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Exercise as medicine for depressive symptoms? A systematic review and meta-analysis with meta-regression

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ABSTRACT

Objective To estimate the efficacy of exercise on depressive symptoms compared with non-active control groups and to determine the moderating effects of exercise on depression and the presence of publication bias.

Design Systematic review and meta-analysis with meta-regression.

Data sources The Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, Embase, SPORTDiscus, PsycINFO, Scopus and Web of Science were searched without language restrictions from inception to 13 September2022 (PROSPERO registration no CRD42020210651).

Eligibility criteria for selecting studies Randomised controlled trials including participants aged 18 years or older with a diagnosis of major depressive disorder or those with depressive symptoms determined by validated screening measures scoring above the threshold value, investigating the effects of an exercise intervention (aerobic and/or resistance exercise) compared with a non-exercising control group.

Results Forty-one studies, comprising 2264 participants post intervention were included in the meta-analysis demonstrating large effects (standardised mean difference (SMD)=−0.946, 95% CI −1.18 to −0.71) favouring exercise interventions which corresponds to the number needed to treat (NNT)=2 (95% CI 1.68 to 2.59). Large effects were found in studies with individuals with major depressive disorder (SMD=−0.998, 95% CI −1.39 to −0.61, k=20), supervised exercise interventions (SMD=−1.026, 95% CI −1.28 to −0.77, k=40) and moderate effects when analyses were restricted to low risk of bias studies (SMD=−0.666, 95% CI −0.99 to −0.34, k=12, NNT=2.8 (95% CI 1.94 to 5.22)).

Conclusion Exercise is efficacious in treating depression and depressive symptoms and should be offered as an evidence-based treatment option focusing on supervised and group exercise with moderate intensity and aerobic exercise regimes. The small sample sizes of many trials and high heterogeneity in methods should be considered when interpreting the results.

WHAT IS ALREADY KNOWN?

⇒ Depression is the leading cause of disability worldwide with potentially increasing prevalence since the COVID-19 pandemic, yet more than two thirds of adults diagnosed with depression remain untreated.
⇒ Exercise is an efficacious treatment option for reducing depressive symptoms for individuals with depression.
⇒ However, evidence reported by meta-analyses reveals heterogeneous effects and is not up to date.

WHAT ARE THE NEW FINDINGS?

⇒ This methodologically sound systematic review and meta-analysis with meta-regression is the largest synthesis of the effect of exercise on major depressive disorder (MDD) and depressive symptoms covering 41 included studies, accounting for 2.264 adult participants postintervention.
⇒ Results show moderate to large effects of exercise on depressive symptoms even when limiting the analysis to low risk of bias studies or only MDD, although high heterogeneity among the studies was addressed with meta-regression.
⇒ Non-inferiority trials indicate that exercise is non-inferior to current first line treatments, and evidence that exercise is effective at long-term follow-ups are needed to clarify the identified evidence gaps.

INTRODUCTION

Depression is a prevalent and disabling disorder associated with reduced quality of life, medical comorbidity and mortality.[1 2] Over 300 million people live with depressive disorder, equating to approximately 4.4% of the world's population.[3] The prevalence of depression has increased during the COVID-19 pandemic[4–7] by an estimated 27.6%,[7] highlighting the need for appropriate, accessible and cost-effective treatment options.[8]

Currently, recommended treatments include psychotherapy and antidepressant medication (or a combination of both).[9] However, psychotherapy achieves remission rates of only 50% while typically being cost-intensive.[10] Side effects and relapses from antidepressant medication commonly occur[11] as can withdrawal symptoms.[12] Importantly, about two thirds of adults with depression do not receive adequate treatment.[13] Untreated depression often

leads to intensification of the illness including the development of comorbidities resulting in even higher costs for society.[14] This attests to the need for rapid and readily available alternative treatment options.

Exercise has been recommended as an adjunct treatment for depression by both the WHO[15] and National Institute for Health and Care Excellence (NICE) guidelines.[16] Evidence for these recommendations included results from multiple meta-analyses investigating the antidepressant effect of exercise in people with depression.[17–20] However, some of these meta-analyses[18 21] found moderate, weak or no effects of exercise while others reported large effects.[17 19 20] These mixed results stem from methodological and conceptual differences regarding inclusion criteria and analytical approaches. For example, some studies focused on individuals with a diagnosis of major depressive disorder (MDD) while excluding studies that evaluated the presence of depression based on validated screening measures.[18] Others[17] investigated the effect of exercise alone or as a complementary treatment for depression to pharmacological therapy for studies published from 2003 to 2019. Further, some reviews included studies where patients also received exercise interventions[21] in the control groups. This creates the potential for bias[22] as even light intensity exercise can exert antidepressant effects. Importantly, a cause for concern has been raised in several reviews that exercise does not have a significant effect when restricted to 'low risk of bias' randomised controlled trials (RCTs) .[18 21] Therefore, extant meta-analyses have failed to provide convincing evidence to enable clinicians globally to implement exercise as an evidence-based effective treatment option for depression. One meta-analysis[20] addressed these methodological shortcomings by focusing on studies that included samples with depression using cut-offs on validated screening instruments and samples with MDD diagnosis assessed with diagnostic tools and including only studies that compared exercise versus non-active controls. The authors excluded trials comparing different exercise regimens. However, a large volume of studies has been published within the last 5 years, requiring an updated meta-analysis on the antidepressant effects of exercise, while addressing the shortcomings of previous reviews.

The objective of this meta-analysis was to update the current evidence on the effects of exercise in reducing depressive symptoms in adults with clinically elevated levels of depression including MDD and dysthymia, comparing exercise with non-exercising control groups. Additionally, we aimed to investigate the potential moderators of the antidepressant effects of exercise, and the presence of publication bias.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol number CRD42020210651. The PRISMA Statement was followed[23] in its updated version[24] additionally considering the PERSiST guidance (implementing PRISMA in Exercise, Rehabilitation, Sport medicine and SporTs science).[25]

To structure the eligibility criteria, the PICOS (Patient/Population; Intervention; Comparison, Outcome; Study design) approach was used.[26] Eligible for this meta-analysis included studies that: (1) Investigated participants aged 18 years or older with a primary diagnosis of MDD or dysthymia defined by the Research Diagnostic Criteria,[24] Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-5)[27] or International Classification of Diseases (ICD-10)[28] or adults with depressive symptoms determined by validated screening measures scoring above the threshold value (eg, Beck Depression Inventory (BDI) or Hamilton Rating Scale for Depression (HAM-D)).[29 30] If scales did not have validated cut-offs, the cut-off used by the author was accepted. (2) Investigated an exercise intervention in the treatment of depression, where exercise was defined as planned, structured, repetitive and purposive physical activity with the purpose to improve or maintain physical fitness.[31] Studies using yoga, tai chi or other mind-body activities were excluded, because the focus of such mind-body interventions are behavioural techniques that include, but not limited to, deep breathing, meditation/mindfulness and self-awareness.[32] (3) Included a non-exercising control group, such as usual-care, wait-list control conditions or placebo pills. Studies with any other exercise intervention (such as stretching or low-dose exercise) as a comparator were excluded as well as control and intervention groups commencing standardised interventions (eg, psychotherapy, medication) at the beginning of the intervention even if this was applied to both intervention and control groups (eg, starting medication treatment at the beginning of the intervention in both groups). However, ongoing treatments started at least 3 months before intervention initiation were included. (4) Examined the pre-post effects of exercise interventions on depressive symptoms using a validated depression scale. (5) Were RCTs and were published in peer-reviewed journals or as part of a dissertation. Conference proceedings were not included.

An electronic search of the following databases was conducted: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, Embase, SPORTDiscus and PsycINFO without any (eg, language or date) restrictions from inception to 13 September 2022. The search used a range of relevant terms to capture all potentially eligible results relating to exercise interventions for depressive symptoms (for the full list of search terms, see online supplemental text 1). Duplicate references were removed electronically and manually. To identify unpublished or ongoing studies, clinical trials.gov (www.clinicaltrials.gov) was searched. Additionally, reference lists of all eligible articles of recent reviews investigating the effectiveness of exercise versus control were screened to identify potentially eligible articles. All manuscripts were reviewed by at least two independent reviewers. Three reviewers (NS/LLB, DH) independently determined potentially eligible articles meeting the inclusion criteria using the titles and abstracts. Three independent reviewers (NS/LLB, DH) then applied the eligibility criteria after obtaining the full texts and generated a final list of included articles through consensus. If full-texts were not available, study authors were contacted to provide them. Five investigators (NS/ LLB, DH, FS, AH) judged article eligibility with any disagreements resolved through discussion.

Data extraction

Data extraction was done by three reviewers (NS/ LLB, DH) independently. A systematic extraction form was used for each article to collect the following data: (1) sample description (eg, sample size, mean age of participants); (2) intervention features (eg, type of exercise, length of trial); (3) methodological factors (eg, risk of bias, instruments used for diagnosis and symptom assessment); (4) effects on depressive symptoms (eg, changes in total depressive symptoms scored before and after intervention). For further information of extracted data see online supplemental tables 1, 4 and 5.

Primary outcome

The primary outcome was the mean change in depressive symptoms in the exercise compared with the control group from baseline to postintervention. The primary outcome proposed by the authors was selected if two or more instruments were used.

Study quality assessment

Selected studies were assessed by three independent authors (NS/LLB, DH) given an overall estimation of risk of bias (ie, low risk, some concerns or high risk) according to the revised Cochrane risk-of-bias tool for randomised trials (RoB2).[33] According to RoB2, the following domains were considered for the assessment of risk of bias: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result (see online supplemental table 3).

Data-analysis

A random effects meta-analysis was calculated due to expected heterogeneity. The standardised mean difference (SMD) and 95% CIs were used as the effect size (ES) measure. The SMD was calculated using the difference from pre to post intervention[34] with correlations of 0.7 between the exercise and the control group. All results were calculated on an intention-to-treat basis. Heterogeneity was calculated using the I^2.[35] Sensitivity analyses with pre-post-correlations of 0.6 and 0.8 were calculated to investigate changes in effect with less or more conservative values. Sensitivity analyses were further calculated excluding one study due to unequal distribution of psychotherapy among the intervention and control group and excluding studies with high risk for bias. Potential moderators (see table 1) of the antidepressant effects of exercise were investigated using linear meta-regression analyses for all studies and, separately, for studies including only patients with a diagnosis of MDD and/or dysthymia. Meta-regression assumptions were tested in JASP. Subgroup analyses were calculated to estimate the effect across depression classification, risk of bias, differing control conditions, intensity of exercise, exercise type, exercising in a group or individually, sample sizes and supervision (by different supervisors). We also calculated the mean difference (MD) on studies that assessed depressive symptoms using the Hamilton scale for depression or the BDI separately. Significance level was set at 0.05.[36] Publication bias was assessed with visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau[37] and Egger bias test.[38] Whenever significant, the Duval and Tweedie Trim and Fill was applied.[39] Fail safe number of negative studies that would be required to nullify (ie, make $p>0.05$) the ES were calculated.[40] All analyses were performed using Comprehensive Meta-Analysis software,[38] and number needed to treat (NNT)[41] analyses were calculated using Lenhard and Lenhard[42] with the formula of converting Cohens' d to NNT from Furukawa and Leucht.[43] Additionally, studies reporting (severe) adverse events and side effects were listed.

RESULTS

Search results

Searching of databases yielded 15 734 studies and an additional 84 studies were identified through other sources. Following removal of duplicates, 7100 potentially eligible studies remained for which abstracts were screened. At full text stage, 207 studies were reviewed and 166 removed because they failed to meet inclusion criteria (see online supplemental table 2 for references and exclusion reasons). The remaining 41 studies were included in the review and quantitative synthesis (see figure 1).

Study characteristics

In total, 2544 participants are included in the review and 2264 completed treatments (post-treatment n) and were included in the meta-analytical calculations, 1227 in intervention groups and 1037 in control groups. Twenty-one studies assessed depressive symptoms,[44–64] while MDD was diagnosed in 20 studies.[65–84] Percentage of females ranged from 26% to 100%, mean age from 18.8 to 87.9 years. Of the 41 included RCTs, studies originated from North and South America, Europe, Asia and Australia. See online supplemental table 1 for characteristics of selected studies (further characteristics are summarised in online supplemental tables 4 and 5).

Risk of bias

Risk of bias assessment revealed 12 studies to be rated of low risk of bias,[49 58 60 65 66 68–70 74 79 80 82] while 7 were rated with some concerns.[44 45 48 51 55 73 76] For 22 studies, RoB2 indicated high risk for bias.[46 47 50 52–54 56 57 59 61–64 67 71 72 75 77 78 81 83 84] For full details, see online supplemental table 3.

Main analysis

The main analysis of pooled data from 41 studies showed a large effect favouring exercise for a pre-post-correlation of 0.7 (SMD=−0.946, 95% CI −1.18 to −0.71, $p<0.001$, $I^2=82.49$, $p<0.001$; see figure 2). Publication bias was indicated by Begg-Mazumdar Kendall's Tau[37] (=−0.379, $p<0.001$ and the Egger[38] tests (intercept=−2.706, $p<0.001$). However, Duval and Tweedies' trim and fill method did not affect the effect. Fail-safe number of additional negative studies was 2789. The visual inspection of the funnel plot (see online supplemental figure 1) did not indicate risk of bias. Sensitivity analyses revealed a trivial change in the effect from −0.930 (95% CI −1.16 to −0.70, $p<0.001$, $I^2=82.032$, $p<0.001$) for a 0.8 pre-post-correlation to −0.957 (95% CI −1.19 to −0.72, $p<0.001$, $I^2=82.820$, $p<0.001$) for a 0.6 pre-post-correlation. Excluding one study[74] due to unequal distribution of psychotherapy treatments among the intervention and control group (20% vs 0%, respectively) revealed an effect of SMD=−0.938 (95% CI −1.17 to −0.70, $p<0.001$, $I^2=82.703$, $p<0.001$). Excluding studies with high risk of bias (see online supplemental table 3) rendered a moderate effect favouring exercise intervention (SMD=−0.717, 95% CI −1.01 to −0.43, $p<0.001$, $I^2=82.372$, $p<0.001$). Excluding studies with less than 6 weeks of intervention (see online supplemental table 1) showed a large effect favouring exercise intervention (SMD=−0.959, 95% CI −1.21 to −0.71, $p<0.001$, $I^2=84.132$, $p<0.001$). I^2 is suggesting substantial heterogeneity for the analyses.

Subgroup analyses

Subgroup analyses (summarised in table 1) showed that the beneficial effect of exercise on depression remained for all subgroups regarding depression classification, risk of bias, group exercise, the sample size of the trial and supervision by exercise professionals. Aerobic (SMD=−1.156) and resistance training (−1.042) as exercise types showed large effects whereas mixed aerobic and resistance training showed small effects (−0.455). Large effects were also found for studies including sample sizes in the intervention arm of less than 25 participants (SMD=−0.868 to −1.281) whereas larger samples of participants revealed moderate effects (SMD=−0.532).

Table 1 Subgroup meta-analysis of studies included in the quantitative analyses

Analysis	Number of RCTs	Meta-analysis				Heterogeneity	Trim and fill effect size (95% CI) (adjusted studies)
		SMD	95% CI		P value	I^2	
Main analysis	41	−0.946	−1.18	−0.71	<0.001	82.490	Unchanged
Depression classification							
MDD*	20	−0.998	−1.39	−0.61	<0.001	84.746	−1.167 (−1.59 to −0.74)(2)
Depressive symptoms	21	−0.915	−1.21	−0.62	<0.001	78.974	Unchanged
Risk of bias							
Low risk of bias	12	−0.666	−0.99	−0.34	<0.001	80.218	−0.367 (−0.72 to −0.01) (4, right of mean)
Some concerns	7	−0.829	−1.49	−0.16	0.015	86.926	−1.151 (−1.86 to −0.45) (2)
High risk of bias	22	−1.199	−1.59	−0.81	<0.001	81.484	Unchanged
Type of control condition							
Usual care	22	−0.949	−1.25	−0.65	<0.001	82.951	Unchanged
Wait list	11	−1.238	−1.69	−0.79	<0.001	73.749	−1.008 (−1.43 to −0.59) (3, right of mean)
Health education	3	−1.123	−2.56	0.31	0.125	93.955	Unchanged
Intensity of exercise†							
Light	2	−1.041	−2.53	0.45	0.170	88.867	N/A
Moderate	26	−1.132	−1.45	−0.81	<0.001	84.972	−1.403 (−1.80 to −1.00) (4)
Vigorous	10	−0.924	−1.47	−0.38	0.001	85.472	Unchanged
Exercise type†							
Aerobic	30	−1.156	−1.46	−0.85	<0.001	81.392	−1.264 (−1.59 to −0.94) (2)
Resistance	7	−1.042	−1.87	−0.22	0.013	87.944	Unchanged
Mixed‡	10	−0.455	−0.80	−0.11	0.009	80.237	Unchanged
Group exercise†							
Yes	27	−0.848	−1.10	−0.59	<0.001	80.503	Unchanged
No	13	−0.802	−1.24	−0.36	<0.001	83.312	−0.881 (−1.32 to −0.44) (1)
Supervision†							
Yes§	40	−1.026	−1.28	−0.77	<0.001	83.926	−1.115 (−1.38 to −0.85) (2)
No	6	−0.451	−0.91	0.00	0.052	63.553	−0.122 (−0.63 to 0.39) (3, right of mean)
Type of supervision†							
Exercise professional	18	−0.984	−1.34	−0.63	<0.001	78.879	Unchanged
Other professional/student	14	−1.278	−1.81	−0.74	<0.001	85.356	Unchanged
Sample size intervention arm†							
n≥25	12	−0.532	−0.81	−0.26	<0.001	81.445	Unchanged
n<25	35	−1.166	−1.49	−0.84	<0.001	81.239	−1.370 (−1.72 to −1.02) (4)
n≥10	34	−0.868	−1.11	−0.63	<0.001	84.568	−0.913 (−1.16 to −0.67) (1)
n<10	13	−1.281	−1.87	−0.70	<0.001	75.817	−1.568 (−2.22 to −0.91) (2)

See online supplemental tables 3–5 for detailed categorisation for each study.
*Including three studies with MDD and dysthymia.[67 81 82]
†Data for a second intervention group within the same study were included for these analyses.
‡Mixed exercise=aerobic and resistance exercise.
§Two studies were partly supervised, see online supplemental table 5).
MDD, major depressive disorder; RCT, randomised clinical trials; SMD, standard mean difference.

