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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]

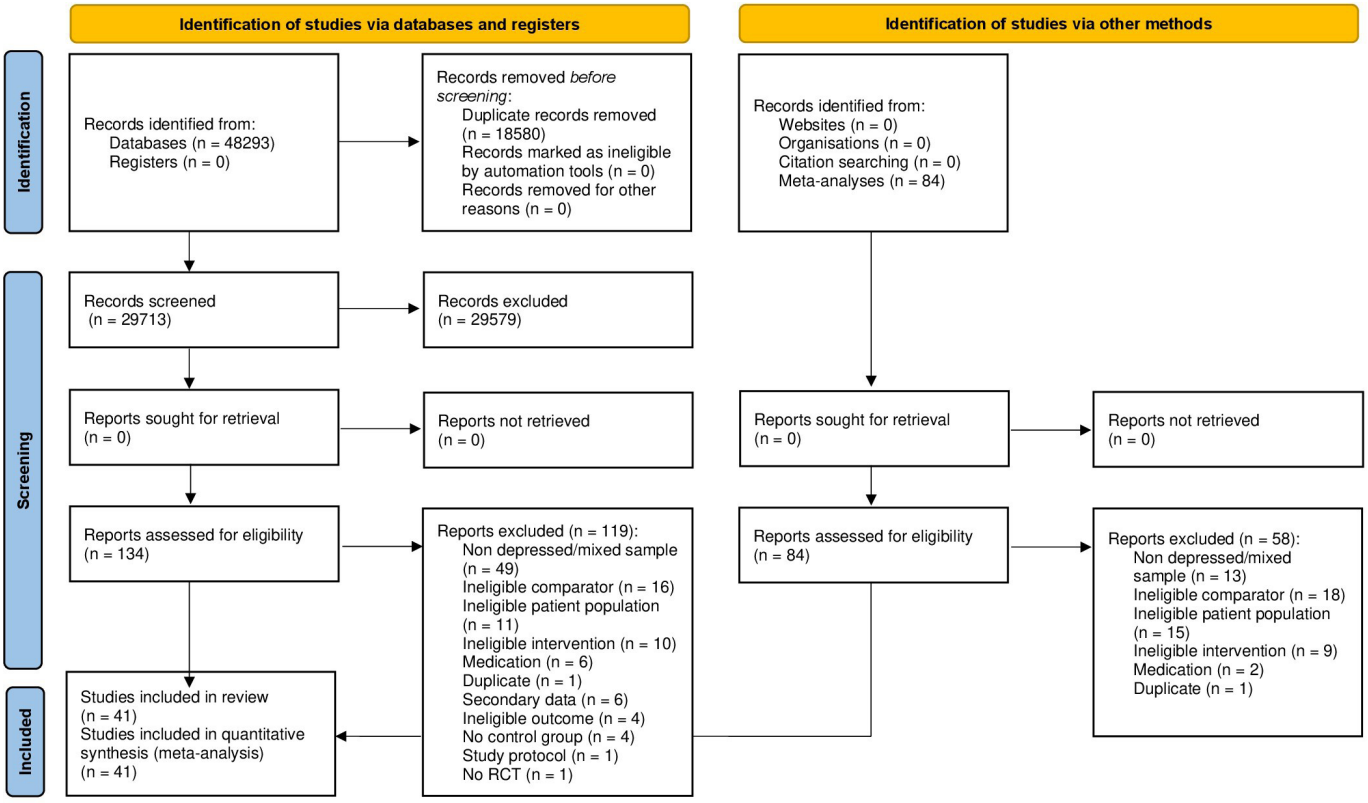

Figure 1 Flowchart of study selection. Flowchart adapted from the PRISMA 2020 statement.[42] RCT, randomised controlled trial.

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.

