced by knowledge of the intervention. Bias in measurement of the outcome was rated "low" if all categories were considered as low.

5. Bias in selection of the reported result was rated "low" if it was unlikely that the results were selected from multiple measurements or analyses, and data were analysed in accordance with a pre-specified plan. If no pre-specified plan was available but it was unlikely that results were selected from multiple measurements or analyses, the domain was rated "some concerns". If it was suspected that results were selected from multiple measurements or analyses, the domain was rated "high".

Overall risk of bias was rated "low" if all domains were rated "low", it was rated "some concerns" if the study was judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain, and it was was rated "high" if at least one domain was considered as "high".

Confidence of Network Meta-analysis (CINeMA) rating

We used the CINeMA framework to assess the overall credibility of the results.[3] CINeMA is based on the following domains: 1) within-study bias, 2) reporting bias, 3) indirectness, 4) imprecision, 5) heterogeneity, and 6) incoherence. Within-study bias was evaluated using the RoB-2 tool. Reporting bias for each comparison was coded as "suspected" or "undetected" based on the completeness of the research and availability of published data. Indirectness was assessed as described below. To assess imprecision, heterogeneity, and incoherence, we set the clinically significant effect size to 0.35.[4]

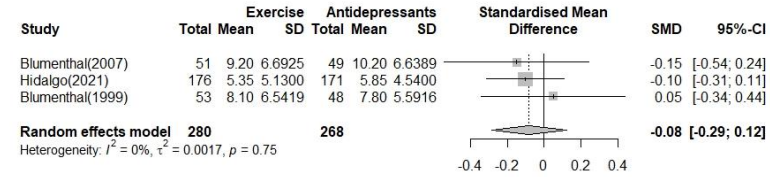
Indirectness

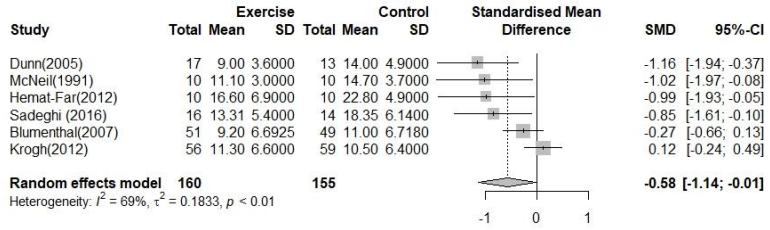
Indirectness was assessed based on recommended guidelines.[5] We evaluated whether studies differed in relation to 1) population, 2) intervention, 3) outcome, and 4) whether a study showed direct evidence for at least one comparison of interest. Study indirectness was coded as "low" if three or more outcomes were considered to be "low" and no more than one was "unclear", and coded as "high" if two or more outcomes were considered to be "high", whereas any other combination was coded as "moderate".

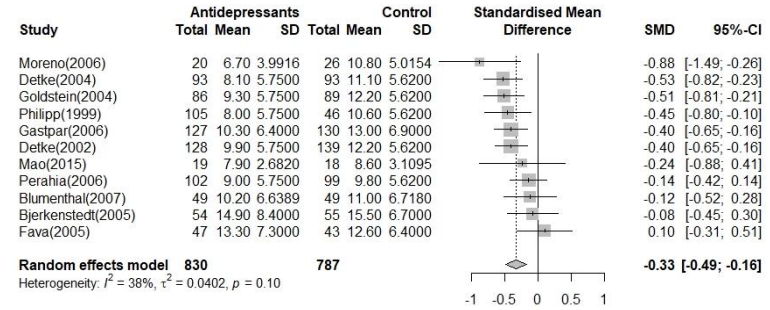
1. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
2. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
3. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine.* 2020;17(4):e1003082.
4. Kroenke K, Stump TE, Chen CX, et al. Minimally important differences and severity thresholds are estimated for the PROMIS depression scales from three randomized clinical trials. *Journal of affective disorders*. 2020;266:100-108. doi:10.1016/j.jad.2020.01.101
5. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology*. 2011;64(12):1303-1310.