Subgroup analyses with health education, with light exercise interventions, or with unsupervised training only including small numbers of analysed studies showed comparable SMDs but no significant effects. Subgroup analyses with studies with low or moderate risk of bias confirm results by showing similar outcomes (see online supplemental table 6) as well as subgroup analyses for studies with the diagnosis of MDD and dysthymia (see online supplemental table 7).

Adverse events and side effects

In 10 studies, it was documented that no (serious) adverse events occurred.[52 62 63 69 73 74 80–82] Three of these studies reported minor adverse events like muscle or joint pain, headache and fatigue.[52 70 74] One study reported that adverse events occurred but did not provide further information.[79] Three studies reported few side effects like worsening of pre-existing orthopaedic injuries or admittance to psychiatric ward due to major depression.[46 66 71]

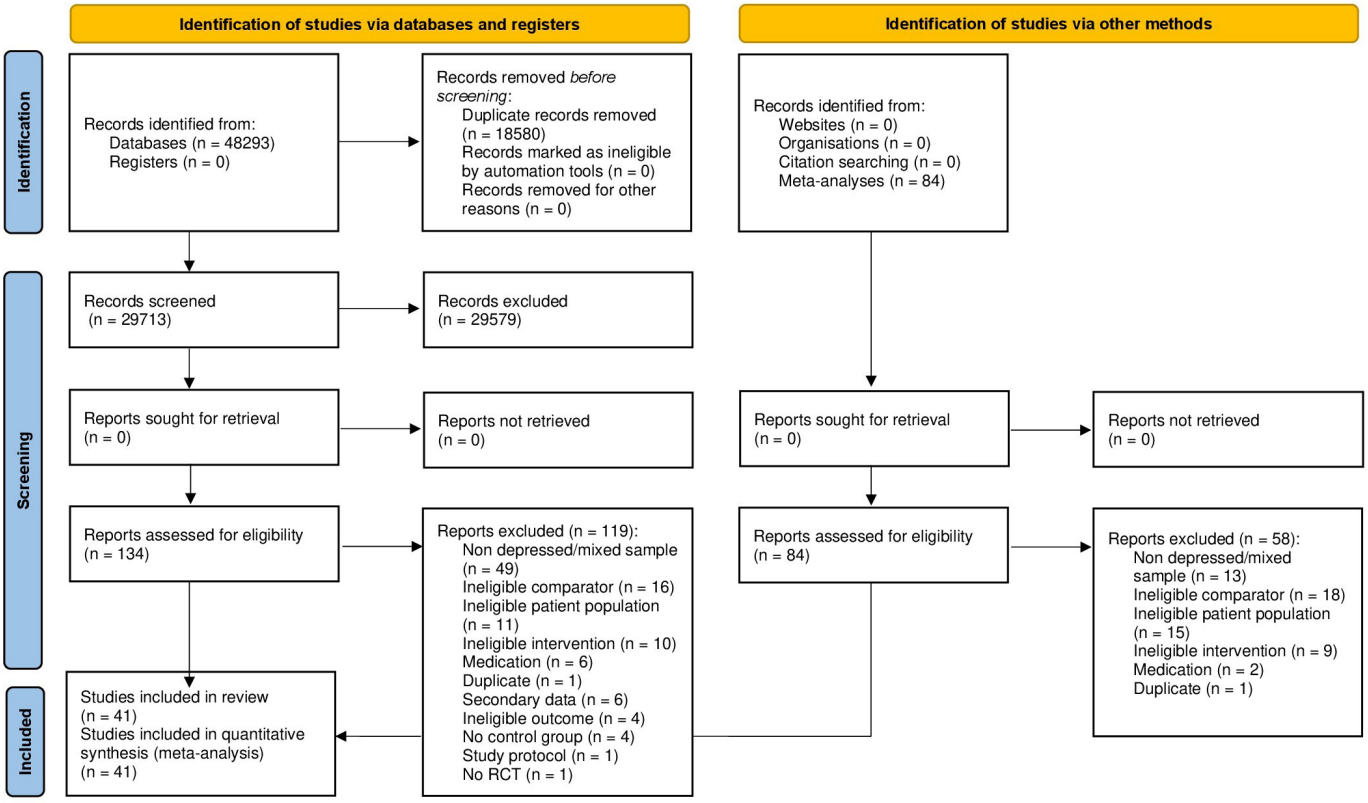

Figure 1 Flowchart of study selection. Flowchart adapted from the PRISMA 2020 statement.[42] RCT, randomised controlled trial.

Meta-regression

Meta-regression (see table 2) was calculated for the main analysis and MDD only. In the main analysis, duration of trial in weeks moderated the effect of exercise on depression, with shorter trials associated with larger effects (β=0.032, 95% CI 0.01 to 0.09, p=0.032, R^2=0.06). For MDD only, higher antidepressant use by the control group was associated with smaller effects (β=−0.013, 95% CI −0.02 to −0.01, p=0.012, R^2=0.28). A meta-regression with studies with low and moderate risk of bias (see online supplemental table 8) rendered a moderating effect of duration of trials overall (β=0.064, 95% CI 0.01 to 0.126, p=0.04, R^2=0.12) as well as for MDD only (β=0.070, 95% CI 0.01 to 0.14, p=0.034, R^2=0.26).

Mean change and numbers needed to treat (NNT)

We found a mean change of −4.70 points (95% CI −6.25 to −3.15, p<0.001, n=685) on the HAM-D and for the BDI of −6.49 points (95% CI −8.55 to −4.42, p<0.001, n=275) as an additional improvement effect of exercise over control conditions. The calculated NNT was 2.0 (95% CI 1.68 to 2.59) for the main-analysis, and 2.8 (95% CI 1.94 to 5.22) for the low risk of bias studies. For MDD, only the NNT was 1.9 (95% CI 1.49 to 2.99) and 1.6 (95% CI 1.58 to 2.41) in supervision by other professionals/students.

DISCUSSION

This is the largest meta-analysis investigating the effects of exercise for depressive symptoms within samples with diagnosed or indicated depression. Among 41 RCTs, we found that exercise interventions had a large effect favouring exercise over control conditions. Publication bias tests indicate an underestimation of this effect. Subgroup analyses resolved several key questions that lacked clarity from previous reviews;[17–20] specifically, the positive effect of exercise remained significant regardless of risk of bias, depression classification, exercise type, group setting, type of supervision or sample size. Subgroup analyses with health education (k=3), with light exercise interventions (k=2) or with unsupervised training (k=6) showed comparable SMDs but no statistical significance, which can be attributable to the lack of power due to the small numbers of studies included in the subgroup analyses. Surprisingly, the combination of mixed aerobic and resistance training showed smaller effects than aerobic or resistance training as single interventions. We also found a decline in ES from large to moderate for studies with sample sizes in the intervention arm of 25 or more participants. Focusing on solely diagnosed MDD, significant effects of exercise were found for all subgroup analyses except for light and mixed exercise, unsupervised training and for studies with some concern for risk of bias which can again be attributable to a lack of power due to the small number of included studies in the analyses (k=2 to 3). Limiting analyses to studies with low risk of bias and some concerns according to ROB 2 reveal similar results but with ESs declining from high to moderate for most analyses (see online supplemental table 6). Meta-regressions indicated a moderating effect of trial duration favouring shorter interventions and remained robust in meta-regressions without studies of high risk of bias. Regarding the type of exercise, most trial arms (k=30) investigated aerobic exercise detecting large effects followed by resistance training with comparable outcomes. In terms of the exercise intensity, only two arms investigated light intensity exercise while 26 and 10 trials applied moderate and vigorous intensity respectively, with all trials evidencing large effects. Supervised exercise revealed large ESs compared with unsupervised exercise with small effects. Minimal differences were detected between group and non-group exercise interventions favouring group exercise, with both showing large effects.

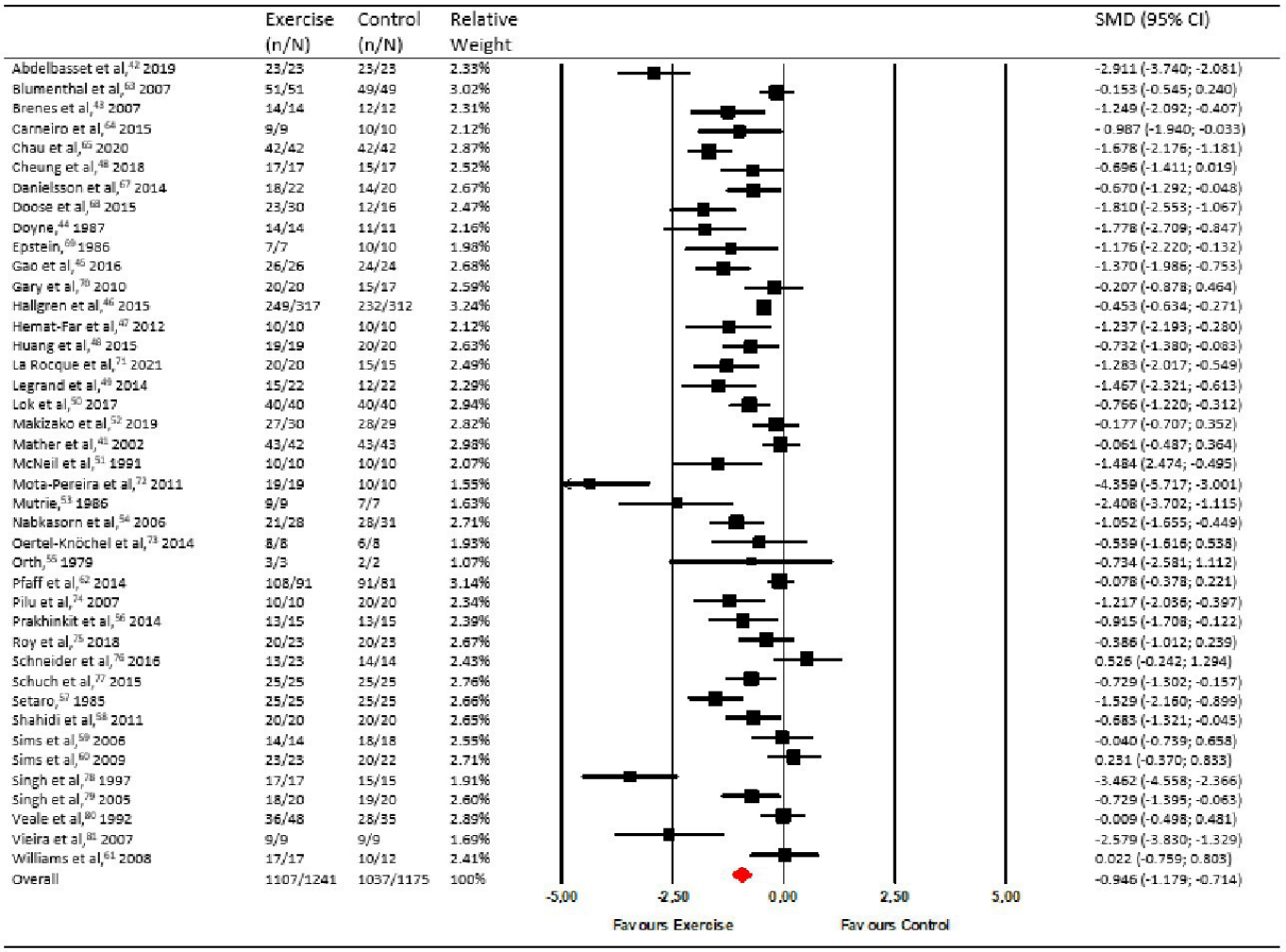

Figure 2 Meta-analysis of overall studies. N, preintervention n, postintervention, SMD, standardised difference.

Table 2 Meta-regression of moderators/correlates of effects of exercise on depression

Moderator	Number of RCTs	β	95% CI		P value	R^2‡
Main analysis						
Mean age exercise	30	0.014	0.00	0.03	0.046	0.02
Mean age control	30	0.014	0.00	0.03	0.041	0.02
Duration of trial (in weeks)*	46	0.047	0.00	0.09	0.032	0.06
Weekly frequency*	46	0.004	−0.17	0.18	0.959	0.00
Minutes per session*	42	0.008	−0.01	0.02	0.268	0.00
Sample size†	41	0.002	−0.00	0.01	0.160	0.00
MDD (+dysthymia) only						
Mean age exercise	15	0.009	−0.02	0.04	0.585	0.00
Mean age control	15	0.013	−0.02	0.05	0.432	0.00
Duration of trial (in weeks)*	22	0.035	−0.02	0.09	0.218	0.01
Weekly frequency*	22	0.023	−0.20	0.25	0.844	0.00
Minutes per session*	20	−0.005	−0.03	0.02	0.746	0.03
Sample size†	20	0.008	−0.00	0.02	0.090	0.04

*Data for a second intervention group within the same study were included for these analyses.
†Average sample size pre-post intervention.
‡R^2 equal to R^2 analogue.
RCT, randomised controlled trial.

Intervention arms with samples sizes ≥25 revealed moderate effects (see table 1 for details).

A recent meta-analysis of Cuijpers *et al*[85] found a moderate ES for psychotherapy treatment for depression across all age groups (g=0.75), and also when solely including studies with low risk of bias (g=0.51); while in terms of antidepressant efficacy, Cipriani *et al*[86] found medication to be more effective in comparison to placebo with Odds ratio of 2.13 indicating a small ES of d=0.417. This is notable as the presented results suggest exercise to qualify as an efficacious treatment option for depressive symptoms among individuals with depression.

These results extend the findings from an earlier meta-analysis of Schuch *et al*[20] (based on 25 studies including 1487 participants, revealing high heterogeneity of I^2 82.10%). Notably, the present findings are based on an additional 17 studies[44 45 48 52 53 55 59 62 67–69 71 74 78 79 84] since Schuch *et al*'s[20] review and 4[45 55 68 74] studies following the most recent meta-analysis by Carneiro *et al*,[17] comprising only 15 studies focusing on different inclusion criteria including medication in treatment and control arm conditions.

In contrast to Krogh *et al*,[18] the analyses including only low risk of bias studies resulted in moderate effects with wide 95% CIs ranging from −0.99 to −0.34. Of note, we used the current risk of bias tool (RoB2) and included a greater number of low risk of bias trials compared with Krogh *et al*'s[18] meta-analysis (11 vs 4). To reduce risk of bias, we compared exercise treatment groups with non-exercising control groups only. From the included 35 trials in the Cochrane Meta-Analysis by Cooney *et al*[21] consisting of 1356 participants, they reported 63% heterogeneity for the main analyses, the current review excluded 13 of these studies as groups were labelled as either 'controls' (ie, they received psychotherapy or pharmacotherapy) or groups labelled as 'exercise' groups (ie, they received a combination of exercise and another form of therapy or no therapy at all) or participants did not meet criteria for depression (see Ref. 22 for a critical appraisal). Krogh *et al*[18] also included 35 trials comprising 2498 participants with high heterogeneity (I^2=81%) of which the current review excluded 17 studies with control groups that received stretching, relaxation or compared exercise to psychotherapy, medication or combined exercise with psychotherapy. Morres *et al*[19] included 11 trials involving 455 patients revealing low and non-statistically significant heterogeneity (I^2=21%) but focused on aerobic exercise only; however, five of these studies were excluded from the current review because they included medication, active control conditions or cognitive or counselling therapy as comparator conditions. Carneiro *et al*[17] included 15 studies in their meta-analysis with a total sample size of 1532 individuals focusing on pharmacological treatment, exercise treatment and combined exercise with psychotherapy, of which the current review excluded 7 studies due to the inclusion of pharmacological therapy as a comparator condition either alone or in combination with psychotherapy. A further study was also excluded because participants were offered internet guided text modules on how to become more physically active but no actual exercise intervention was administered. Carneiro *et al*.[17] overall reported moderate heterogeneity (I^2= 33%).

This summary reveals that a notable methodological limitation based on the former published meta-analyses in this field, included a proportion of trials with questionable intervention or control group conditions, which resulted in the inability to detect the effect of exercise per se (while excluding other forms of interventions). Hence, this notable shortcoming was addressed in this current meta-analytic review. Although we explored heterogeneity with sub-analyses and meta regression, we also found similar large heterogeneity comparable to previous larger meta-analyses[18 20 21] which guarantees comparability, yet needs to be considered when interpreting the results.

