Revista Brasileira de Psiquiatria. 2016;38:247–254
Associação Brasileira de Psiquiatria
doi:10.1590/1516-4446-2016-1915

REVIEW ARTICLE

Exercise for depression in older adults: a meta-analysis of randomized controlled trials adjusting for publication bias

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Objective: To evaluate the antidepressant effects of exercise in older adults, using randomized controlled trial (RCT) data.
Methods: We conducted a meta-analysis of exercise in older adults, addressing limitations of previous works. RCTs of exercise interventions in older people with depression ($\geqslant$ 60 years) comparing exercise vs. control were eligible. A random-effects meta-analysis calculating the standardized mean difference (SMD) (95% confidence interval [95%CI]), meta-regressions, and trim, fill, and fail-safe number analyses were conducted.
Results: Eight RCTs were included, representing 138 participants in exercise arms and 129 controls. Exercise had a large and significant effect on depression (SMD = -0.90 [95%CI -0.29 to -1.51]), with a fail-safe number of 71 studies. Significant effects were found for 1) mixed aerobic and anaerobic interventions, 2) at moderate intensity, 3) that were group-based, 4) that utilized mixed supervised and unsupervised formats, and 5) in people without other clinical comorbidities.
Conclusion: Adjusting for publication bias increased the beneficial effects of exercise in three subgroup analysis, suggesting that previous meta-analyses have underestimated the benefits of exercise due to publication bias. We advocate that exercise be considered as a routine component of the management of depression in older adults.

Keywords: Exercise; depression; older adults; publication bias; meta-analysis

Introduction

Depression in older adults is common, with prevalence estimates ranging from 4.6 to 9.3%.[1] Late-life depression is a serious societal burden, resulting in increased health care costs,[2] increased risk of morbidity and suicide, and impairments in physical, social, and cognitive functioning, all of which are associated with increased disability and mortality.[3]

Antidepressants remain the most common treatment choice, with selective serotonin re-uptake inhibitors considered the first-line option.[4] However, antidepressants are associated with many side effects, including falls,[5] cardiovascular events, fractures, epilepsy, hyponatremia, and increased risk of all-cause mortality.[6] Hence, there is a need for alternative strategies to improve depression in older adults.

Exercise has been studied as a potential non-pharmacological treatment for late-life depression.[7] A meta-analysis including seven studies[7] found a small to moderate effect (standardized mean difference [SMD] = -0.34, 95% confidence interval [95%CI]) -0.52 to -0.17) of exercise on depression. However, this review was conducted on data available 5 years ago and the authors included one large trial in which half of participants were not depressed or did not meet standardized criteria for depression or elevated depressive symptoms.[8] Other pertinent questions remain unanswered in the literature on exercise and depression in older adults. For instance, no meta-regression of potential moderators of the antidepressant effect of exercise in randomized controlled trials (RCTs) in older adults with depression has been reported, despite high heterogeneity across studies. Although publication bias is known to be a potential threat to the validity of meta-analysis,[9] no previous meta-analysis has considered its impact on the results obtained. A meta-analysis of psychotherapies for depression found that publication bias resulted in overstatement of effect sizes (ESs).[10] In the literature on exercise for depression, one recent meta-analysis including adults demonstrated that publication bias resulted in underrepresentation of the true effect of exercise; adjusting for publication bias increased the ES from 0.98 to 1.15 (95%CI 0.68-1.27).[11] A systematic

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Submitted Jan 12 2016, accepted Mar 09 2016.

review and meta-analysis focused on older adults also found evidence of publication bias; however, adjusted ES estimates were not provided.[7]

The present review aimed to address these limitations. Specific aims were: 1) to establish the effects of exercise on depression in older people with depression, using all available data, comparing exercise vs. non-active control groups; 2) to identify moderators, including sample characteristics (gender, medication use, and severity of baseline symptoms) and exercise intervention variables (length of intervention, frequency of exercise sessions, and supervision), that could influence the effects of exercise on depression; 3) to assess the possible influence of publication bias on the relationship between exercise and depression in older people; and 4) to evaluate the strength of the current evidence by calculating the number of negative studies required to nullify our conclusions.