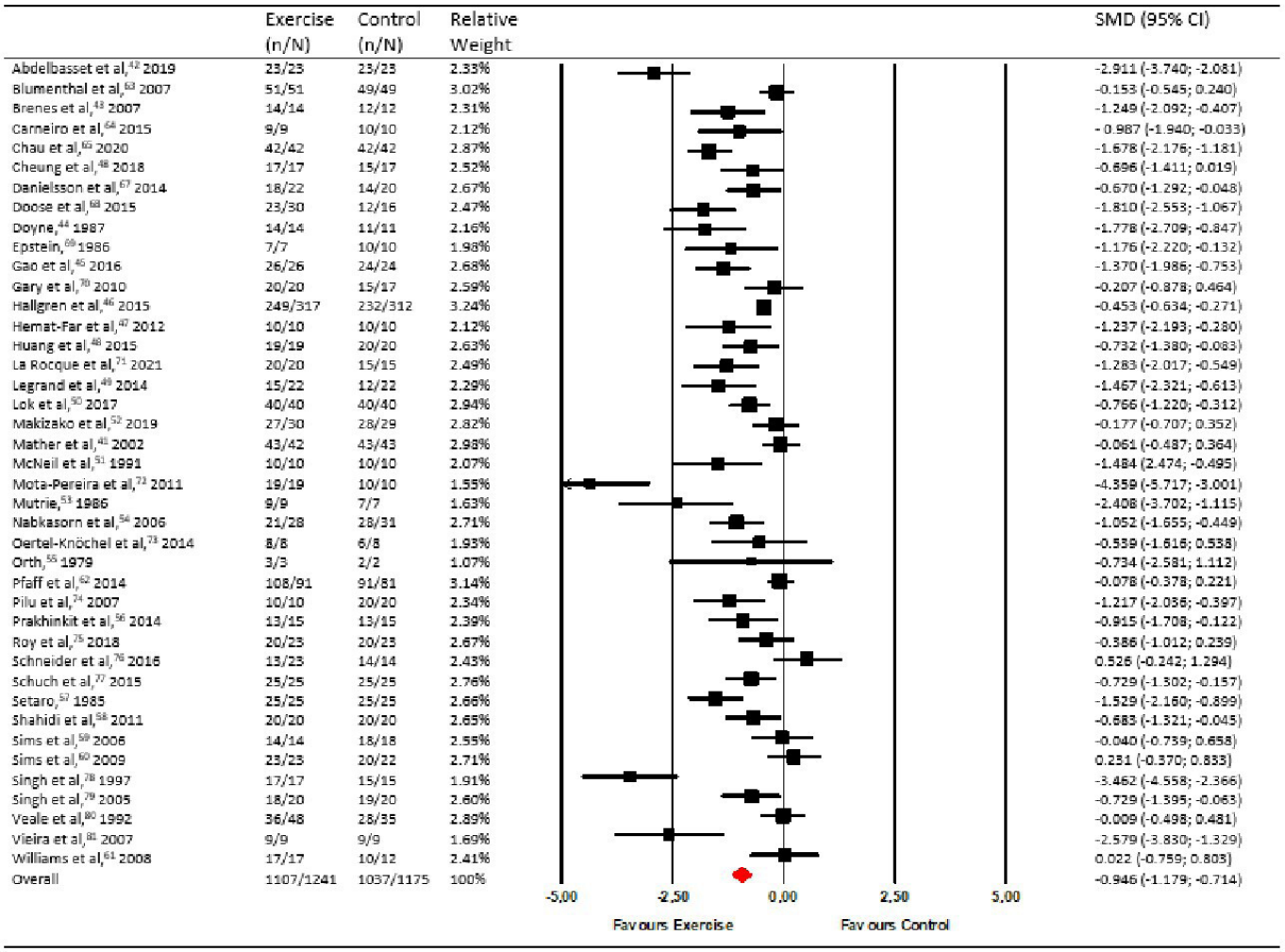

Figure 2 Meta-analysis of overall studies. N, preintervention n, postintervention, SMD, standardised difference.

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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