Our meta-regressions indicated that shorter trials are associated with larger effects than longer trials. A possible explanation is that larger trials had more dropouts, and higher dropout rates can reduce the effect in intention to treat analyses.[87] Alternatively, it is possible that the effect wanes with the time. However, all but three studies had interventions lasting 16 weeks or less and further studies with longer follow-ups should confirm this effect.[88] Also, we have found that studies in which control groups had a higher percentage of participants taking antidepressants identified smaller effects of exercise. This is expected as the difference on the magnitude of the improvement on depressive symptoms is smaller when exercise is compared with effective treatments, such as the use of pharmacological antidepressants, or when compared with controls without any treatment.[87]

Clinical implications included that if 100 people were each in the control and the exercise group, 20 participants in the control and 54 in the exercise group for the main analysis and 43 in the exercise group for the low risk of bias studies, analyses can be expected to have favourable outcomes.[89] The NNT for the main-analysis was 2, while it was 2.8 in the low risk of bias studies, 1.9 in MDD only and 1.6 in supervision by other professionals/students. This effect is comparable to recent meta-analyses with psychotherapy revealing a NNT of 2.5 for the main analyses and 3.5 in the low risk of bias studies and for medication of 4.3.[85 86] Based on a NNT of 2 for the main analyses this means that for every two people treated with exercise, it is expected at least one to have a large magnitude reduction in depressive symptoms.[43] Furthermore, exercise showed an additional declining effect over control conditions of −4.70 points in the HAM-D as a diagnostic clinician measure in 16 studies and −6.49 in the BDI in eight studies indicating a clinically meaningful reduction of depressive symptoms from moderate to mild depression. According to the NICE guidelines, a three-point change is indicated as clinically meaningful for both measures.[16]

Limitations

We acknowledge that limitations lie in the high heterogeneity of the included studies that can stem from different control group conditions, cultural backgrounds, gender distribution, variable forms of assessments and diagnosis of depression severity or MDD. Notwithstanding, we have performed several subgroup analyses and meta-regressions to explore the sources of this heterogeneity. Additionally, most of the included studies comprised small sample sizes for example, 13 studies with intervention arms of ≤10 participants in each group postintervention which we addressed with subanalyses. However, studies with larger samples sizes showed smaller but still moderate effects. Some subanalyses showed non-significant results as they lacked power due to the small number of studies included. In principle, the overreliance of significance testing should be avoided and interpretation of results based on SMD and 95% CI along with p values. Mostly seen wider ranges in CIs within the analyses can stem to a large extent from smaller studies (eg, 10 studies with n<10) and small number of studies in the subanalyses (especially less than k=10) which brings some uncertainty pertaining to the true effect. However, for the main analyses, 95% CIs were documented for exercise conditions comprising moderate intensity, aerobic exercise, group exercise and supervised exercise (ranging between 26 and 41 included studies), thus indicating

moderate to large effects even for the lower limits. These outcomes provide adequate evidence to support the recommendation that exercise has utility in treating depression based on the aforementioned conditions. Long-term effects could not be investigated due to missing follow-up data for most studies. Moreover, it was not possible to control for placebo effects due to the nature of the interventions. Furthermore, 6 out of the 41 included studies were published prior to 2001 and can therefore be assigned to the pre-CONSORT era. This means that these earlier trials might not reflect the current standards and/or feature incomplete reporting of methodological details that was introduced with the CONSORT guidelines and checklist, therefore increasing scope in biased risk assessments and heterogeneity.[22 90]

Further steps need to be undertaken to consider exercise as a first-line treatment for depression alongside psychotherapy and medication, including conducting non-inferiority trials to demonstrate that exercise is non-inferior to current first line treatments, and evidence that exercise is effective at long-term follow-ups. Future large-scale research studies should also investigate which patients benefit most from which exercise condition and identify any groups for whom exercise might not be the optimal treatment choice. It is noteworthy that the studies included in the current and former reviews consisted of samples which met the trial inclusion criteria comprising individuals that were willing, motivated and physically able to take part in the exercise regimen (eg, assessed by the Physical Activity Readiness Questionnaire[91]) and excluded individuals with diagnoses that exercise may pose a risk (for example, individuals with cardiovascular diseases that require physician guidance to undertake exercise). Further, adverse events and outcomes due to exercise may occur in rare instances (nevertheless, they should be reported which was not documented for the majority of studies in this review), and not everyone has access to any form of exercise or exercise with the needed quality (eg, with a former sport medical examination). It is also noteworthy that the included studies were mainly conducted in high-income and upper-middle income countries, for example, no study was identified from the African continent. Future study designs should consider these relevant points including motivational aspects of attendance and samples from developing countries or rural areas to increase the generalisability of the results for healthcare.

Further strengthening the evidence base for exercise also has utility as it may be a less stigmatising treatment option for depressed individuals who may be reluctant to seek and adhere to psychotherapy and/or medication.

CONCLUSION

The findings from this review represent the most up to date and comprehensive meta-analysis of the available evidence and further supports the use of exercise focusing specifically on supervised and group exercise with moderate intensity and aerobic exercise regimes. This offers a further evidence-based treatment option for the large amount of untreated individuals with depression, including individuals who refuse or cannot tolerate medication and/or psychotherapy. However, given the high heterogeneity and mainly small and selected samples of the included studies, this requires individual decisions involving the treating physician to determine if and which conditions of exercise are the optimal treatment of choice while also recognising the potential synergistic effects of exercise in managing both physical and mental well-being. Updated guidelines as well as routine clinical decisions regarding interventions for treating depression should consider the current findings. This is particularly timely, following the post COVID-19 pandemic, given that rates of depression have continued to increase worldwide.

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Contributors AH and FS conceived and designed the study. AH, LLB and FS had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. NS/LLB and DH did the literature search. AH, LLB, NS, DH and FS conducted the analyses, interpreted the data and wrote the first draft of the manuscript. All authors contributed to critical revision of the report for important intellectual content.

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Supplementary Material

Exercise as Medicine for Depressive Symptoms?
A Systematic Review and Meta-analysis with Meta regression

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Supplementary Text 1. Full search terms

MeSH terms

((exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial))

Cochrane/ Embase

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR "physical medicine" OR resistance OR lift*):ti,ab,kw AND (depression OR dysthymia):ti,ab,kw AND (randomized control trial" OR "randomized clinical trial):ti,ab,kw in Trials (Word variations have been searched)

PubMed

((exercis*[Title/Abstract] OR aerobic*[Title/Abstract] OR running[Title/Abstract] OR jogging[Title/Abstract] OR walk*[Title/Abstract] OR hiking[Title/Abstract] OR swim*[Title/Abstract] OR aquatic*[Title/Abstract] OR cycling[Title/Abstract] OR bicycl*[Title/Abstract] OR strength*[Title/Abstract] AND activit*[Title/Abstract] OR fitness[Title/Abstract] OR train*[Title/Abstract] OR physical medicine[Title/Abstract] OR resistance[Title/Abstract] OR lift*[Title/Abstract]) AND (depression[Title/Abstract] OR dysthymia[Title/Abstract])) AND (randomized controlled trial[Title/Abstract] OR clinical trial[Title/Abstract])

PsychINFO

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial)

SPORTDiscus

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial)

Medline

((TS=(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*)) AND TS=(depression OR dysthymia)) AND TS=(randomized controlled trial OR clinical trial)

Scopus

TITLE-ABS-KEY ((exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* AND activit* OR fitness OR train* OR physical AND medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized AND controlled AND trial OR clinical AND trial))

Web of Science

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial) (Topic)

Supplementary Table 1. Data of Studies Included in Systematic Review

Study	Sample size (n)		Outcome[a]	Pre (mean (SD))		Post (mean (SD))		Intervention			Control group condition	Diagnosis
	Exercise	Control		Exercise	Control	Exercise	Control	Type of intervention	Wks	Sessions per wk/ time per session		
Abdelbasset et al,[45] 2019	23	23	PHQ-9	16.12 (3.10)	15.95 (3.14)	3.65 (1.21)	8.54 (2.14)	Aerobic exercise	12	3/30-60 min[b]	Usual care (standard medical treatment)	Depressive symptoms
Blumenthal et al,[66] 2007 (supervised exercise)	51	49	HAM-D, BDI-II	16.40 (3.70)	17.20 (4.30)	9.20 (6.10)	11.00 (7.00)	Aerobic exercise	16	3/45 min	Placebo	MDD
Blumenthal et al,[66] 2007 (homebased exercise)	53	49	HAM-D, BDI-II	17.30 (4.60)	17.20 (4.30)	10.20 (6.70)	11.00 (7.00)	Aerobic exercise	16	3/45 min	Placebo	MDD
Brenes et al,[46] 2007	14	12	HAM-D, GDS	12.70 (3.40)	9.50 (3.70)	7.80 (4.30)	10.90 (5.80)	Mixed exercise	16	3/60 min	Usual care (phone calls to discuss health status)	Depressive symptoms
Carneiro et al,[67] 2015	9	10	BDI-II, DASS-21	45.56 (9.65)	46.10 (11.52)	34.89 (10.56)	49.40 (16.72)	Aerobic exercise	16	3/45 min	Usual care (pharmacological therapy)	MDD & Dysthymia
Chau et al,[68] 2020	42	42	HAM-D, DASS-21	25.93 (6.59)	25.62 (8.03)	12.57 (8.06)	25.58 (7.81)	Mixed exercise	12	3/60 min	Wait-list	MDD
Cheung et al,[48] 2018	17	17	HAM-D	18.50 (3.20)	19.40 (3.60)	9.80 (5.60)	14.50 (5.30)	Aerobic exercise	12	3/40 min	Usual care (usual psychiatric care)	MDD

Danielsson et al,[70] 2014	22	20	MADRS	24.60 (4.10)	23.40 (5.00)	-10.30[c] (1.60)	-4.60[c] (1.70)	Aerobic exercise	10	2/60 min	Usual care (standard care)	MDD
Doose et al,[71] 2015	30	16	HAM-D, BDI-II	13.97 (2.58)	14.67 (3.91)	-9.48[d] (11.38-7.58)	-1.24[d] (-3.85-1.37)	Aerobic exercise	8	3/60 min	Wait-list	MDD
Doyne et al,[47] 1987 (running condition)	14	11	HAM-D, BDI, DACL	13.36 (4.43)	12.58 (4.58)	6.64 (3.61)	13.58 (5.14)	Aerobic exercise	8	4/25 min	Wait-list	Depressive symptoms
Doyne et al,[47] 1987 (weightlifting)	15	11	HAM-D, BDI, DACL	13.80 (7.78)	12.58 (4.58)	5.13 (3.44)	13.58 (5.14)	Resistance exercise	8	4/45 min	Wait-list	Depressive symptoms
Epstein,[72] 1986	7	10	BDI, SDS	25.29 (6.52)	22.00 (7.16)	9.00 (10.94)	16.30 (7.44)	Aerobic exercise	8	3/30 min	Wait-list	MDD
Gao et al,[48] 2016	26	24	SDS	0.58 (0.10)	0.59 (0.11)	0.43 (0.09)	0.57 (0.10)	Aerobic exercise	12	5/60-90 min[b]	Usual care (lived normally without intervention)	Depressive symptoms
Gary et al,[73] 2010	20	17	HAM-D	15.40 (3.40)	15.20 (3.60)	8.40 (5.60)	9.30 (4.90)	Aerobic exercise	12	3/weekly increase by 5 min to 60 min[b]	Usual care (usually provided health care)	MDD
Hallgren et al,[49] 2015	317	312	MADRS	22.20 (6.80)	20.90 (7.50)	11.30 (7.90)	13.80 (8.90)	Mixed exercise	12	3/60 min	Usual care (treatment as usual)	Depressive symptoms
Hemat-Far et al,[50] 2012	10	10	BDI	25.00 (5.30)	23.80 (4.70)	16.60 (6.90)	22.80 (4.90)	Aerobic exercise	8	3/40-60 min[b]	Usual care (pursue normal live)	Depressive symptoms
Huang et al,[51] 2015	19	20	GDS-15	8.63 (3.56)	7.20 (2.19)	4.63 (2.49)	5.20 (1.69)	Mixed exercise	12	3/50 min	Usual care	Depressive symptoms

La Rocque et al,[74] 2020	20	15	HAM-D	12.00 (3.77)	13.93 (3.71)	6.75 (6.05)	16.33 (5.84)	Aerobic exercise	8	2/50-60 min[b]	Wait-list	MDD
Legrand et al,[52] 2014	22	22	BDI-II	21.67 (6.78)	19.25 (9.34)	12.80 (4.38)	19.67 (8.17)	Aerobic exercise	7	2/30 min	Wait-list	Depressive symptoms
Lok et al,[53] 2017	40	40	BDI	17.46 (8.07)	19.89 (5.00)	11.89 (4.23)	17.71 (4.61)	Aerobic exercise	10	4/70 min	Wait-list	Depressive symptoms
Makizako et al,[55] 2019	30	29	GDS-15	7.10 (2.50)	6.40 (2.50)	5.30 (2.50)	5.10 (3.10)	Mixed exercise	20	1/90 min	Health education	Depressive symptoms
Mather et al,[44] 2002	43	43	HRSD	16.70 (10.83)[e]	17.40 (10.83)[e]	12.60 (7.02)	13.70 (6.02)	Mixed exercise	10	2/55-65 min[b]	Health education	Depressive symptoms
McNeil et al,[54] 1991	10	10	BDI	16.60 (3.10)	15.20 (2.40)	11.10 (3.00)	14.70 (3.70)	Aerobic exercise	6	3/20-40 min[b]	Wait-list	Depressive symptoms
Mota-Pereira et al,[75] 2011	19	10	HAM-D, BDI	19.32 (1.69)	13.00 (1.42)	12.48 (1.74)	13.60 (1.34)	Aerobic exercise	6	5/30-45 min[b]	Usual care (pharmacothe rapy)	MDD
Mutrie,[56] 1986 (aerobic exercise)	9	7	BDI, POMS	22.44 (6.82)	23.00 (5.80)	9.46 (4.28)	21.42 (5.26)	Aerobic exercise	4	3/20 min	Wait-list	Depressive symptoms
Mutrie,[56] 1986 (strength & stretching)	8	7	BDI, POMS	21.86 (4.21)	23.00 (5.80)	14.63 (7.63)	21.42 (5.26)	Mixed exercise	4	3/20 min	Wait-list	Depressive symptoms
Nabkasorn et al,[57] 2006	28	31	CES-D	20.10 (0.90)	18.80 (7.00)	14.40 (4.12)	17.50 (4.23)	Aerobic exercise	8	5/50 min	Usual care (usual daily routine)	Depressive symptoms

Oertel-Knöchel et al,[76] 2014	8	8	BDI-II	26.25 (10.21)	25.50 (11.83)	18.75 (9.50)	24.00 (13.09)	Aerobic exercise	4	3/75 min	Wait-list	MDD
Orth,[58] 1979	3	2	DACL, MMPI	14.00 (3.60)	19.50 (7.00)	7.00 (6.50)	16.50 (2.12)	Aerobic exercise	4	5/30 min	Self-monitoring	Depressive symptoms
Pfaff et al,[65] 2014	108	92	SIGMA	21.02 (9.4)	21.66 (8.4)	14.43 (9.8)	14.32 (9.3)	Mixed exercise	12	5/30 min + 3x resistance training	Usual care (usual medical care)	MDD
Pilu et al,[77] 2007	10	20	HAM-D	20.50 (7.10)	19.30 (5.70)	8.10 (5.20)	16.70 (9.10)	Resistance exercise	32	2/60 min	Usual care (pharmacothe rapy)	MDD
Prakhinkit et al,[59] 2014 (traditional walking)	15	15	TGDS-30	17.30 (1.00)	17.90 (0.70)	15.50 (0.90)	18.60 (0.60)	Aerobic exercise	12	3/20-30 min[b]	Usual care (sedentary control group)	Depressive symptoms
Prakhinkit et al,[59] 2014 (Buddhism walking)	15	15	TGDS-30	16.08 (0.90)	17.90 (0.70)	8.60 (0.60)	18.60 (0.60)	Aerobic exercise	12	3/20-30 min[b]	Usual care (sedentary control group)	Depressive symptoms
Roy et al,[78] 2018	23	23	HAM-D, DSSS	19.30 (4.83)	16.55 (4.14)	15.00 (4.93)	13.85 (3.16)	Aerobic exercise	1.5	7/20 min	Usual care (treatment as usual)	MDD
Schneider et al,[79] 2016	15	14	HAM-D, BDI-II	15.70 (4.60)	17.40 (4.30)	10.60 (6.10)	5.80 (5.41)	Mixed exercise	24	Biweekly 2/20-65 min[b]	Usual care (enhanced usual care condition)	MDD
Schuch et al,[80] 2015	25	25	HAM-D	26.52 (1.80)	26.96 (2.70)	7.42 (4.47)	11.12 (4.47)	Aerobic exercise	12	3/unclear	Usual care (treatment as usual)	MDD
Setaro,[60] 1985	25	25	MMPI	68.92 (5.27)	68.56 (3.87)	62.00 (6.51)	69.88 (3.96)	Aerobic exercise	10	2/unclear	Usual care (no activity or treatment)	Depressive symptoms