Methods

This systematic review followed the PRISMA statement[12] and the MOOSE guidelines.[13]

Inclusion criteria

Studies were eligible for inclusion in this meta-analysis if they met the following criteria:

1) Investigated older adults (minimum age of participants = 60 years) with a primary diagnosis of major depressive disorder (MDD), according to established criteria (e.g., DSM[14] or ICD[15]), or those with increased depressive symptoms determined by a validated screening measure (e.g., the Hamilton Depression Scale[16] [HAM-D], Beck Depression Inventory[17] [BDI], Geriatric Depression Scale[18] [GDS], or others). Studies included in this criteria were those that included participants with at least mild (or equivalent) scores on validated scales or, in case the scale did not have a validated cutoff, the cutoff used by the author was accepted. We also included studies that included some participants with other related diagnoses, such as dysthymia, that is classified into the category of chronic persistent depressive disorders.[14]

2) Measured depressive symptoms before and after intervention using a validated measure (e.g., HAM-D, BDI, and GDS).

3) Were RCTs investigating exercise, as defined by Caspersen et al.[19] as planned, structured, repetitive, and purposive physical activity, in the sense that improvement or maintenance of one or more components of physical fitness is an objective in the active arm of the trial. Trials that used yoga, *tai chi*, or *qigong* were not included since previous studies found significant heterogeneity in these trials when compared with conventional aerobic or strength exercises.[7]

4) Included a non-active control group, such as usual-care/usual-treatment, wait-list control conditions, placebo pills, or other social activities (trials that included any other exercise interventions - such as stretching or low-dose exercise - as comparators were excluded).

5) Were published in peer-reviewed journals or as dissertations.

Information sources and searches

Potentially eligible studies were identified in a two-step process. First, three authors (BS, FBS, SR) reviewed all articles identified (both included and excluded with reasons) by the recent Cochrane review on exercise for depression.[20] Second, three independent reviewers (BS, FBS, SR) searched the Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus, and PubMed databases, without language restrictions, from January 2013 until August 1, 2015, using the keywords ([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]). In addition, the reference lists of all eligible articles of recent reviews investigating the effectiveness of exercise vs. control in adults or older people were screened to identify potentially eligible articles.[7,20-22]

Study selection

Three authors (BS, FBS, SR) determined potentially eligible articles that met the inclusion criteria. After removal of duplicates, two independent reviewers screened all potentially eligible articles on the basis of titles and abstracts. After obtaining the full texts, the three authors then applied the eligibility criteria and, through consensus, generated a final list of articles for inclusion.

Outcomes

Our primary outcome of interest was the mean change in depressive symptoms in the exercise group, assessed by any validated scale, from baseline to post-intervention, in comparison with the mean change observed in the control group, calculated as the SMD and respective 95% CI. If an author reported the results of two outcome measures meeting our criteria (i.e., mean change/pre- and post-test change in depressive symptoms according to two different measures), we used the primary outcome chosen by the author. If this was not clear, we attempted to use the HAM-D or BDI to increase homogeneity in our results. For studies reporting the effects of two or more different exercise groups (home-based and supervised, aerobic and anaerobic, high- and low-dose), the arm reporting the greater ES was included in the analysis.

Data extraction

Two authors (FBS, SR) independently extracted data using a data extraction form designed to collect sample-related (number of participants, percentage of women, percentage of participants taking antidepressants, presence of clinical comorbidities, severity of baseline symptoms), exercise-related (trial duration, intensity of

intervention according to the American College of Sports Medicine [ACSM] classification,[23] weekly frequency), and methodological factors (study quality, instruments used for diagnosis and symptom assessment, supervision). Lastly, we extracted data for the primary outcome (means and standard deviation [SDs]) from both groups, pre- and post-intervention. If this was not available, we used the pre- and post-test mean change and SD, if reported within the study. In the event that a study reported two or more exercise groups, the group exposed to the highest intensity, volume, or dose was considered for analysis.