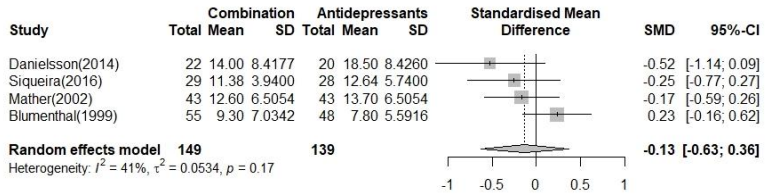
eAppendix 3. Pairwise meta-analyses

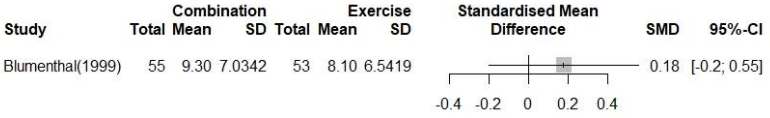
Comparative effectiveness on depressive symptoms from pairwise meta-analyses



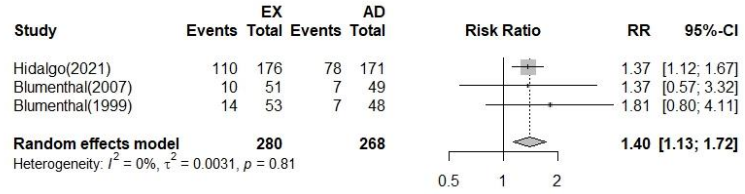


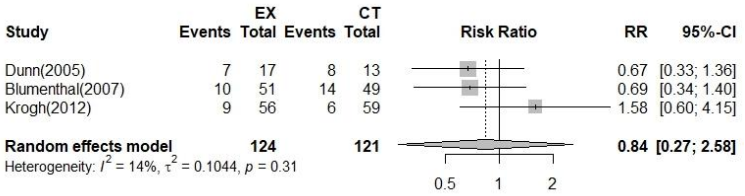


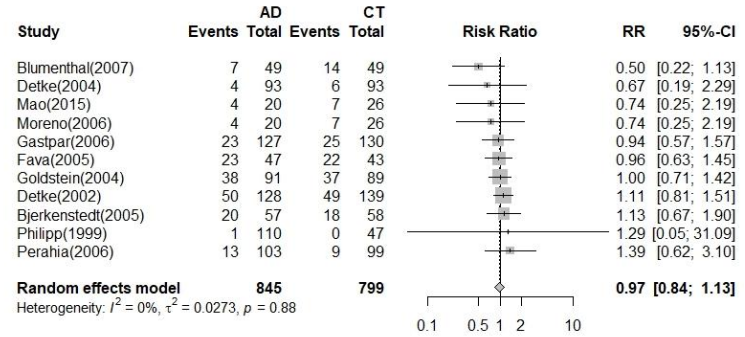


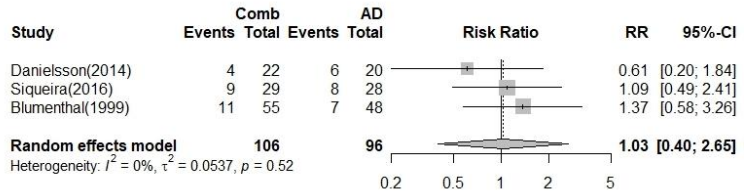


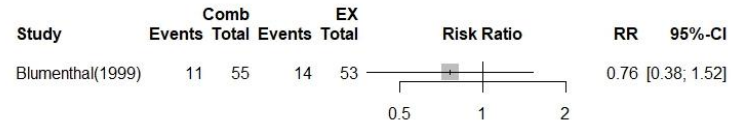
Comparative effectiveness on acceptability from pairwise meta-analyses











eAppendix 4. References

Bjerkenstedt L, Edman GV, Alken RG, Mannel M. Hypericum extract LI 160 and fluoxetine in mild to moderate depression: a randomized, placebo-controlled multi-center study in outpatients. *European archives of psychiatry and clinical neuroscience*. Feb 2005;255(1):40-7. doi:10.1007/s00406-004-0532-z

Blumenthal J, Babyak M, Moore K, et al. Effects of Exercise Training on Older Patients With Major Depression. *Archives of internal medicine*. 10/01 1999;159:2349-56. doi:10.1001/archinte.159.19.2349

Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. Sep-Oct 2007;69(7):587-96. doi:10.1097/PSY.0b013e318148c19a

Danielsson L, Papoulias I, Petersson EL, Carlsson J, Waern M. Exercise or basic body awareness therapy as add-on treatment for major depression: a controlled study. *Journal of affective disorders*. Oct 2014;168:98-106. doi:10.1016/j.jad.2014.06.049

Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *Journal of psychiatric research*. Nov-Dec 2002;36(6):383-90. doi:10.1016/s0022-3956(02)00060-2

Detke MJ, Wiltse CG, Mallinckrodt CH, McNamara RK, Demitrack MA, Bitter I. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*. Dec 2004;14(6):457-70. doi:10.1016/j.euroneuro.2004.01.002

Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO. Exercise treatment for depression: Efficacy and dose response. *American journal of preventive medicine*. January 2005;28(1):1-8

Fava M, Alpert J, Nierenberg AA, et al. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *Journal of clinical psychopharmacology*. Oct 2005;25(5):441-7. doi:10.1097/01.jcp.0000178416.60426.29

Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: A double-blind, randomised, multicentre, placebo-controlled study. *Pharmacopsychiatry*. March 2006;39(2):66-75

Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. *Journal of clinical psychopharmacology*. Aug 2004;24(4):389-99. doi:10.1097/01.jcp.0000132448.65972.d9

Hemat-Far A, Shahsavari A, Mousavi SR. Effects of selected aerobic exercises on the depression and concentrations of plasma serotonin in the depressed female students aged 18 to 25. *Journal of Applied Research*. 2012;12(1):47-52

Hidalgo JL-T, Sotos JR, Group D-E. Effectiveness of Physical Exercise in Older Adults With Mild to Moderate Depression. *The Annals of Family Medicine*. 2021;19(4):302-309. doi:10.1370/afm.2670

Krogh J, Videbech P, Thomsen C, Gluud C, Nordentoft M. DEMO-II Trial. Aerobic Exercise versus Stretching Exercise in Patients with Major Depression-A Randomised Clinical Trial. *PLoS One*. 31 Oct 2012;7 (10) (e48316)

Mao JJ, Xie SX, Zee J, et al. Rhodiola rosea versus sertraline for major depressive disorder: A randomized placebo-controlled trial. *Phytomedicine : international journal of phytotherapy and phytopharmacology*. Mar 15 2015;22(3):394-9. doi:10.1016/j.phymed.2015.01.010

Mather AS, Rodriguez C, Guthrie MF, McHarg AM, Reid IC, McMurdo MET. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder. *British Journal of Psychiatry*. 2002;180(MAY):411-415

McNeil JK, LeBlanc EM, Joyner M. The effect of exercise on depressive symptoms in the moderately depressed elderly. *Psychology and aging*. Sep 1991;6(3):487-8. doi:10.1037//0882-7974.6.3.487

Moreno RA, Teng CT, Almeida KM, Tavares Junior H. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. *Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999)*. Mar 2006;28(1):29-32. doi:10.1590/s1516-44462006000100007

Perahia DG, Wang F, Mallinckrodt CH, Walker DJ, Detke MJ. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *European psychiatry : the journal of the Association of European Psychiatrists*. Sep 2006;21(6):367-78. doi:10.1016/j.eurpsy.2006.03.004

Philipp M, Kohnen R, Hiller KO. Hypericum extract versus imipramine or placebo in patients with moderate depression: Randomised multicentre study of treatment for eight weeks. *British Medical Journal*. 11 Dec 1999;319(7224):1534-1538

Sadeghi K, Ahmadi SM, Ahmadi SM, et al. A Comparative Study of the Efficacy of Cognitive Group Therapy and Aerobic Exercise in the Treatment of Depression among the Students. *Global journal of health science*. Oct 1 2016;8(10):54171. doi:10.5539/gjhs.v8n10p1

Siqueira CC, Valiengo LL, Carvalho AF, et al. Antidepressant Efficacy of Adjunctive Aerobic Activity and Associated Biomarkers in Major Depression: A 4-Week, Randomized, Single-Blind, Controlled Clinical Trial. *PLoS One*. 2016;11(5):e0154195 doi:10.1371/journal.pone.0154195