Shahidi et al,[61] 2011	20	20	GDS-30	15.30 (5.40)	15.20 (3.90)	11.10 (6.20)	15.20 (6.10)	Aerobic exercise	N/A	Unclear/30 min	Unclear	Depressive symptoms
Sims et al,[62] 2006	14	18	GDS	12.64 (3.61)	12.22 (3.51)	12.23 (5.22)	12.00 (4.26)	Resistance exercise	10	3/unclear	Information and advice for local options of exercise	Depressive symptoms
Sims et al,[63] 2009	23	22	CES-D	15.43 (7.49)	23.27 (8.86)	15.13 (8.49)	20.62 (11.79)	Resistance exercise	10	2/unclear	Wait-list	Depressive symptoms
Singh et al,[81] 1997	17	15	HAM-D, DSM-IV, BDI, GDS	12.30 (0.90)	11.40 (1.00)	5.30 (1.30)	8.90 (1.30)	Resistance exercise	10	3/50 min	Health education	MDD & Dysthymia
Singh et al,[82] 2005 (high intensity)	20	20	HAM-D, GDS	18.00 (4.50)	19.70 (3.90)	8.50 (5.50)	14.40 (6.00)	Resistance exercise	8	3/65 min	Usual care (usual care from GP)	MDD & Dysthymia
Singh et al,[82] 2005 (low intensity)	20	20	HAM-D, GDS	19.50 (5.30)	19.70 (3.90)	12.40 (6.30)	14.40 (6.00)	Resistance exercise	8	3/65 min	Usual care (usual care from GP)	MDD & Dysthymia
Veale et al,[83] 1992	48	35	CIS, BDI	35.87 (1.07)	37.57 (1.49)	16.80 (2.06)	26.39 (2.50)	Aerobic exercise	12	3/unclear	Usual care (usual psychiatric treatment)	MDD
Vieira et al,[84] 2007	9	9	HAM-D	30.22 (3.04)	31.11 (3.51)	24.88 (2.13)	32.66 (3.12)	Aerobic exercise	12	2/50 min	Usual care	MDD
Williams et al,[64] 2008 (mixed exercise)	16	12	CSDD	11.05 (2.79)	14.58 (5.75)	8.37 (5.78)	11.75 (8.10)	Mixed exercise	16	5/30 min	Social conversation	Depressive symptoms
Williams et al,[64] 2008 (supervised walking)	17	12	CSDD	12.18 (5.00)	14.58 (5.75)	9.68 (6.57)	11.75 (8.10)	Aerobic exercise	16	5/30 min	Social conversation	Depressive symptoms

Note. BDI=Beck Depression Inventory. CES=Centre for Epidemiologic Studies Depression. CIS=Clinical Interview Schedule. CSDD=Cornel Scale for Depression in Dementia. DACL=Depression Adjective Check Lists. DASS=Depression Anxiety Stress Scale. DSSS=Depression Somatic Symptom scale. GDS=Geriatric Depression Scale. HAM-D=Hamilton Depression Scale. MADRS=Montgomery-Asberg Depression Rating Scale. MDD=Major Depressive Disorder. MMPI=Minnesota Multiphasic Personality Inventory. PHQ-9=Patient Health Questionnaire. POMS=Profile of Mood States. TGDS=Thai Geriatric Depression Scale. SDS=Severity of Dependence Scale. HRSD=Hamilton Rating Scale for Depression. DACL=Depression Adjective Checklist. SIGMA=screening tool for the assessment and design of human-centered work activities. Usual care=no treatment but including psychiatric, pharmaco-, and psychotherapeutic treatment if required. Mixed exercise=aerobic and resistance exercise. Studies with two exercise groups were compared to the same control group. [a]In case of more than one outcome, mean and SD of the first named outcome are reported. Primary outcome as indicated by authors or, if not indicated, rated by a clinician were included in the main analyses. [b]For varying minutes per session, the average was used for calculations. [c]Values are presented as mean changes with standard errors. [d]Values are presented as least Square Means (95%CI). [e]Calculation of SDs from confidence intervals.

Supplementary Table 2. List of excluded studies at full-text screening stage, with brief reasons

	Author	Reason for exclusion
1.	Abdelbasset et al, 2021	Non depressed
2.	Abedi et al, 2015	Non depressed
3.	Abrahao et al, 2015	Ineligible patient population
4.	Abrantes et al, 2017	Ineligible intervention
5.	Aider et al, 2014	Ineligible patient population
6.	Akandere et al, 2011	Non depressed
7.	Almeida et al, 2022	Ineligible intervention
8.	Alves et al, 2013	Non depressed
8.	Ansai et al, 2015	Non depressed
9.	Antunes et al, 2005	Non depressed
10.	Armstrong et al, 2004	Non depressed
11.	Bang et al, 2016	Non depressed
12.	Belvederri Murri et al, 2015	Medication
13.	Bernard, Ninot, Cyprien et al, 2015	Ineligible outcome
14.	Bernard, Ninot, Bernard et al, 2015	Non depressed
15.	Blumenthal et al, 1999	Medication
16.	Blumenthal et al, 2012	Non depressed
17.	Bolier et al, 2013	Ineligible intervention
18.	Bonnet, 2005	Ineligible intervention
19.	Bosscher, 1993	Ineligible comparator
20.	Boström et al, 2015	Non depressed
21.	Brinsley et al, 2022	Non depressed
21.	Brittle et al, 2009	Non depressed
22.	Brown et al, 2009	Non depressed
23.	Buettner, 2002	Non depressed
24.	Buschert et al, 2019	Ineligible comparator
25.	Callaghan et al, 2011	Ineligible comparator
26.	Carneiro et al, 2016	Non depressed
27.	Carta et al, 2022	Non depressed
28.	Carter et al. 2022	Ineligible age
29.	Chalder et al, 2012	Ineligible intervention
28.	Chan et al, 2012	Ineligible intervention
29.	Chen et al, 2017	Non depressed
30.	Chu et al, 2008	Ineligible comparator
31.	Ciccolo et al, 2022	Ineligible intervention
31.	Conradsson et al, 2010	Non depressed
32.	Courneya et al, 2007	Ineligible patient population
33.	Craft et al, 2007	Ineligible comparator
34.	de la Cerda et al, 2011	Medication
35.	de Lima et al, 2016	Non depressed
36.	Dalgas et al, 2010	Ineligible patient population
37.	Damush et al, 1999	Non depressed

38.	Deschamps et al, 2015	Ineligible comparator
39.	Dorscht et al, 2019	Ineligible comparator
40.	Dunn et al, 2002	No control group
41.	Dunn et al, 2005	Ineligible comparator
42.	Ellard et al, 2014	Non depressed
43.	Euteneuer et al, 2017	Ineligible intervention
44.	Eyigor et al, 2010	Ineligible comparator
45.	Fang et al, 2013	Ineligible comparator
46.	Foley et al, 2008	Ineligible comparator
47.	Forsyth et al, 2015	Ineligible patient population
48.	Geliebter et al, 1997	Non depressed
49.	Gerber et al, 2013	Non depressed
50.	Gerber et al, 2020	Ineligible comparator
51.	Goldfield et al, 2015	Ineligible patient population
52.	Greer et al, 2015	No control group
53.	Guifeng et al, 2015	Ineligible comparator
54.	Gujral et al, 2019	Medication
55.	Häkkinen et al, 2001	Ineligible patient population
56.	Hanssen et al, 2018	Ineligible comparator
57.	Haussleiter et al, 2020	Ineligible comparator
58.	He et al, 2022	Ineligible comparator
58.	Helgadottir et al, 2018	Secondary data
59.	Herman et al, 2002	Duplicate
60.	Herring et al, 2011	Ineligible patient population
61.	Hess-Homeier, 1981	Ineligible intervention
62.	Ho et al, 2014	Ineligible comparator
63.	Hoffmann et al, 2008	Duplicate
64.	Hoffmann et al, 2010	Ineligible patient population
65.	Holmgren et al, 2010	Non depressed
66.	Huipeng et al, 2013	Ineligible comparator
67.	Imboden et al, 2019	Ineligible comparator
68.	Isaksen et al, 2016	Non depressed
69.	Jaggers et al, 2015	Non depressed
70.	Jin et al, 2019	Non depressed
71.	Jinchun et al, 2015	Ineligible comparator
72.	Kahl et al, 2015	Ineligible outcome
73.	Karahan et al, 2017	Ineligible patient population
74.	Karg et al, 2020	Ineligible comparator
75.	Kekäläinen et al, 2018	Non depressed
76.	Kerling et al, 2015	Ineligible comparator
77.	Kerr et al, 2008	Non depressed
78.	Kerse et al, 2010	Non depressed
79.	Kim et al, 2019	Non depressed
80.	Klein et al, 1985	Ineligible comparator
81.	Knapen et al, 2003	Ineligible patient population
82.	Knubben et al, 2007	Ineligible intervention
83.	Kraepelien et al, 2015	Secondary data
84.	Kratz et al, 2014	Ineligible intervention

85. Krogh et al, 2007	Ineligible comparator
86. Krogh et al, 2009	Ineligible comparator
87. Krogh et al, 2012	Ineligible comparator
88. Krogh et al, 2013	Ineligible outcome
89. Kruisdijk et al, 2012	Ineligible patient population
90. Kruisdijk et al, 2019	Ineligible patient population
91. Kruisdijk et al, 2020	Ineligible patient population
92. Lau et al, 2004	Ineligible patient population
93. Le Cheminant et al, 2014	Non depressed
94. Legrand et al, 2007	Medication
95. Legrand et al, 2015	Medication
96. Levinger et al, 2011	Non depressed
97. Li et al, 2019	Ineligible intervention
98. Lincoln et al, 2011	Ineligible patient population
99. Lopez-Torres Hidalgo et al, 2019	No RCT
100. Mailey et al, 2010	Ineligible patient population
101. Majumder et al, 2015	Ineligible patient population
102. Martins et al, 2011	Non depressed
103. Martinsen et al, 1985	Ineligible comparator
104. Martiny et al, 2015	Ineligible comparator
105. Mata et al, 2012	Non depressed
106. Matthews et al, 2011	Non depressed
107. Mendham et al, 2021	Non depressed
108. Meyer et al, 2022	Ineligible intervention
108. Midtgaard et al, 2012	No control group
109. Moraes et al, 2022	Ineligible comparator
109. Nasstasia et al, 2019	Ineligible patient population
110. Naumann et al, 2020	Ineligible comparator
111. Neidig et al, 2003	Non depressed
112. Neviani et al, 2017	Secondary data
113. Ng et al, 2017	Non depressed
114. Niederer et al, 2017	Ineligible comparator
115. Nordbrandt et al, 2015	Non depressed
116. Norvell et al, 1993	Non depressed
117. Nyberg et al, 2015	Ineligible patient population
118. Oeland et al, 2010	Ineligible patient population
119. Ökzan et al, 2020	Non depressed
120. Olson et al, 2017	Ineligible comparator
121. O'Reilly et al, 1999	Non depressed
122. Palmer et al, 1995	Non depressed
123. Patten et al, 2017	Ineligible intervention
124. Payne et al, 2008	Non depressed
125. Penninx et al, 2002	Non depressed
126. Pentecost et al, 2015	Ineligible intervention
127. Pereira et al, 2013	Ineligible comparator
128. Perna et al, 2010	Non depressed
129. Peterson et al, 2014	Non depressed
130. Philippot et al, 2022	Ineligible comparator

130. Pibernik-Okanovic et al, 2011	Ineligible patient population
131. Piette et al, 2011	Ineligible intervention
132. Porter et al, 2011	Non depressed
133. Puterman et al, 2021	Non depressed
134. Putiri et al, 2012	Ineligible patient population
135. Prakhinkit et al, 2014	No control group
136. Rantakokko et al, 2015	Non depressed
137. Razazian et al, 2016	Non depressed
138. Reuter, 1984	Ineligible intervention
139. Rueter, 1980	Ineligible comparator
140. Sadeghi et al, 2016	Ineligible comparator
141. Salehi et al, 2016	Medication
142. Sarsan et al, 2006	Non depressed
143. Schmitter et al, 2020	Study protocol
144. Scholz et al, 2006	Non depressed
145. Sherwood et al, 2016	Ineligible outcome
146. Singh et al, 2001	Secondary data
147. Siqueira et al, 2016	Medication
148. Sparrow et al, 2011	Non depressed
149. Steiner, Bigatti, Ang et al, 2015	Non depressed
150. Steiner, Richardson, Himle et al, 2015	Ineligible intervention
151. Ström et al, 2013	Ineligible intervention
152. Tapps et al, 2013	Non depressed
153. Teychenne et al, 2019	Non depressed
154. Teychenne et al, 2021	Ineligible patient population
155. Toni et al, 2016	Secondary data
156. Trivedi et al, 2011	Ineligible comparator
157. Van der Kooi et al, 2007	Ineligible patient population
158. Van der Waerden et al, 2013	Non depressed
159. Vankova et al, 2014	Non depressed
160. Verhoeven et al. 2022	Ineligible comparator
160. Verrusio et al, 2014	Ineligible intervention
161. Vieira et al, 2018	Non depressed
162. Vizza et al, 2016	Ineligible patient population
163. Wang et al, 2022	Ineligible intervention
163. Zanetidou et al, 2017	Secondary data
164. Zanuso et al, 2012	Non depressed
165. Zeibig et al, 2021	Ineligible patient population
166. Zeng et al, 2020	Ineligible intervention

Note. Of the k=218 papers reviewed in full-text, k=177 were excluded.

Supplementary Table 3. Risk of Bias Assessment (RoB2)

Study	Intervention group	Comparator	D1	D2	D3	D4	D5	Overall
Abdelbasset et al,[42] 2019	Aerobic exercise	Usual care	!	+	+	+	+	!
Blumenthal et al,[63] 2007	Aerobic exercise	Placebo	+	+	+	+	+	+
Brenes et al,[43] 2007	Mixed exercise	Usual care	!	+	+	-	!	-
Carneiro et al,[64] 2015	Usual care*aerobic exercise	Usual care	+	!	+	-	!	-
Chau et al,[65] 2020	Mixed exercise	Wait-list	+	+	+	+	+	+
Cheung et al,[48] 2018	Aerobic exercise	Usual care	+	+	+	+	+	+
Danielsson et al,[67] 2014	Usual care*aerobic exercise	Usual care	+	+	+	+	+	+
Doose et al,[68] 2015	Aerobic exercise	Wait-list	!	+	+	-	+	-
Doyne et al,[44] 1987	Mixed exercise	Wait-list	+	+	-	+	+	-
Epstein,[69] 1986	Aerobic exercise	Wait-list	!	-	!	!	!	-
Gao et al,[45] 2016	Aerobic exercise	Usual care	+	!	+	!	+	!
Gary et al,[70] 2010	Aerobic exercise	Usual care	!	!	+	+	+	!
Hallgren et al,[46] 2015	Mixed exercise	Usual care	+	+	+	+	+	+
Hemat-Far et al,[47] 2012	Aerobic exercise	Usual care	-	!	+	-	+	-

Huang et al,[48] 2015	Mixed exercise	Usual care	
La Rocque et al,[71] 2020	Aerobic exercise	Wait-list	
Legrand et al,[49] 2014	Aerobic exercise	Wait-list	
Lok et al,[50] 2017	Aerobic exercise	Wait-list	
Makizako et al,[52] 2019	Mixed exercise	Health education	
Mather et al,[41] 2002	Mixed exercise	Health education	
McNeil et al,[51] 1991	Aerobic exercise	Wait-list	
Mota-Pereira et al,[72] 2011	Usual care*aerobic exercise	Usual care	
Mutrie,[53] 1986	Mixed exercise	Wait-list	
Nabkasorn et al,[54] 2006	Aerobic exercise	Usual care	
Oertel-Knöchel et al,[73] 2014	Aerobic exercise	Wait-list	
Orth,[55] 1979	Aerobic exercise	Self-monitoring	
Pfaff et al,[62] 2014	Mixed exercise	Usual care	
Pilu et al,[74] 2007	Usual care*resistance exercise	Usual care	
Prakhinkit et al,[56] 2014	Aerobic exercise	Usual care	
Roy et al,[75] 2018	Aerobic exercise	Usual care	

Schneider et al,[76] 2016	Mixed exercise	Usual care	+	+	+	+	+	+
Schuch et al,[77] 2015	Aerobic exercise	Usual care	+	+	+	+	+	+
Setaro,[57] 1985	Aerobic exercise	Usual care	+	+	+	+	+	+
Shahidi et al,[58] 2011	Aerobic exercise	Unclear	-	-	-	!	!	-
Sims et al,[59] 2006	Resistance exercise	Advise for activity	+	+	+	!	-	-
Sims et al,[60] 2009	Resistance exercise	Wait-list	+	+	+	!	-	-
Singh et al,[78] 1997	Resistance exercise	Health education	-	!	+	-	!	-
Singh et al,[79] 2005	Resistance exercise	Usual care	+	+	+	+	+	+
Veale et al,[80] 1992	Aerobic exercise	Usual care	-	-	+	!	!	-
Vieira et al,[81] 2007	Aerobic exercise	Usual care	!	+	+	-	!	-
Williams et al,[61] 2008	Mixed exercise	Social conversation	+	+	+	+	-	-

Note. + = low risk, ! = some concerns, - = high risk, D1 = Randomisation process, D2 = Deviations from the intended interventions, D3 = Missing outcome data, D4 = Measurement of the outcome, D5 = Selection of the reported result.