Risk of bias and quality assessment

Three authors (FBS, JR, BS) assessed study quality in terms of the presence of high, low, or unclear risk of bias, according to the Cochrane Handbook definition.[24] The risk of bias was assessed by considering random sequence generation, allocation concealment, blinding of participants, blinding of those delivering the intervention, blinding of outcome assessors, incomplete data by outcome, selective reporting, and other factors. To be considered of high quality, studies had to report adequate allocation concealment AND presentation of outcomes data according to intention-to-treat principles AND blinding of outcome assessors. The criteria used for risk-of-bias assessment were based on previous studies.[20]

Meta-analysis

We performed meta-analysis using a random effects models due to expected heterogeneity, with SMD and 95%CIs used as the ES. First, we calculated the SMD statistic and corresponding 95%CIs to establish the effects of exercise on depression in older adults across all studies, using Comprehensive Meta-Analysis version 3 software (CMA Biostat, Englewood, NJ, USA). We then conducted a sensitivity analysis, computing the effects of exercise on depression in high-quality studies only. Subsequently, we conducted meta-regression analyses to investigate potential moderators of the antidepressant effects of exercise. Potential moderators were chosen *a priori* and included sex, age, use of medication, trial duration, and weekly intervention frequency. Next, we conducted subgroup analyses to compare exercise response according to depression diagnosis, study setting (inpatient, outpatient, mixed), high quality (low risk of bias) vs. low quality, presence of other major clinical comorbidities (yes or no), supervision (yes, no, unclear), exercise type (aerobic, resistance, mixed), and exercise intensity. Heterogeneity was assessed with Cochran's Q and the I^2 statistic for each analysis.[24] Publication bias was assessed with the Begg-Mazumdar rank correlation test (yielding Kendall's tau)[25] and Egger's bias test.[26] In addition, we conducted a trim and fill adjusted analysis[27] to remove the most extreme small studies from the positive side of the funnel plot and recalculated the ES at each iteration, until the funnel plot was symmetric about the (new) ES for all analysis. Finally, the classic fail-safe number of negative studies that would be required to nullify (i.e., make $p > 0.05$) our ES was calculated.[28] SMDs $\leqslant 0.4$ were considered indicative of small effects, those between 0.41 and 0.7 were considered moderate, and those > 0.7 were considered large effects.[29]

Results

Search results

In the first stage of the search strategy, eight RCTs were identified from a previous review.[30-37] In the second stage, following the removal of duplicates, our search identified 819 potentially relevant articles. At the full-text review stage, we reviewed 49 articles (all eight from the first stage and 41 from our second-stage searches); of these, 40 were excluded with reasons. This yielded nine full-text,

Table 1 Summary of included studies

Study	Sample size (n)		Age (mean or range)		Sex (% female)		Antidepressant use (% taking)		Outcome	Trial duration (weeks)	Diagnosis
	Exercise	Control	Exercise	Control	Exercise	Control	Exercise	Control			
Brenes[30]	14	12	73.5	73.9	64	50	0	0	HAM-D	16	Depressive symptoms
Huang[38]	19	20	76.42	75.85	57.9	55	0	0	GDS-15	12	Depressive symptoms
McNeil[32]	10	10	?	?	?	?	0	0	BDI	6	Depressive symptoms
Shahidi[33]	20	20	65.7	68.4	100	100	?	?	GDS	?	Depressive symptoms
Sims[34]	23	21	67.95	66.27	39	41	?	?	PHQ-9	10	Depressive symptoms
Singh[35]	17	15	70	72	70.5	53.3	0	0	BDI	10	MDD + dysthymia
Singh[36]	18	19	69	69	55	50	0	42	HAM-D	8	MDD + dysthymia
Williams & Tappen[37]	17	12	71-101	71-101	?	?	?	?	CSDD	16	Depressive symptoms

BDI = Beck Depression Inventory; CSDD = Cornell Scale for Depression in Dementia; GDS = Geriatric Depression Scale; HAM-D = Hamilton Depression Scale; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire.