Supplementary Table 4. Descriptives of Included Studies

Author, year, country	Age (mean or range)		Gender (% females)		Antidepressant use (% taking)		Thesis or Peer-reviewed article
	Exercise	Control	Exercise	Control	Exercise	Control	
Abdelbasset et al,[42] 2019, Saudi-Arabia	52.60	52.90	31.00	26.00	N/A	N/A	Peer-reviewed
Blumenthal et al,[63] 2007, USA	52.00	52.00	75.00	77.00	0	0	Peer-reviewed
Brenes et al,[43] 2007, USA	73.50	73.90	64.00	50.00	0	0	Peer-reviewed
Carneiro et al,[64] 2015, Portugal	52.78	47.80	100	100	100	100	Peer-reviewed
Chau et al,[65] 2020, Hong Kong	N/A	N/A	74.00	86.00	83.00	83.00	Peer-reviewed
Cheung et al,[48] 2018, Hong Kong/ China	47.40	48.10	88.20	70.60	94.12	88.24	Peer-reviewed
Danielsson et al,[67] 2014, Sweden	44.70	46.30	73.00	80.00	100	100	Peer-reviewed
Doose et al,[68] 2015, Germany	46.10	51.25	60.00	68.80	50.00	75.00	Peer-reviewed
Doyne et al,[44] 1987, USA	28.58	29.46	100	100	0	0	Peer-reviewed
Epstein,[69] 1986, USA	24-60	24-60	N/A	N/A	N/A	N/A	Thesis
Gao et al,[45] 2016, China	54.50	53.50	100	100	0	0	Peer-reviewed
Gary et al,[70] 2010, USA	30-70	30-70	N/A	N/A	N/A	N/A	Peer-reviewed

Hallgren et al,[46] 2015, Sweden	18-71	18-71	N/A	N/A	31.00	24.00	Peer-reviewed
Hemat-Far et al,[47] 2012, Iran	18-25	18-25	100	100	N/A	N/A	Peer-reviewed
Huang et al,[48] 2015, Taiwan	76.42	75.85	57.90	55.00	0	0	Peer-reviewed
La Rocque et al,[71] 2020, Canada	34.85	29.40	100	100	20.00	46.70	Peer-reviewed
Legrand et al,[49] 2014, France	19 - 30	19-30	100	100	0	0	Peer-reviewed
Lok et al,[50] 2017, Turkey	≥65.00	≥65.00	42.50	47.50	0	0	Peer-reviewed
Makizako et al,[52] 2019, Japan	73.10	73.00	53.30	51.70	0	0	Peer-reviewed
Mather et al,[41] 2002, United Kingdom	63.70	66.20	84.00	53.00	100	100	Peer-reviewed
McNeil et al,[51] 1991, Canada	N/A	N/A	N/A	N/A	0	0	Peer-reviewed
Mota-Pereira et al,[72] 2011, Portugal	48.68	45.33	57.90	80.00	100	100	Peer-reviewed
Mutrie,[53] 1986, United Kingdom	45.70	41.10	N/A	N/A	0	0	Thesis
Nabkasorn et al,[54] 2006, Thailand	18.70	18.80	100	100	0	0	Peer-reviewed
Oertel-Knöchel et al,[73] 2014, Germany	36.60	42.20	50.00	37.50	100	100	Peer-reviewed
Orth,[55] 1979, USA	N/A	N/A	N/A	N/A	N/A	N/A	Thesis
Pfaff et al,[62] 2014, Australia	61.20	60.70	62.00	64.10	60.20	47.80	Peer-reviewed

Pilu et al,[74] 2007, Italy	40-60	40-60	100	100	100	100	Peer-reviewed
Prakhinkit et al,[56] 2014, Thailand	74.80	81.00	100	100	0	0	Peer-reviewed
Roy et al,[75] 2018, India	31.10	32.90	100	100	N/A	N/A	Peer-reviewed
Schneider et al,[76] 2016, USA	53.30	53.60	100	100	N/A	N/A	Peer-reviewed
Schuch et al,[77] 2015, Brazil	38.84	41.76	72.00	76.00	84.00	96.00	Peer-reviewed
Setaro,[57] 1985, USA	N/A	N/A	N/A	N/A	N/A	N/A	Thesis
Shahidi et al,[58] 2011, Iran	65.70	68.40	100	100	N/A	N/A	Peer-reviewed
Sims et al,[59] 2006, Australia	75.25	74.30	85.71	50.00	0	0	Peer-reviewed
Sims et al,[60] 2009, Australia	67.95	66.27	39.00	41.00	0	0	Peer-reviewed
Singh et al,[78] 1997, USA	70.00	72.00	70.60	53.30	0	0	Peer-reviewed
Singh et al,[79] 2005, Australia	69.00	69.00	55.00	50.00	0	0	Peer-reviewed
Veale et al,[80] 1992, United Kingdom	19-58	19-58	N/A	N/A	45.00	34.00	Peer-reviewed
Vieira et al,[81] 2007, Brazil	N/A	N/A	100	100	100	100	Peer-reviewed
Williams et al,[61] 2008, USA	71-101	71-101	N/A	N/A	36.00	36.00	Peer-reviewed

Note. Not available (N/A).

Supplementary Table 5. Characteristics of Included Studies

Study	Comorbidities	Group exercise	Setting	Intensity	Supervised	Type of supervision
Abdelbasset et al,[42] 2019	Yes	Unclear	Outpatient	Moderate	Supervised	Unclear
Blumenthal et al,[63] 2007 (supervised exercise)	No	Yes	Outpatient	Vigorous	Supervised	Unclear
Blumenthal et al,[63] 2007 (homebased exercise)	No	No	Outpatient	Vigorous	Unsupervised	None
Brenes et al,[43] 2007	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (certified ACSM exercise leader)
Carneiro et al,[64] 2015	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (physical training teacher)
Chau et al,[65] 2020	No	Yes	Inpatient	Moderate	Supervised	Exercise professional (physiotherapist)
Cheung et al,[48] 2018	No	No	Outpatient	Moderate	Supervised	Exercise professional (qualified personal trainer)
Danielsson et al,[67] 2014	No	No	Outpatient	Vigorous	Supervised	Exercise professional (physiotherapist)
Doose et al,[68] 2015	No	Yes	Outpatient	Light	Supervised	Other (teams of coaches and medical students)
Doyne et al,[44] 1987	No	No	Outpatient	Vigorous	Supervised	Other (trained undergraduate exercise

(running condition)						monitors)
Doyne et al,[44] 1987 (weightlifting)	No	No	Outpatient	Moderate	Supervised	Other (trained undergraduate exercise monitors)
Epstein,[69] 1986	No	Yes	Outpatient	Moderate	Supervised	Other (clinical graduate students)
Gao et al,[45] 2016	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (professional coach and doctor)
Gary et al,[70] 2010	Yes	No	Outpatient	Moderate	Unsupervised	None
Hallgren et al,[46] 2015	No	Yes	Outpatient	Light to vigorous[b]	Supervised	N/A
Hemat-Far et al,[47] 2012	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Huang et al,[48] 2015	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (trained physical fitness instructor)
La Rocque et al,[71] 2020	Yes	Yes	Outpatient	Moderate	Supervised	Exercise professional (professional exercise instructor)
Legrand et al,[49] 2014	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (certified zumba instructor)
Lok et al,[50] 2017	Unclear	Yes	Outpatient	Moderate	Supervised	Other (researcher)
Makizako et al,[52] 2019	Yes	Yes	Outpatient	Moderate	Supervised	Exercise professional (trained instructors)
Mather et al,[41] 2002	No	Yes	Outpatient	Unclear	Supervised	Other (instructor)
McNeil et al,[51] 1991	No	No	Outpatient	Vigorous	66% supervised & 33% unsupervised[c]	Other (undergraduate psychology student)

Mota-Pereira et al,[72] 2011	No	No	Outpatient	Moderate	20% supervised & 80% unsupervised[c]	Exercise professional
Mutrie,[53] 1986 (aerobic exercise)	No	Unclear	Outpatient	Moderate	Unsupervised	None
Mutrie,[53] 1986 (strength & stretching)	No	Unclear	Outpatient	Vigorous	Unsupervised	None
Nabkasorn et al,[54] 2006	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (physical fitness instructor)
Oertel-Knöchel et al,[73] 2014	No	Yes	Inpatient	Moderate	Supervised	Exercise professional (trained physical fitness instructor
Orth,[55] 1979	No	Unclear	Outpatient	Moderate	Unsupervised	None
Pfaff et al,[62] 2014	No	No	Outpatient	Moderate to vigorous	Unsupervised	None
Pilu et al,[74] 2007	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (skilled instructor with isef (physical education) diploma, psychology degree and post-degree diploma in sport psychopathology (MS)
Prakhinkit et al,[56] 2014 (traditional walking)	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Prakhinkit et al,[56] 2014 (Buddhism walking)	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Roy et al,[75] 2018	Unclear	Yes	Inpatient	Moderate	Supervised	Other (registered nurse)
Schneider et al,[76] 2016	Yes	Yes[a]	Outpatient	Moderate	Supervised	Exercise professional (pilates/yoga

						instructor)
Schuch et al,[77] 2015	No	No	Inpatients	Unclear	Supervised	Exercise professional (researcher and sport-scientist)
Setaro,[57] 1985	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (certified aerobic dance instructor)
Shahidi et al,[58] 2011	No	Yes	Outpatient	Unclear	Unclear	Unclear
Sims et al,[59] 2006	No	No	Outpatient	Vigorous	Supervised	Unclear
Sims et al,[60] 2009	Yes	Yes	Outpatient	Vigorous	Supervised	Exercise professional (accredited fitness trainer)
Singh et al,[78] 1997	No	Yes	Outpatient	Vigorous	Supervised	Other (researcher/principal investigator)
Singh et al,[79] 2005 (high intensity)	No	Yes	Outpatient	Vigorous	Supervised	Unclear
Singh et al,[79] 2005 (low intensity)	No	Yes	Outpatient	Light	Supervised	Unclear
Veale et al,[80] 1992	No	Yes	Outpatient	Unclear	Supervised	Unclear
Vieira et al,[81] 2007	No	Yes	Inpatient	Moderate	Supervised	Unclear
Williams et al,[61] 2008 (mixed exercise)	Yes	No	Outpatient	Unclear	Supervised	Other (graduate nursing or physical therapy students)
Williams et al,[61] 2008 (supervised walking)	Yes	No	Outpatients	Unclear	Supervised	Other (graduate nursing or physical therapy students)

Note. Not available (N/A). American College of Sports Medicine (ACSM). [a]Participants were asked to additionally train once a week at home. [b]Participants were randomized to light, moderate, and vigorous intensity exercise. In the subgroup analysis, this study was rated as moderate. [c]Study was rated as supervised in the subgroup analyses.

Supplementary Table 6. Subgroup Meta-analysis of Studies Included in the Quantitative Analyses with Low and Moderate Risk of Bias

Analysis	Number of RCTs	Meta analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]
		SMD	95% CI		p- value	I^2	
Main analysis	19	-0.717	-1.01	-0.43	**<.001**	82.372	-0.897 (-1.219; -0.575) [3]
Depression classification							
MDD[a]	11	-0.567	-0.94	-0.20	.003	78.114	Unchanged
Depressive symptoms	8	-0.951	-1.47	-0.43	**<.001**	87.373	-1.115 (-1.707; -0.523) [1]
Type of control condition							
Usual care	12	-0.763	-1.13	-0.40	**<.001**	83.728	-0.973 (-1.403; -0.543) [2]
Wait list	3	-1.315	-1.89	-0.74	**<.001**	46.548	-1.678 (-2.252; -1.105) [2]
Health education	2	-0.107	-0.44	0.23	.528	0.000	N/A
Intensity of exercise[b]							
Light	1	-0.293	-0.95	0.37	.383	0.000	N/A
Moderate	13	-0.775	-1.17	-0.38	**<.001**	85.562	-0.977 (-1.422; -0.532) [2]
Vigorous	4	-0.324	-0.61	-0.04	.028	28.767	-0.254 (-0.550; 0.043) [1, right of mean]
Exercise type[b]							
Aerobic	12	-0.891	-1.32	-0.46	**<.001**	81.277	-1.254 (-1.760; -0.747) [4]
Resistance	2	-0.508	-0.98	-0.04	.033	0.000	N/A
Mixed[c]	7	-0.396	-0.79	-0.00	.049	84.939	Unchanged
Group exercise[b]							
Yes	13	-0.646	-0.97	-0.38	**<.001**	80.129	Unchanged
No	6	-0.330	-0.58	-0.08	.010	33.470	-0.205 (-0.474; 0.063) [2, right of mean]
Supervision[b]							

Yes[d]	17	-0.769	-1.08	-0.46	**<.001**	82.500	-0.906 (-1.236; -0.576) [2]
No	4	-0.119	-0.34	0.10	.293	0.000	-0.098 (-0.308; 0.111) [2, right of mean]
Type of supervision[b]							
Exercise professional	11	-0.830	-1.22	-0.45	**<.001**	74.192	Unchanged
Other professional/ student	1	-0.061	-0.49	0.36	.778	0.000	N/A
Sample size intervention arm[b]							
n≥25	9	-0.516	-0.84	-0.19	**.002**	84.053	-0.576 (-0.890; -0.261) [1]
n<25	12	-0.801	-1.25	-0.35	**<.001**	76.648	-1.148 (-1.612; -0.683) [4]
n≥10	19	-0.665	-0.94	-0.39	**<.001**	83.059	Unchanged
n<10	2	-0.588	-1.52	0.34	.215	0.000	N/A

Note. See Supplement eTable 2, 3 and 4 for detailed categorization for each study. MDD=Major depressive Disorder; RCT=Randomized Controlled Trial, SMD=Standard mean difference. [a]Including 3 studies with MDD & Dysthymia[46,77,78]. [b]Data for a second intervention group within the same study were included for these analyses. [c]Mixed exercise=aerobic and resistance exercise. [d]Two studies were partly supervised, see Supplement Table 5.

Supplementary Table 7. Subgroup Analysis for Studies with MDD Diagnosis[a]

Analysis	Number of RCTs	Meta analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]
		SMD	95% CI		p- value	I^2	
Main analysis MDD	20	-0.998	-1.39	-0.61	**<.001**	85.746	-1.167 (-1.591; -0.742) [2]
Risk of bias							
Low risk of bias	9	-0.607	-1.03	-0.18	**.005**	82.240	-0.462 (-0.921; -0.003) [1, right of mean]
Some concerns	2	-0.300	-0.87	0.27	.302	0.000	N/A
High risk of bias	9	-1.687	-2.53	-0.84	**<.001**	89.056	Unchanged
Type of control condition							
Usual care	13	-0.762	-1.19	-0.34	**<.001**	81.767	-0.999 (-1.480; -0.518) [2]
Wait list	5	-1.443	-1.82	-1.07	**<.001**	18.443	-1.606 (-2.017; -1.195) [2]
Health education	1	-3.462	-4.56	-2.37	**<.001**	0.000	N/A
Intensity of exercise[b]							
Light	2	-1.041	-2.53	0.45	.170	88.867	N/A
Moderate	12	-1.012	-1.57	-0.45	**<.001**	86.889	-1.317 (-1.987; -0.639) [2]
Vigorous	5	-0.881	-1.62	-0.15	**.019**	88.544	-1.152 (-2.039; -0.265) [1]
Exercise type[b]							
Aerobic	15	-0.893	-1.29	-0.50	**<.001**	80.672	-1.084 (-1.535; -0.633) [2]
Resistance	4	-1.354	-2.48	-0.23	**.018**	87.859	-1.752 (-3.010; -0.499) [1]
Mixed[c]	3	-0.430	-1.62	0.77	.481	94.350	Unchanged
Group exercise[b]							
Yes	15	-0.985	-1.44	-0.53	**<.001**	84.222	Unchanged
No	7	-0.743	-1.29	-0.19	**.008**	85.582	-1.175 (-1.926; -0.424) [2]
Supervision[b]							
Yes	19	-1.066	-1.48	-0.66	**<.001**	84.441	-1.333 (-1.807; -0.860) [3]
No	3	-0.110	-0.33	0.11	.334	0.000	-0.078 (-0.265; 0.108) [2,

							right of mean]
Type of supervision[b]							
Exercise professional	10	-1.077	-1.64	-0.52	**<.001**	81.997	-1.450 (-2.037; -0.863) [3]
Other professional/ student	4	-1.664	-2.88	-0.45	**.007**	87.977	Unchanged
Sample size intervention arm[b]							
n≥25	6	-0.444	-0.91	0.02	.061	86.212	-0.530 (-0.969; -0.090) [1]
n<25	16	-1.144	-1.63	-0.66	**<.001**	82.403	-1.358 (-1.883; -0.834) [2]
n≥10	16	-0.671	-1.02	-0.32	**<.001**	83.953	-0.809 (-1.172; -0.447) [2]
n<10	6	-1.736	-2.70	-0.77	**<.001**	79.899	Unchanged

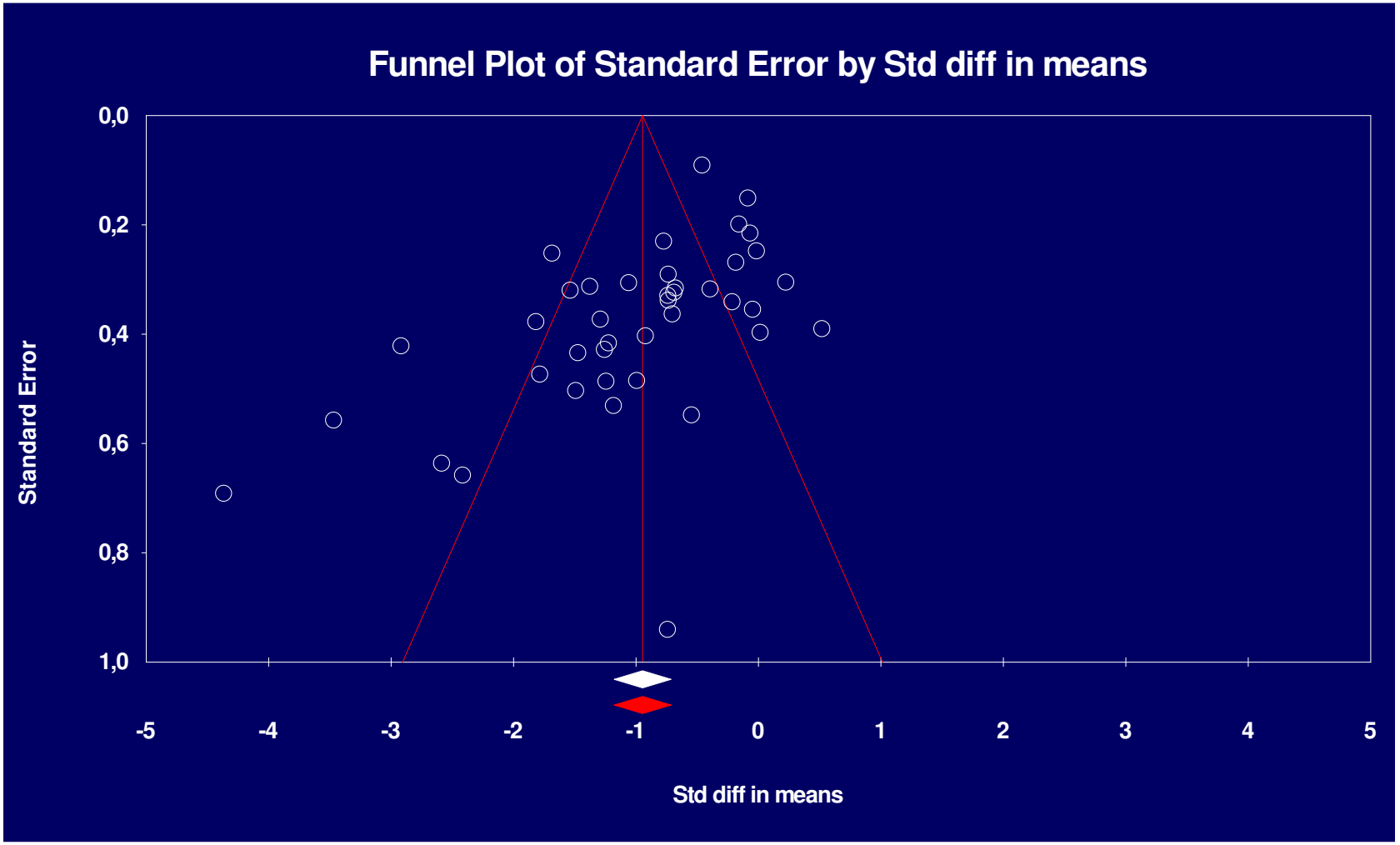
Note. [a]Including 3 studies with MDD & Dysthymia. [b]Data for a second intervention group within the same study were included for these analyses. [c]Mixed exercise=aerobic and resistance exercise.

Supplementary Table 8. Meta Regression of Moderators/Correlates of Effects of Exercise on Depression for Studies with Low and Moderate Risk of Bias

Moderator	Number of RCTs	β	95%CI		p-value	$R^{2\,c}$
Main exercise response						
Mean age exercise	16	0.013	-0.01	0.04	.272	0.00
Mean age control	16	0.015	-0.01	0.04	.206	0.00
Duration of trial (in weeks)[a]	21	0.064	0.00	0.13	**.039**	0.12
Weekly frequency[a]	21	-0.005	-0.18	0.17	.954	0.00
Minutes per session[a]	19	-0.004	-0.02	0.02	.707	0.00
Sample size[b]	19	0.001	-0.00	0.00	.483	0.00
MDD (+ Dysthymia) only						
Mean age exercise	10	0.021	-0.00	0.04	.078	0.39
Mean age control	10	0.022	-0.00	0.05	.052	0.46
Duration of trial (in weeks)[a]	13	0.070	0.01	0.14	**.034**	0.26
Weekly frequency[a]	13	0.049	-0.15	0.24	.623	0.00
Minutes per session[a]	12	-0.021	-0.05	0.00	.095	0.26
Sample size[b]	11	0.002	-0.01	0.01	.614	0.00

Note. [a]data for a second intervention group within the same study were included for these analyses. [b]Average sample size pre-post intervention. c R2 equal to R2 analog.

Supplementary Figure 1. Funnel Plot of Standard Error by SMD



Supplementary Material

Exercise as Medicine for Depressive Symptoms?
A Systematic Review and Meta-analysis with Meta regression

Andreas Heißel, Darlene Heinen, Luisa Leonie Brokmeier, Nora Skarabis, Maria Kangas, Davy Vancampfort, Brendon Stubbs, Joseph Firth, Philip B. Ward, Simon Rosenbaum, Mats Hallgren, Felipe Schuch

Supplementary Text 1. Full search terms

MeSH terms

((exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial))

Cochrane/ Embase

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR "physical medicine" OR resistance OR lift*):ti,ab,kw AND (depression OR dysthymia):ti,ab,kw AND (randomized control trial" OR "randomized clinical trial):ti,ab,kw in Trials (Word variations have been searched)

PubMed

((exercis*[Title/Abstract] OR aerobic*[Title/Abstract] OR running[Title/Abstract] OR jogging[Title/Abstract] OR walk*[Title/Abstract] OR hiking[Title/Abstract] OR swim*[Title/Abstract] OR aquatic*[Title/Abstract] OR cycling[Title/Abstract] OR bicycl*[Title/Abstract] OR strength*[Title/Abstract] AND activit*[Title/Abstract] OR fitness[Title/Abstract] OR train*[Title/Abstract] OR physical medicine[Title/Abstract] OR resistance[Title/Abstract] OR lift*[Title/Abstract]) AND (depression[Title/Abstract] OR dysthymia[Title/Abstract])) AND (randomized controlled trial[Title/Abstract] OR clinical trial[Title/Abstract])

PsychINFO

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial)

SPORTDiscus

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial)

Medline

((TS=(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*)) AND TS=(depression OR dysthymia)) AND TS=(randomized controlled trial OR clinical trial)

Scopus

TITLE-ABS-KEY ((exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* AND activit* OR fitness OR train* OR physical AND medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized AND controlled AND trial OR clinical AND trial))

Web of Science

(exercis* OR aerobic* OR running OR jogging OR walk* OR hiking OR swim* OR aquatic* OR cycling OR bicycl* OR strength* and activit* OR fitness OR train* OR physical medicine OR resistance OR lift*) AND (depression OR dysthymia) AND (randomized controlled trial OR clinical trial) (Topic)

Supplementary Table 1. Data of Studies Included in Systematic Review

Study	Sample size (n)		Outcome[a]	Pre (mean (SD))		Post (mean (SD))		Intervention			Control group condition	Diagnosis
	Exercise	Control		Exercise	Control	Exercise	Control	Type of intervention	Wks	Sessions per wk/ time per session		
Abdelbasset et al,[45] 2019	23	23	PHQ-9	16.12 (3.10)	15.95 (3.14)	3.65 (1.21)	8.54 (2.14)	Aerobic exercise	12	3/30-60 min[b]	Usual care (standard medical treatment)	Depressive symptoms
Blumenthal et al,[66] 2007 (supervised exercise)	51	49	HAM-D, BDI-II	16.40 (3.70)	17.20 (4.30)	9.20 (6.10)	11.00 (7.00)	Aerobic exercise	16	3/45 min	Placebo	MDD
Blumenthal et al,[66] 2007 (homebased exercise)	53	49	HAM-D, BDI-II	17.30 (4.60)	17.20 (4.30)	10.20 (6.70)	11.00 (7.00)	Aerobic exercise	16	3/45 min	Placebo	MDD
Brenes et al,[46] 2007	14	12	HAM-D, GDS	12.70 (3.40)	9.50 (3.70)	7.80 (4.30)	10.90 (5.80)	Mixed exercise	16	3/60 min	Usual care (phone calls to discuss health status)	Depressive symptoms
Carneiro et al,[67] 2015	9	10	BDI-II, DASS-21	45.56 (9.65)	46.10 (11.52)	34.89 (10.56)	49.40 (16.72)	Aerobic exercise	16	3/45 min	Usual care (pharmacological therapy)	MDD & Dysthymia
Chau et al,[68] 2020	42	42	HAM-D, DASS-21	25.93 (6.59)	25.62 (8.03)	12.57 (8.06)	25.58 (7.81)	Mixed exercise	12	3/60 min	Wait-list	MDD
Cheung et al,[48] 2018	17	17	HAM-D	18.50 (3.20)	19.40 (3.60)	9.80 (5.60)	14.50 (5.30)	Aerobic exercise	12	3/40 min	Usual care (usual psychiatric care)	MDD

Danielsson et al,[70] 2014	22	20	MADRS	24.60 (4.10)	23.40 (5.00)	-10.30[c] (1.60)	-4.60[c] (1.70)	Aerobic exercise	10	2/60 min	Usual care (standard care)	MDD
Doose et al,[71] 2015	30	16	HAM-D, BDI-II	13.97 (2.58)	14.67 (3.91)	-9.48[d] (11.38-7.58)	-1.24[d] (-3.85-1.37)	Aerobic exercise	8	3/60 min	Wait-list	MDD
Doyne et al,[47] 1987 (running condition)	14	11	HAM-D, BDI, DACL	13.36 (4.43)	12.58 (4.58)	6.64 (3.61)	13.58 (5.14)	Aerobic exercise	8	4/25 min	Wait-list	Depressive symptoms
Doyne et al,[47] 1987 (weightlifting)	15	11	HAM-D, BDI, DACL	13.80 (7.78)	12.58 (4.58)	5.13 (3.44)	13.58 (5.14)	Resistance exercise	8	4/45 min	Wait-list	Depressive symptoms
Epstein,[72] 1986	7	10	BDI, SDS	25.29 (6.52)	22.00 (7.16)	9.00 (10.94)	16.30 (7.44)	Aerobic exercise	8	3/30 min	Wait-list	MDD
Gao et al,[48] 2016	26	24	SDS	0.58 (0.10)	0.59 (0.11)	0.43 (0.09)	0.57 (0.10)	Aerobic exercise	12	5/60-90 min[b]	Usual care (lived normally without intervention)	Depressive symptoms
Gary et al,[73] 2010	20	17	HAM-D	15.40 (3.40)	15.20 (3.60)	8.40 (5.60)	9.30 (4.90)	Aerobic exercise	12	3/weekly increase by 5 min to 60 min[b]	Usual care (usually provided health care)	MDD
Hallgren et al,[49] 2015	317	312	MADRS	22.20 (6.80)	20.90 (7.50)	11.30 (7.90)	13.80 (8.90)	Mixed exercise	12	3/60 min	Usual care (treatment as usual)	Depressive symptoms
Hemat-Far et al,[50] 2012	10	10	BDI	25.00 (5.30)	23.80 (4.70)	16.60 (6.90)	22.80 (4.90)	Aerobic exercise	8	3/40-60 min[b]	Usual care (pursue normal live)	Depressive symptoms
Huang et al,[51] 2015	19	20	GDS-15	8.63 (3.56)	7.20 (2.19)	4.63 (2.49)	5.20 (1.69)	Mixed exercise	12	3/50 min	Usual care	Depressive symptoms

La Rocque et al,[74] 2020	20	15	HAM-D	12.00 (3.77)	13.93 (3.71)	6.75 (6.05)	16.33 (5.84)	Aerobic exercise	8	2/50-60 min[b]	Wait-list	MDD
Legrand et al,[52] 2014	22	22	BDI-II	21.67 (6.78)	19.25 (9.34)	12.80 (4.38)	19.67 (8.17)	Aerobic exercise	7	2/30 min	Wait-list	Depressive symptoms
Lok et al,[53] 2017	40	40	BDI	17.46 (8.07)	19.89 (5.00)	11.89 (4.23)	17.71 (4.61)	Aerobic exercise	10	4/70 min	Wait-list	Depressive symptoms
Makizako et al,[55] 2019	30	29	GDS-15	7.10 (2.50)	6.40 (2.50)	5.30 (2.50)	5.10 (3.10)	Mixed exercise	20	1/90 min	Health education	Depressive symptoms
Mather et al,[44] 2002	43	43	HRSD	16.70 (10.83)[e]	17.40 (10.83)[e]	12.60 (7.02)	13.70 (6.02)	Mixed exercise	10	2/55-65 min[b]	Health education	Depressive symptoms
McNeil et al,[54] 1991	10	10	BDI	16.60 (3.10)	15.20 (2.40)	11.10 (3.00)	14.70 (3.70)	Aerobic exercise	6	3/20-40 min[b]	Wait-list	Depressive symptoms
Mota-Pereira et al,[75] 2011	19	10	HAM-D, BDI	19.32 (1.69)	13.00 (1.42)	12.48 (1.74)	13.60 (1.34)	Aerobic exercise	6	5/30-45 min[b]	Usual care (pharmacothe rapy)	MDD
Mutrie,[56] 1986 (aerobic exercise)	9	7	BDI, POMS	22.44 (6.82)	23.00 (5.80)	9.46 (4.28)	21.42 (5.26)	Aerobic exercise	4	3/20 min	Wait-list	Depressive symptoms
Mutrie,[56] 1986 (strength & stretching)	8	7	BDI, POMS	21.86 (4.21)	23.00 (5.80)	14.63 (7.63)	21.42 (5.26)	Mixed exercise	4	3/20 min	Wait-list	Depressive symptoms
Nabkasorn et al,[57] 2006	28	31	CES-D	20.10 (0.90)	18.80 (7.00)	14.40 (4.12)	17.50 (4.23)	Aerobic exercise	8	5/50 min	Usual care (usual daily routine)	Depressive symptoms

Oertel-Knöchel et al,[76] 2014	8	8	BDI-II	26.25 (10.21)	25.50 (11.83)	18.75 (9.50)	24.00 (13.09)	Aerobic exercise	4	3/75 min	Wait-list	MDD
Orth,[58] 1979	3	2	DACL, MMPI	14.00 (3.60)	19.50 (7.00)	7.00 (6.50)	16.50 (2.12)	Aerobic exercise	4	5/30 min	Self-monitoring	Depressive symptoms
Pfaff et al,[65] 2014	108	92	SIGMA	21.02 (9.4)	21.66 (8.4)	14.43 (9.8)	14.32 (9.3)	Mixed exercise	12	5/30 min + 3x resistance training	Usual care (usual medical care)	MDD
Pilu et al,[77] 2007	10	20	HAM-D	20.50 (7.10)	19.30 (5.70)	8.10 (5.20)	16.70 (9.10)	Resistance exercise	32	2/60 min	Usual care (pharmacothe rapy)	MDD
Prakhinkit et al,[59] 2014 (traditional walking)	15	15	TGDS-30	17.30 (1.00)	17.90 (0.70)	15.50 (0.90)	18.60 (0.60)	Aerobic exercise	12	3/20-30 min[b]	Usual care (sedentary control group)	Depressive symptoms
Prakhinkit et al,[59] 2014 (Buddhism walking)	15	15	TGDS-30	16.08 (0.90)	17.90 (0.70)	8.60 (0.60)	18.60 (0.60)	Aerobic exercise	12	3/20-30 min[b]	Usual care (sedentary control group)	Depressive symptoms
Roy et al,[78] 2018	23	23	HAM-D, DSSS	19.30 (4.83)	16.55 (4.14)	15.00 (4.93)	13.85 (3.16)	Aerobic exercise	1.5	7/20 min	Usual care (treatment as usual)	MDD
Schneider et al,[79] 2016	15	14	HAM-D, BDI-II	15.70 (4.60)	17.40 (4.30)	10.60 (6.10)	5.80 (5.41)	Mixed exercise	24	Biweekly 2/20-65 min[b]	Usual care (enhanced usual care condition)	MDD
Schuch et al,[80] 2015	25	25	HAM-D	26.52 (1.80)	26.96 (2.70)	7.42 (4.47)	11.12 (4.47)	Aerobic exercise	12	3/unclear	Usual care (treatment as usual)	MDD
Setaro,[60] 1985	25	25	MMPI	68.92 (5.27)	68.56 (3.87)	62.00 (6.51)	69.88 (3.96)	Aerobic exercise	10	2/unclear	Usual care (no activity or treatment)	Depressive symptoms