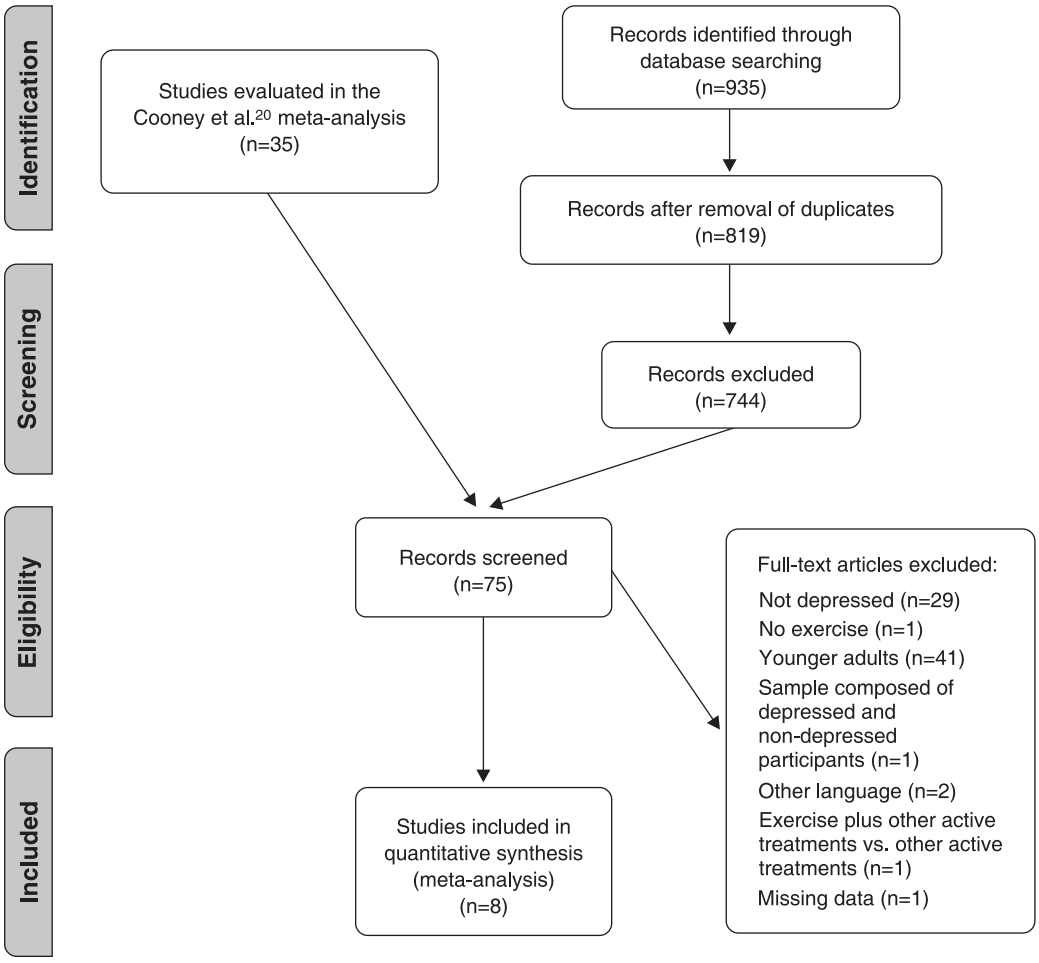

Figure 1 Flowchart of study selection.

peer-reviewed articles that met the eligibility criteria.[30-38] Eight of these studies were from the first stage and one was from the second stage (details summarized in Figure 1). Of these, eight[30,32-38] provided complete data and were included in our meta-analysis.

Characteristics of included trials and participants

The eight included studies assessed a population of 267 adults with depression, of whom 138 and 129 were randomized to exercise and control conditions, respectively.