Shahidi et al,[61] 2011	20	20	GDS-30	15.30 (5.40)	15.20 (3.90)	11.10 (6.20)	15.20 (6.10)	Aerobic exercise	N/A	Unclear/30 min	Unclear	Depressive symptoms
Sims et al,[62] 2006	14	18	GDS	12.64 (3.61)	12.22 (3.51)	12.23 (5.22)	12.00 (4.26)	Resistance exercise	10	3/unclear	Information and advice for local options of exercise	Depressive symptoms
Sims et al,[63] 2009	23	22	CES-D	15.43 (7.49)	23.27 (8.86)	15.13 (8.49)	20.62 (11.79)	Resistance exercise	10	2/unclear	Wait-list	Depressive symptoms
Singh et al,[81] 1997	17	15	HAM-D, DSM-IV, BDI, GDS	12.30 (0.90)	11.40 (1.00)	5.30 (1.30)	8.90 (1.30)	Resistance exercise	10	3/50 min	Health education	MDD & Dysthymia
Singh et al,[82] 2005 (high intensity)	20	20	HAM-D, GDS	18.00 (4.50)	19.70 (3.90)	8.50 (5.50)	14.40 (6.00)	Resistance exercise	8	3/65 min	Usual care (usual care from GP)	MDD & Dysthymia
Singh et al,[82] 2005 (low intensity)	20	20	HAM-D, GDS	19.50 (5.30)	19.70 (3.90)	12.40 (6.30)	14.40 (6.00)	Resistance exercise	8	3/65 min	Usual care (usual care from GP)	MDD & Dysthymia
Veale et al,[83] 1992	48	35	CIS, BDI	35.87 (1.07)	37.57 (1.49)	16.80 (2.06)	26.39 (2.50)	Aerobic exercise	12	3/unclear	Usual care (usual psychiatric treatment)	MDD
Vieira et al,[84] 2007	9	9	HAM-D	30.22 (3.04)	31.11 (3.51)	24.88 (2.13)	32.66 (3.12)	Aerobic exercise	12	2/50 min	Usual care	MDD
Williams et al,[64] 2008 (mixed exercise)	16	12	CSDD	11.05 (2.79)	14.58 (5.75)	8.37 (5.78)	11.75 (8.10)	Mixed exercise	16	5/30 min	Social conversation	Depressive symptoms
Williams et al,[64] 2008 (supervised walking)	17	12	CSDD	12.18 (5.00)	14.58 (5.75)	9.68 (6.57)	11.75 (8.10)	Aerobic exercise	16	5/30 min	Social conversation	Depressive symptoms

Note. BDI=Beck Depression Inventory. CES=Centre for Epidemiologic Studies Depression. CIS=Clinical Interview Schedule. CSDD=Cornel Scale for Depression in Dementia. DACL=Depression Adjective Check Lists. DASS=Depression Anxiety Stress Scale. DSSS=Depression Somatic Symptom scale. GDS=Geriatric Depression Scale. HAM-D=Hamilton Depression Scale. MADRS=Montgomery-Asberg Depression Rating Scale. MDD=Major Depressive Disorder. MMPI=Minnesota Multiphasic Personality Inventory. PHQ-9=Patient Health Questionnaire. POMS=Profile of Mood States. TGDS=Thai Geriatric Depression Scale. SDS=Severity of Dependence Scale. HRSD=Hamilton Rating Scale for Depression. DACL=Depression Adjective Checklist. SIGMA=screening tool for the assessment and design of human-centered work activities. Usual care=no treatment but including psychiatric, pharmaco-, and psychotherapeutic treatment if required. Mixed exercise=aerobic and resistance exercise. Studies with two exercise groups were compared to the same control group. [a]In case of more than one outcome, mean and SD of the first named outcome are reported. Primary outcome as indicated by authors or, if not indicated, rated by a clinician were included in the main analyses. [b]For varying minutes per session, the average was used for calculations. [c]Values are presented as mean changes with standard errors. [d]Values are presented as least Square Means (95%CI). [e]Calculation of SDs from confidence intervals.

Supplementary Table 2. List of excluded studies at full-text screening stage, with brief reasons

	Author	Reason for exclusion
1.	Abdelbasset et al, 2021	Non depressed
2.	Abedi et al, 2015	Non depressed
3.	Abrahao et al, 2015	Ineligible patient population
4.	Abrantes et al, 2017	Ineligible intervention
5.	Aider et al, 2014	Ineligible patient population
6.	Akandere et al, 2011	Non depressed
7.	Almeida et al, 2022	Ineligible intervention
8.	Alves et al, 2013	Non depressed
8.	Ansai et al, 2015	Non depressed
9.	Antunes et al, 2005	Non depressed
10.	Armstrong et al, 2004	Non depressed
11.	Bang et al, 2016	Non depressed
12.	Belvederri Murri et al, 2015	Medication
13.	Bernard, Ninot, Cyprien et al, 2015	Ineligible outcome
14.	Bernard, Ninot, Bernard et al, 2015	Non depressed
15.	Blumenthal et al, 1999	Medication
16.	Blumenthal et al, 2012	Non depressed
17.	Bolier et al, 2013	Ineligible intervention
18.	Bonnet, 2005	Ineligible intervention
19.	Bosscher, 1993	Ineligible comparator
20.	Boström et al, 2015	Non depressed
21.	Brinsley et al, 2022	Non depressed
21.	Brittle et al, 2009	Non depressed
22.	Brown et al, 2009	Non depressed
23.	Buettner, 2002	Non depressed
24.	Buschert et al, 2019	Ineligible comparator
25.	Callaghan et al, 2011	Ineligible comparator
26.	Carneiro et al, 2016	Non depressed
27.	Carta et al, 2022	Non depressed
28.	Carter et al. 2022	Ineligible age
29.	Chalder et al, 2012	Ineligible intervention
28.	Chan et al, 2012	Ineligible intervention
29.	Chen et al, 2017	Non depressed
30.	Chu et al, 2008	Ineligible comparator
31.	Ciccolo et al, 2022	Ineligible intervention
31.	Conradsson et al, 2010	Non depressed
32.	Courneya et al, 2007	Ineligible patient population
33.	Craft et al, 2007	Ineligible comparator
34.	de la Cerda et al, 2011	Medication
35.	de Lima et al, 2016	Non depressed
36.	Dalgas et al, 2010	Ineligible patient population
37.	Damush et al, 1999	Non depressed

38.	Deschamps et al, 2015	Ineligible comparator
39.	Dorscht et al, 2019	Ineligible comparator
40.	Dunn et al, 2002	No control group
41.	Dunn et al, 2005	Ineligible comparator
42.	Ellard et al, 2014	Non depressed
43.	Euteneuer et al, 2017	Ineligible intervention
44.	Eyigor et al, 2010	Ineligible comparator
45.	Fang et al, 2013	Ineligible comparator
46.	Foley et al, 2008	Ineligible comparator
47.	Forsyth et al, 2015	Ineligible patient population
48.	Geliebter et al, 1997	Non depressed
49.	Gerber et al, 2013	Non depressed
50.	Gerber et al, 2020	Ineligible comparator
51.	Goldfield et al, 2015	Ineligible patient population
52.	Greer et al, 2015	No control group
53.	Guifeng et al, 2015	Ineligible comparator
54.	Gujral et al, 2019	Medication
55.	Häkkinen et al, 2001	Ineligible patient population
56.	Hanssen et al, 2018	Ineligible comparator
57.	Haussleiter et al, 2020	Ineligible comparator
58.	He et al, 2022	Ineligible comparator
58.	Helgadottir et al, 2018	Secondary data
59.	Herman et al, 2002	Duplicate
60.	Herring et al, 2011	Ineligible patient population
61.	Hess-Homeier, 1981	Ineligible intervention
62.	Ho et al, 2014	Ineligible comparator
63.	Hoffmann et al, 2008	Duplicate
64.	Hoffmann et al, 2010	Ineligible patient population
65.	Holmgren et al, 2010	Non depressed
66.	Huipeng et al, 2013	Ineligible comparator
67.	Imboden et al, 2019	Ineligible comparator
68.	Isaksen et al, 2016	Non depressed
69.	Jaggers et al, 2015	Non depressed
70.	Jin et al, 2019	Non depressed
71.	Jinchun et al, 2015	Ineligible comparator
72.	Kahl et al, 2015	Ineligible outcome
73.	Karahan et al, 2017	Ineligible patient population
74.	Karg et al, 2020	Ineligible comparator
75.	Kekäläinen et al, 2018	Non depressed
76.	Kerling et al, 2015	Ineligible comparator
77.	Kerr et al, 2008	Non depressed
78.	Kerse et al, 2010	Non depressed
79.	Kim et al, 2019	Non depressed
80.	Klein et al, 1985	Ineligible comparator
81.	Knapen et al, 2003	Ineligible patient population
82.	Knubben et al, 2007	Ineligible intervention
83.	Kraepelien et al, 2015	Secondary data
84.	Kratz et al, 2014	Ineligible intervention

85. Krogh et al, 2007	Ineligible comparator
86. Krogh et al, 2009	Ineligible comparator
87. Krogh et al, 2012	Ineligible comparator
88. Krogh et al, 2013	Ineligible outcome
89. Kruisdijk et al, 2012	Ineligible patient population
90. Kruisdijk et al, 2019	Ineligible patient population
91. Kruisdijk et al, 2020	Ineligible patient population
92. Lau et al, 2004	Ineligible patient population
93. Le Cheminant et al, 2014	Non depressed
94. Legrand et al, 2007	Medication
95. Legrand et al, 2015	Medication
96. Levinger et al, 2011	Non depressed
97. Li et al, 2019	Ineligible intervention
98. Lincoln et al, 2011	Ineligible patient population
99. Lopez-Torres Hidalgo et al, 2019	No RCT
100. Mailey et al, 2010	Ineligible patient population
101. Majumder et al, 2015	Ineligible patient population
102. Martins et al, 2011	Non depressed
103. Martinsen et al, 1985	Ineligible comparator
104. Martiny et al, 2015	Ineligible comparator
105. Mata et al, 2012	Non depressed
106. Matthews et al, 2011	Non depressed
107. Mendham et al, 2021	Non depressed
108. Meyer et al, 2022	Ineligible intervention
108. Midtgaard et al, 2012	No control group
109. Moraes et al, 2022	Ineligible comparator
109. Nasstasia et al, 2019	Ineligible patient population
110. Naumann et al, 2020	Ineligible comparator
111. Neidig et al, 2003	Non depressed
112. Neviani et al, 2017	Secondary data
113. Ng et al, 2017	Non depressed
114. Niederer et al, 2017	Ineligible comparator
115. Nordbrandt et al, 2015	Non depressed
116. Norvell et al, 1993	Non depressed
117. Nyberg et al, 2015	Ineligible patient population
118. Oeland et al, 2010	Ineligible patient population
119. Ökzan et al, 2020	Non depressed
120. Olson et al, 2017	Ineligible comparator
121. O'Reilly et al, 1999	Non depressed
122. Palmer et al, 1995	Non depressed
123. Patten et al, 2017	Ineligible intervention
124. Payne et al, 2008	Non depressed
125. Penninx et al, 2002	Non depressed
126. Pentecost et al, 2015	Ineligible intervention
127. Pereira et al, 2013	Ineligible comparator
128. Perna et al, 2010	Non depressed
129. Peterson et al, 2014	Non depressed
130. Philippot et al, 2022	Ineligible comparator

130. Pibernik-Okanovic et al, 2011	Ineligible patient population
131. Piette et al, 2011	Ineligible intervention
132. Porter et al, 2011	Non depressed
133. Puterman et al, 2021	Non depressed
134. Putiri et al, 2012	Ineligible patient population
135. Prakhinkit et al, 2014	No control group
136. Rantakokko et al, 2015	Non depressed
137. Razazian et al, 2016	Non depressed
138. Reuter, 1984	Ineligible intervention
139. Rueter, 1980	Ineligible comparator
140. Sadeghi et al, 2016	Ineligible comparator
141. Salehi et al, 2016	Medication
142. Sarsan et al, 2006	Non depressed
143. Schmitter et al, 2020	Study protocol
144. Scholz et al, 2006	Non depressed
145. Sherwood et al, 2016	Ineligible outcome
146. Singh et al, 2001	Secondary data
147. Siqueira et al, 2016	Medication
148. Sparrow et al, 2011	Non depressed
149. Steiner, Bigatti, Ang et al, 2015	Non depressed
150. Steiner, Richardson, Himle et al, 2015	Ineligible intervention
151. Ström et al, 2013	Ineligible intervention
152. Tapps et al, 2013	Non depressed
153. Teychenne et al, 2019	Non depressed
154. Teychenne et al, 2021	Ineligible patient population
155. Toni et al, 2016	Secondary data
156. Trivedi et al, 2011	Ineligible comparator
157. Van der Kooi et al, 2007	Ineligible patient population
158. Van der Waerden et al, 2013	Non depressed
159. Vankova et al, 2014	Non depressed
160. Verhoeven et al. 2022	Ineligible comparator
160. Verrusio et al, 2014	Ineligible intervention
161. Vieira et al, 2018	Non depressed
162. Vizza et al, 2016	Ineligible patient population
163. Wang et al, 2022	Ineligible intervention
163. Zanetidou et al, 2017	Secondary data
164. Zanuso et al, 2012	Non depressed
165. Zeibig et al, 2021	Ineligible patient population
166. Zeng et al, 2020	Ineligible intervention

Note. Of the k=218 papers reviewed in full-text, k=177 were excluded.

Supplementary Table 3. Risk of Bias Assessment (RoB2)

Study	Intervention group	Comparator	D1	D2	D3	D4	D5	Overall
Abdelbasset et al,[42] 2019	Aerobic exercise	Usual care	!	+	+	+	+	!
Blumenthal et al,[63] 2007	Aerobic exercise	Placebo	+	+	+	+	+	+
Brenes et al,[43] 2007	Mixed exercise	Usual care	!	+	+	-	!	-
Carneiro et al,[64] 2015	Usual care*aerobic exercise	Usual care	+	!	+	-	!	-
Chau et al,[65] 2020	Mixed exercise	Wait-list	+	+	+	+	+	+
Cheung et al,[48] 2018	Aerobic exercise	Usual care	+	+	+	+	+	+
Danielsson et al,[67] 2014	Usual care*aerobic exercise	Usual care	+	+	+	+	+	+
Doose et al,[68] 2015	Aerobic exercise	Wait-list	!	+	+	-	+	-
Doyne et al,[44] 1987	Mixed exercise	Wait-list	+	+	-	+	+	-
Epstein,[69] 1986	Aerobic exercise	Wait-list	!	-	!	!	!	-
Gao et al,[45] 2016	Aerobic exercise	Usual care	+	!	+	!	+	!
Gary et al,[70] 2010	Aerobic exercise	Usual care	!	!	+	+	+	!
Hallgren et al,[46] 2015	Mixed exercise	Usual care	+	+	+	+	+	+
Hemat-Far et al,[47] 2012	Aerobic exercise	Usual care	-	!	+	-	+	-

Huang et al,[48] 2015	Mixed exercise	Usual care	
La Rocque et al,[71] 2020	Aerobic exercise	Wait-list	
Legrand et al,[49] 2014	Aerobic exercise	Wait-list	
Lok et al,[50] 2017	Aerobic exercise	Wait-list	
Makizako et al,[52] 2019	Mixed exercise	Health education	
Mather et al,[41] 2002	Mixed exercise	Health education	
McNeil et al,[51] 1991	Aerobic exercise	Wait-list	
Mota-Pereira et al,[72] 2011	Usual care*aerobic exercise	Usual care	
Mutrie,[53] 1986	Mixed exercise	Wait-list	
Nabkasorn et al,[54] 2006	Aerobic exercise	Usual care	
Oertel-Knöchel et al,[73] 2014	Aerobic exercise	Wait-list	
Orth,[55] 1979	Aerobic exercise	Self-monitoring	
Pfaff et al,[62] 2014	Mixed exercise	Usual care	
Pilu et al,[74] 2007	Usual care*resistance exercise	Usual care	
Prakhinkit et al,[56] 2014	Aerobic exercise	Usual care	
Roy et al,[75] 2018	Aerobic exercise	Usual care	

Schneider et al,[76] 2016	Mixed exercise	Usual care	+	+	+	+	+	+
Schuch et al,[77] 2015	Aerobic exercise	Usual care	+	+	+	+	+	+
Setaro,[57] 1985	Aerobic exercise	Usual care	+	+	+	+	+	+
Shahidi et al,[58] 2011	Aerobic exercise	Unclear	-	-	-	!	!	-
Sims et al,[59] 2006	Resistance exercise	Advise for activity	+	+	+	!	-	-
Sims et al,[60] 2009	Resistance exercise	Wait-list	+	+	+	!	-	-
Singh et al,[78] 1997	Resistance exercise	Health education	-	!	+	-	!	-
Singh et al,[79] 2005	Resistance exercise	Usual care	+	+	+	+	+	+
Veale et al,[80] 1992	Aerobic exercise	Usual care	-	-	+	!	!	-
Vieira et al,[81] 2007	Aerobic exercise	Usual care	!	+	+	-	!	-
Williams et al,[61] 2008	Mixed exercise	Social conversation	+	+	+	+	-	-

Note. + = low risk, ! = some concerns, - = high risk, D1 = Randomisation process, D2 = Deviations from the intended interventions, D3 = Missing outcome data, D4 = Measurement of the outcome, D5 = Selection of the reported result.

Supplementary Table 4. Descriptives of Included Studies

Author, year, country	Age (mean or range)		Gender (% females)		Antidepressant use (% taking)		Thesis or Peer-reviewed article
	Exercise	Control	Exercise	Control	Exercise	Control	
Abdelbasset et al,[42] 2019, Saudi-Arabia	52.60	52.90	31.00	26.00	N/A	N/A	Peer-reviewed
Blumenthal et al,[63] 2007, USA	52.00	52.00	75.00	77.00	0	0	Peer-reviewed
Brenes et al,[43] 2007, USA	73.50	73.90	64.00	50.00	0	0	Peer-reviewed
Carneiro et al,[64] 2015, Portugal	52.78	47.80	100	100	100	100	Peer-reviewed
Chau et al,[65] 2020, Hong Kong	N/A	N/A	74.00	86.00	83.00	83.00	Peer-reviewed
Cheung et al,[48] 2018, Hong Kong/ China	47.40	48.10	88.20	70.60	94.12	88.24	Peer-reviewed
Danielsson et al,[67] 2014, Sweden	44.70	46.30	73.00	80.00	100	100	Peer-reviewed
Doose et al,[68] 2015, Germany	46.10	51.25	60.00	68.80	50.00	75.00	Peer-reviewed
Doyne et al,[44] 1987, USA	28.58	29.46	100	100	0	0	Peer-reviewed
Epstein,[69] 1986, USA	24-60	24-60	N/A	N/A	N/A	N/A	Thesis
Gao et al,[45] 2016, China	54.50	53.50	100	100	0	0	Peer-reviewed
Gary et al,[70] 2010, USA	30-70	30-70	N/A	N/A	N/A	N/A	Peer-reviewed

Hallgren et al,[46] 2015, Sweden	18-71	18-71	N/A	N/A	31.00	24.00	Peer-reviewed
Hemat-Far et al,[47] 2012, Iran	18-25	18-25	100	100	N/A	N/A	Peer-reviewed
Huang et al,[48] 2015, Taiwan	76.42	75.85	57.90	55.00	0	0	Peer-reviewed
La Rocque et al,[71] 2020, Canada	34.85	29.40	100	100	20.00	46.70	Peer-reviewed
Legrand et al,[49] 2014, France	19 - 30	19-30	100	100	0	0	Peer-reviewed
Lok et al,[50] 2017, Turkey	≥65.00	≥65.00	42.50	47.50	0	0	Peer-reviewed
Makizako et al,[52] 2019, Japan	73.10	73.00	53.30	51.70	0	0	Peer-reviewed
Mather et al,[41] 2002, United Kingdom	63.70	66.20	84.00	53.00	100	100	Peer-reviewed
McNeil et al,[51] 1991, Canada	N/A	N/A	N/A	N/A	0	0	Peer-reviewed
Mota-Pereira et al,[72] 2011, Portugal	48.68	45.33	57.90	80.00	100	100	Peer-reviewed
Mutrie,[53] 1986, United Kingdom	45.70	41.10	N/A	N/A	0	0	Thesis
Nabkasorn et al,[54] 2006, Thailand	18.70	18.80	100	100	0	0	Peer-reviewed
Oertel-Knöchel et al,[73] 2014, Germany	36.60	42.20	50.00	37.50	100	100	Peer-reviewed
Orth,[55] 1979, USA	N/A	N/A	N/A	N/A	N/A	N/A	Thesis
Pfaff et al,[62] 2014, Australia	61.20	60.70	62.00	64.10	60.20	47.80	Peer-reviewed

Pilu et al,[74] 2007, Italy	40-60	40-60	100	100	100	100	Peer-reviewed
Prakhinkit et al,[56] 2014, Thailand	74.80	81.00	100	100	0	0	Peer-reviewed
Roy et al,[75] 2018, India	31.10	32.90	100	100	N/A	N/A	Peer-reviewed
Schneider et al,[76] 2016, USA	53.30	53.60	100	100	N/A	N/A	Peer-reviewed
Schuch et al,[77] 2015, Brazil	38.84	41.76	72.00	76.00	84.00	96.00	Peer-reviewed
Setaro,[57] 1985, USA	N/A	N/A	N/A	N/A	N/A	N/A	Thesis
Shahidi et al,[58] 2011, Iran	65.70	68.40	100	100	N/A	N/A	Peer-reviewed
Sims et al,[59] 2006, Australia	75.25	74.30	85.71	50.00	0	0	Peer-reviewed
Sims et al,[60] 2009, Australia	67.95	66.27	39.00	41.00	0	0	Peer-reviewed
Singh et al,[78] 1997, USA	70.00	72.00	70.60	53.30	0	0	Peer-reviewed
Singh et al,[79] 2005, Australia	69.00	69.00	55.00	50.00	0	0	Peer-reviewed
Veale et al,[80] 1992, United Kingdom	19-58	19-58	N/A	N/A	45.00	34.00	Peer-reviewed
Vieira et al,[81] 2007, Brazil	N/A	N/A	100	100	100	100	Peer-reviewed
Williams et al,[61] 2008, USA	71-101	71-101	N/A	N/A	36.00	36.00	Peer-reviewed

Note. Not available (N/A).

Supplementary Table 5. Characteristics of Included Studies

Study	Comorbidities	Group exercise	Setting	Intensity	Supervised	Type of supervision
Abdelbasset et al,[42] 2019	Yes	Unclear	Outpatient	Moderate	Supervised	Unclear
Blumenthal et al,[63] 2007 (supervised exercise)	No	Yes	Outpatient	Vigorous	Supervised	Unclear
Blumenthal et al,[63] 2007 (homebased exercise)	No	No	Outpatient	Vigorous	Unsupervised	None
Brenes et al,[43] 2007	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (certified ACSM exercise leader)
Carneiro et al,[64] 2015	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (physical training teacher)
Chau et al,[65] 2020	No	Yes	Inpatient	Moderate	Supervised	Exercise professional (physiotherapist)
Cheung et al,[48] 2018	No	No	Outpatient	Moderate	Supervised	Exercise professional (qualified personal trainer)
Danielsson et al,[67] 2014	No	No	Outpatient	Vigorous	Supervised	Exercise professional (physiotherapist)
Doose et al,[68] 2015	No	Yes	Outpatient	Light	Supervised	Other (teams of coaches and medical students)
Doyne et al,[44] 1987	No	No	Outpatient	Vigorous	Supervised	Other (trained undergraduate exercise

(running condition)						monitors)
Doyne et al,[44] 1987 (weightlifting)	No	No	Outpatient	Moderate	Supervised	Other (trained undergraduate exercise monitors)
Epstein,[69] 1986	No	Yes	Outpatient	Moderate	Supervised	Other (clinical graduate students)
Gao et al,[45] 2016	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (professional coach and doctor)
Gary et al,[70] 2010	Yes	No	Outpatient	Moderate	Unsupervised	None
Hallgren et al,[46] 2015	No	Yes	Outpatient	Light to vigorous[b]	Supervised	N/A
Hemat-Far et al,[47] 2012	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Huang et al,[48] 2015	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (trained physical fitness instructor)
La Rocque et al,[71] 2020	Yes	Yes	Outpatient	Moderate	Supervised	Exercise professional (professional exercise instructor)
Legrand et al,[49] 2014	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (certified zumba instructor)
Lok et al,[50] 2017	Unclear	Yes	Outpatient	Moderate	Supervised	Other (researcher)
Makizako et al,[52] 2019	Yes	Yes	Outpatient	Moderate	Supervised	Exercise professional (trained instructors)
Mather et al,[41] 2002	No	Yes	Outpatient	Unclear	Supervised	Other (instructor)
McNeil et al,[51] 1991	No	No	Outpatient	Vigorous	66% supervised & 33% unsupervised[c]	Other (undergraduate psychology student)

Mota-Pereira et al,[72] 2011	No	No	Outpatient	Moderate	20% supervised & 80% unsupervised[c]	Exercise professional
Mutrie,[53] 1986 (aerobic exercise)	No	Unclear	Outpatient	Moderate	Unsupervised	None
Mutrie,[53] 1986 (strength & stretching)	No	Unclear	Outpatient	Vigorous	Unsupervised	None
Nabkasorn et al,[54] 2006	No	Yes	Outpatient	Moderate	Supervised	Exercise professional (physical fitness instructor)
Oertel-Knöchel et al,[73] 2014	No	Yes	Inpatient	Moderate	Supervised	Exercise professional (trained physical fitness instructor
Orth,[55] 1979	No	Unclear	Outpatient	Moderate	Unsupervised	None
Pfaff et al,[62] 2014	No	No	Outpatient	Moderate to vigorous	Unsupervised	None
Pilu et al,[74] 2007	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (skilled instructor with isef (physical education) diploma, psychology degree and post-degree diploma in sport psychopathology (MS)
Prakhinkit et al,[56] 2014 (traditional walking)	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Prakhinkit et al,[56] 2014 (Buddhism walking)	No	Unclear	Outpatient	Moderate	Supervised	Other (researcher)
Roy et al,[75] 2018	Unclear	Yes	Inpatient	Moderate	Supervised	Other (registered nurse)
Schneider et al,[76] 2016	Yes	Yes[a]	Outpatient	Moderate	Supervised	Exercise professional (pilates/yoga

						instructor)
Schuch et al,[77] 2015	No	No	Inpatients	Unclear	Supervised	Exercise professional (researcher and sport-scientist)
Setaro,[57] 1985	No	Yes	Outpatient	Unclear	Supervised	Exercise professional (certified aerobic dance instructor)
Shahidi et al,[58] 2011	No	Yes	Outpatient	Unclear	Unclear	Unclear
Sims et al,[59] 2006	No	No	Outpatient	Vigorous	Supervised	Unclear
Sims et al,[60] 2009	Yes	Yes	Outpatient	Vigorous	Supervised	Exercise professional (accredited fitness trainer)
Singh et al,[78] 1997	No	Yes	Outpatient	Vigorous	Supervised	Other (researcher/principal investigator)
Singh et al,[79] 2005 (high intensity)	No	Yes	Outpatient	Vigorous	Supervised	Unclear
Singh et al,[79] 2005 (low intensity)	No	Yes	Outpatient	Light	Supervised	Unclear
Veale et al,[80] 1992	No	Yes	Outpatient	Unclear	Supervised	Unclear
Vieira et al,[81] 2007	No	Yes	Inpatient	Moderate	Supervised	Unclear
Williams et al,[61] 2008 (mixed exercise)	Yes	No	Outpatient	Unclear	Supervised	Other (graduate nursing or physical therapy students)
Williams et al,[61] 2008 (supervised walking)	Yes	No	Outpatients	Unclear	Supervised	Other (graduate nursing or physical therapy students)

Note. Not available (N/A). American College of Sports Medicine (ACSM). [a]Participants were asked to additionally train once a week at home. [b]Participants were randomized to light, moderate, and vigorous intensity exercise. In the subgroup analysis, this study was rated as moderate. [c]Study was rated as supervised in the subgroup analyses.

Supplementary Table 6. Subgroup Meta-analysis of Studies Included in the Quantitative Analyses with Low and Moderate Risk of Bias

Analysis	Number of RCTs	Meta analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]
		SMD	95% CI		p- value	I^2	
Main analysis	19	-0.717	-1.01	-0.43	**<.001**	82.372	-0.897 (-1.219; -0.575) [3]
Depression classification							
MDD[a]	11	-0.567	-0.94	-0.20	.003	78.114	Unchanged
Depressive symptoms	8	-0.951	-1.47	-0.43	**<.001**	87.373	-1.115 (-1.707; -0.523) [1]
Type of control condition							
Usual care	12	-0.763	-1.13	-0.40	**<.001**	83.728	-0.973 (-1.403; -0.543) [2]
Wait list	3	-1.315	-1.89	-0.74	**<.001**	46.548	-1.678 (-2.252; -1.105) [2]
Health education	2	-0.107	-0.44	0.23	.528	0.000	N/A
Intensity of exercise[b]							
Light	1	-0.293	-0.95	0.37	.383	0.000	N/A
Moderate	13	-0.775	-1.17	-0.38	**<.001**	85.562	-0.977 (-1.422; -0.532) [2]
Vigorous	4	-0.324	-0.61	-0.04	.028	28.767	-0.254 (-0.550; 0.043) [1, right of mean]
Exercise type[b]							
Aerobic	12	-0.891	-1.32	-0.46	**<.001**	81.277	-1.254 (-1.760; -0.747) [4]
Resistance	2	-0.508	-0.98	-0.04	.033	0.000	N/A
Mixed[c]	7	-0.396	-0.79	-0.00	.049	84.939	Unchanged
Group exercise[b]							
Yes	13	-0.646	-0.97	-0.38	**<.001**	80.129	Unchanged
No	6	-0.330	-0.58	-0.08	.010	33.470	-0.205 (-0.474; 0.063) [2, right of mean]
Supervision[b]							

Yes[d]	17	-0.769	-1.08	-0.46	**<.001**	82.500	-0.906 (-1.236; -0.576) [2]
No	4	-0.119	-0.34	0.10	.293	0.000	-0.098 (-0.308; 0.111) [2, right of mean]
Type of supervision[b]							
Exercise professional	11	-0.830	-1.22	-0.45	**<.001**	74.192	Unchanged
Other professional/ student	1	-0.061	-0.49	0.36	.778	0.000	N/A
Sample size intervention arm[b]							
n≥25	9	-0.516	-0.84	-0.19	**.002**	84.053	-0.576 (-0.890; -0.261) [1]
n<25	12	-0.801	-1.25	-0.35	**<.001**	76.648	-1.148 (-1.612; -0.683) [4]
n≥10	19	-0.665	-0.94	-0.39	**<.001**	83.059	Unchanged
n<10	2	-0.588	-1.52	0.34	.215	0.000	N/A

Note. See Supplement eTable 2, 3 and 4 for detailed categorization for each study. MDD=Major depressive Disorder; RCT=Randomized Controlled Trial, SMD=Standard mean difference. [a]Including 3 studies with MDD & Dysthymia[46,77,78]. [b]Data for a second intervention group within the same study were included for these analyses. [c]Mixed exercise=aerobic and resistance exercise. [d]Two studies were partly supervised, see Supplement Table 5.

Supplementary Table 7. Subgroup Analysis for Studies with MDD Diagnosis[a]

Analysis	Number of RCTs	Meta analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]
		SMD	95% CI		p- value	I^2	
Main analysis MDD	20	-0.998	-1.39	-0.61	**<.001**	85.746	-1.167 (-1.591; -0.742) [2]
Risk of bias							
Low risk of bias	9	-0.607	-1.03	-0.18	**.005**	82.240	-0.462 (-0.921; -0.003) [1, right of mean]
Some concerns	2	-0.300	-0.87	0.27	.302	0.000	N/A
High risk of bias	9	-1.687	-2.53	-0.84	**<.001**	89.056	Unchanged
Type of control condition							
Usual care	13	-0.762	-1.19	-0.34	**<.001**	81.767	-0.999 (-1.480; -0.518) [2]
Wait list	5	-1.443	-1.82	-1.07	**<.001**	18.443	-1.606 (-2.017; -1.195) [2]
Health education	1	-3.462	-4.56	-2.37	**<.001**	0.000	N/A
Intensity of exercise[b]							
Light	2	-1.041	-2.53	0.45	.170	88.867	N/A
Moderate	12	-1.012	-1.57	-0.45	**<.001**	86.889	-1.317 (-1.987; -0.639) [2]
Vigorous	5	-0.881	-1.62	-0.15	**.019**	88.544	-1.152 (-2.039; -0.265) [1]
Exercise type[b]							
Aerobic	15	-0.893	-1.29	-0.50	**<.001**	80.672	-1.084 (-1.535; -0.633) [2]
Resistance	4	-1.354	-2.48	-0.23	**.018**	87.859	-1.752 (-3.010; -0.499) [1]
Mixed[c]	3	-0.430	-1.62	0.77	.481	94.350	Unchanged
Group exercise[b]							
Yes	15	-0.985	-1.44	-0.53	**<.001**	84.222	Unchanged
No	7	-0.743	-1.29	-0.19	**.008**	85.582	-1.175 (-1.926; -0.424) [2]
Supervision[b]							
Yes	19	-1.066	-1.48	-0.66	**<.001**	84.441	-1.333 (-1.807; -0.860) [3]
No	3	-0.110	-0.33	0.11	.334	0.000	-0.078 (-0.265; 0.108) [2,

							right of mean]
Type of supervision[b]							
Exercise professional	10	-1.077	-1.64	-0.52	**<.001**	81.997	-1.450 (-2.037; -0.863) [3]
Other professional/ student	4	-1.664	-2.88	-0.45	**.007**	87.977	Unchanged
Sample size intervention arm[b]							
n≥25	6	-0.444	-0.91	0.02	.061	86.212	-0.530 (-0.969; -0.090) [1]
n<25	16	-1.144	-1.63	-0.66	**<.001**	82.403	-1.358 (-1.883; -0.834) [2]
n≥10	16	-0.671	-1.02	-0.32	**<.001**	83.953	-0.809 (-1.172; -0.447) [2]
n<10	6	-1.736	-2.70	-0.77	**<.001**	79.899	Unchanged

Note. [a]Including 3 studies with MDD & Dysthymia. [b]Data for a second intervention group within the same study were included for these analyses. [c]Mixed exercise=aerobic and resistance exercise.

Supplementary Table 8. Meta Regression of Moderators/Correlates of Effects of Exercise on Depression for Studies with Low and Moderate Risk of Bias

Moderator	Number of RCTs	β	95%CI		p-value	$R^{2\,c}$
Main exercise response						
Mean age exercise	16	0.013	-0.01	0.04	.272	0.00
Mean age control	16	0.015	-0.01	0.04	.206	0.00
Duration of trial (in weeks)[a]	21	0.064	0.00	0.13	**.039**	0.12
Weekly frequency[a]	21	-0.005	-0.18	0.17	.954	0.00
Minutes per session[a]	19	-0.004	-0.02	0.02	.707	0.00
Sample size[b]	19	0.001	-0.00	0.00	.483	0.00
MDD (+ Dysthymia) only						
Mean age exercise	10	0.021	-0.00	0.04	.078	0.39
Mean age control	10	0.022	-0.00	0.05	.052	0.46
Duration of trial (in weeks)[a]	13	0.070	0.01	0.14	**.034**	0.26
Weekly frequency[a]	13	0.049	-0.15	0.24	.623	0.00
Minutes per session[a]	12	-0.021	-0.05	0.00	.095	0.26
Sample size[b]	11	0.002	-0.01	0.01	.614	0.00

Note. [a]data for a second intervention group within the same study were included for these analyses. [b]Average sample size pre-post intervention. c R2 equal to R2 analog.

Supplementary Figure 1. Funnel Plot of Standard Error by SMD