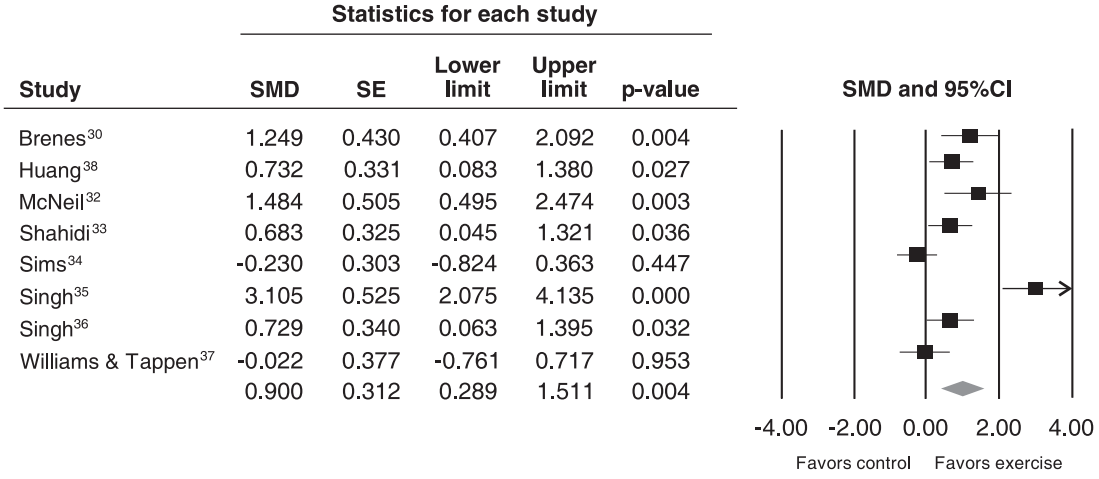

Figure 2 Meta-analysis of all included studies. 95%CI = 95% confidence interval; SE = standard error; SMD = standardized mean difference.

The mean (SD) age was 69.5 (0.71) for exercise and 70.5 (2.12) for control groups, respectively. No study was conducted in a sample exclusively limited to participants with MDD. Two studies[33,34] included participants with other psychiatric diagnosis (dysthymia) and two others included participants with depression as well as participants with additional comorbid diagnoses, such as cardiovascular or neurological diseases.[34,37] The most commonly used measures of depressive symptoms were the HAM-D (n=2), BDI (n=2), and GDS (n=2). The mean trial duration was 12 weeks. Participant details and symptom measures are presented in Table 1. Full details of other characteristics can be obtained from the authors upon request.

Main analysis

Data pooled from the eight included studies showed a large improvement in symptoms of depression favoring the exercise groups (SMD = -0.90, 95%CI 0.28-1.51, p = 0.004, Q = 38, I^2 = 81.63, p < 0.001) (Figure 2). The Begg (tau = 0.71, p = 0.01) and Egger tests indicated publication bias (intercept = 9.66, p = 0.01), likely due to a greater presence of studies reporting a significant association between exercise and improvement in depression. A funnel plot is available from the authors upon request. The ES remained unchanged after adjustment for the trim and fill analysis.

Subgroup analyses

All subgroup analyses are presented in Table 2. Briefly, exercise had significant effects in samples without clinical comorbidities (SMD = -1.25, 95%CI -0.62 to -1.87, p < 0.001), in which mixed interventions combined aerobic exercise and strength training (SMD = -0.92, 95%CI -0.41 to -1.43, p = 0.02) or moderate intensity (SMD = -0.73, 95%CI 0.08 to -1.38, p < 0.001), in a mixed supervised and unsupervised format (SMD = -1.48, 95%CI -0.49 to -2.47, p = 0.003).

Adjustment of publication bias and fail safe number of studies

Upon adjustment for potential publication bias, three analyses were adjusted by the Duval and Tweedie trim and fill method.[27] ESs for all three analyses (group exercise, supervised, and no major comorbidities) all increased after adjustment. The fail-safe number of studies required to nullify the ESs were also relatively higher. In particular, the fail-safe number for the main analysis was n=71, while higher numbers were required to nullify the effect in studies conducted in people without clinical comorbidities (n=81) and in outpatients (n=73) (Table 2).

Meta-regression of antidepressant effects in the main analysis

Baseline depressive symptoms had borderline significance as moderators of the antidepressant effects of exercise (B = 0.156, 95%CI 0.008-0.3223, p = 0.06, R^2 = 0.09). A summary of all meta-regression analyses is presented in Table 3. No other significant moderators were identified.

Mean change in depressive symptoms

The mean improvement on the HAM-D (three studies) was -5.21 points (95%CI 3.15-7.26, p < 0.001), and in the BDI (two studies), -6.19 points (95%CI 4.39-7.99, p < 0.001).

Risk of bias

All studies were considered to be of low quality (high risk of bias). Full details on risk-of-bias assessment can be obtained from the authors upon request.

Discussion

The present study found a large and significant antidepressant effect of exercise in older adults. Specifically, large and significant effects were found for moderate-intensity exercise, in studies that used mixed aerobic and strength training, in both supervised and unsupervised formats, and in samples without major comorbidities. Moreover, our analyses suggested that some results were underestimated due to publication bias, suggesting that previous meta-analyses might have inadvertently underestimated the antidepressant effect of exercise. However, the small number of trials included in this review suggests that caution is warranted in interpretation of our findings.

Our results corroborate the findings of a previous study of depressed older adults experiencing significant depressive symptoms, which revealed significant antidepressant effects of exercise.[7] The magnitude of the findings, however, differs somewhat. Bridle et al.[7] identified a small to moderate reduction in depressive symptoms (SMD = -0.34, 95%CI -0.52 to -0.17), while our analysis found a large effect (SMD = -0.90, 95%CI -0.28 to -1.51). Several factors that may account for the larger ES found in the present analysis. First, the studies used different strategies to calculate ESs. Bridle et al.[7] based estimation of ESs on the difference of the post-intervention value between the intervention and control groups using the SMD ES. In the present review, we estimated the standardized difference in means from baseline to post-intervention and the change in SD. This strategy increased the ES of some studies (such as the Brenes et al.[30] study, from an SMD of -0.55 to an SMD of -1.49). Second, there were important differences in inclusion criteria. In the present study, we did not include studies that enrolled participants who did not meet criteria for elevated depressed symptoms, as assessed by a validated instrument such as the HAM-D, BDI, or GDS. This criterion resulted in the exclusion of the Kerse et al.[8] study from our review, because approximately 47% of the sample did not meet criteria for depressive disorder or increased depressive symptoms. Lastly, we also considered studies that used short-term interventions (less than 3 months' duration) and excluded trials evaluating acute responses to a single

Table 2 Subgroup meta-analysis of all studies

Analysis	RCTs (n)	SMD	95%CI	p-value	Heterogeneity (I^2)	Trim and fill effect size (95%CI, adjusted studies)	Fail-safe number (n)
Main analysis							
Exercise vs. control	8	-0.900	-0.29 to -1.51	**0.004**	81.63	Unchanged	71
Depression classification							
MDD/dysthymia/MiDD	2	-1.883	0.44 to -4.21	0.11	93.06	N/A	N/A
Depressive symptoms	6	-0.560	-0.14 to -0.97	**0.008**	61.00	Unchanged	26
Study setting							
Outpatient/community	7	-1.037	-0.37 to -1.74	**0.002**	82.33	Unchanged	73
Nursing homes	1	-0.022	0.71 to -0.76	0.953	0	N/A	N/A
Intensity of exercise							
Moderate	1	-0.73	0.08 to -1.38	**0.02**	0	N/A	N/A
Vigorous	3	-1.15	0.50 to -2.80	0.17	93.47	Unchanged	11
Exercise type							
Aerobic only	3	-0.66	-0.10 to -1.42	0.09	65.82	Unchanged	4
Resistance only	3	-1.15	0.50 to -2.80	0.174	93.40	Unchanged	11
Mixed	2	-0.92	-0.41 to -1.43	< **0.0001**	0	N/A	N/A
Group exercise							
Yes	6	-0.97	-0.24 to -1.71	**0.009**	84.35	-1.24 (0.38-2.10) (1)	49
No	2	-0.69	0.78 to -2.36	0.356	82.49	N/A	N/A
Supervision							
Supervised	6	-0.86	-0.07 to -1.66	**0.032**	85.19	-1.11 (0.24-1.98) (1)	34
Supervised and unsupervised	1	-1.48	-0.49 to -2.47	**0.003**	0	N/A	N/A
Comorbidities							
No major comorbidities	6	-1.25	-0.62 to -1.87	< **0.001**	74.10	-1.38 (0.78-1.99) (1)	81
Participants with comorbidities	2	-0.14	0.61 to -0.31	0.52	0	N/A	N/A

95%CI = 95% confidence interval; MDD = major depressive disorder; MiDD = minor depressive disorder; N/A = not available; RCTs = randomized clinical trials; SMD = standardized mean difference.
Values in bold are significant.

exercise session, which resulted in the exclusion of the Singh et al. study[39] (SMD = -0.67, 95%CI -1.43 to 0.08) and the inclusion of two trials by the same author, with SMDs of -3.10 and -0.72, respectively.[35,36]

This was the first study to calculate mean-difference changes in depressive symptoms across two commonly used measures in older adults. Specifically, we found a 5.2-point reduction in HAM-D and a 6.2-point reduction in BDI scores. While this reduction is smaller than that reported in a recent meta-analysis focusing on adults,[11] it exceeds the threshold for clinically meaningful change proposed by the National Institute for Health and Care Excellence[40] guidelines for depression treatment.

Our preliminary findings regarding exercise program variables in older adults may be used as inputs to design interventions for clinical practice, as currently available recommendations are based on specific studies rather than on meta-analytical data.[41] First, moderate-intensity exercise promoted large, significant reductions in depressive symptoms, while no significant effect was found for vigorous exercise. This result differs from the findings of a previous meta-analysis of adults (age > 18 years),[11] which showed that both moderate and vigorous exercise promote significant effects on depressive symptoms. We hypothesize that this effect may be because, in older adults, vigorous exercise is actually of higher relative intensity due to the deconditioning that occurs during aging. This issue may be even more pronounced in individuals with depression, who experience decreased aerobic capacity when compared to non-depressed participants.[42]

Second, mixed aerobic exercise and strength training, but not strength training or aerobic exercise alone, were

Table 3 Meta-regression of moderators/correlates of effects of exercise on depression

Moderator	RCTs (n)	β	95%CI	p-value	R^2
Mean age, control	6	0.122	-0.083 to 0.327	0.24	0.02
Mean age, exercise	6	0.049	-0.209 to 0.308	0.70	0.00
Females, exercise (%)	6	0.017	-0.020 to 0.058	0.40	0.00
Females, control (%)	6	0.005	-0.042 to 0.042	0.99	0.00
Baseline depressive symptoms, exercise	8	0.156	0.008 to 0.3223	0.06	0.09
Baseline depressive symptoms, control	8	-0.021	-0.150 to 0.107	0.74	0.00
Dropout, exercise (%)	7	-0.050	-0.195 to 0.095	0.49	0.28
Dropout, control (%)	7	-0.058	-0.168 to 0.052	0.30	0.00
Trial duration	7	-0.017	-0.209 to 0.173	0.85	0.00
Weekly intervention frequency	7	-0.524	-1.268 to 0.219	0.16	0.00

95%CI = 95% confidence interval; RCTs = randomized clinical trials.

effective treatments for depression in older adults. These findings are potentially attributable to the small number of studies included in each subgroup. However, even with two studies, the mixed interventions had significant effects on depression, and should thus be considered as an option to improve muscle strength and cardiorespiratory fitness. Indeed, improvement in fitness should be considered a target in exercise treatment for depression.[43]

Third, group exercise was effective for older patients, while exercise sessions not conducted in a group setting were not significantly efficacious. This may be particularly important in a population known to be at high risk of social isolation.[44] Indeed, future research should consider the mental health benefits of exercise not only as a means of increasing physical activity, but also as a vehicle for promoting social interaction.

Lastly, our data show that special attention should be given to older people with significant comorbidities, such as cardiovascular or neurological diseases. We hypothesize that these comorbidities may limit functional capacity to engage in exercise, and that this limitation may be particularly relevant in older adults, who have an inherently lower exercise capacity due to the impacts of aging on neuromuscular structure and function.[45]

Several theories have been advanced to explain the antidepressant effect of exercise, including hormonal changes (e.g., increased beta-endorphins, serotonergic system adaptations, impact on hormone levels) and effects on neurogenesis (e.g., as demonstrated by increased brain-derived neurotrophic factor [BDNF] levels), inflammation (decreased levels of pro-inflammatory markers and increased levels anti-inflammatory markers), and oxidative stress (decreased levels of pro-oxidative markers and increased levels of antioxidant markers), as well as changes in cortical activity and structure.[46] Indeed, exercise appears to promote adaptations in copeptin and thiobarbituric acid reactive species (TBARS) and total mean frequency in people with depression.[46,47] In addition, preliminary evidence suggests associations of increases in hippocampal volume and serum levels of interleukin-1 beta with symptom improvement.[46] However, exactly which specific mechanisms account for the antidepressant effects of exercise in MDD remains unclear; further research should attempt to elucidate this.

The present review has some limitations. As only eight trials were analyzed, some subgroups were very small, including only one or two trials. In addition, all included studies had small sample sizes ($n < 50$). Therefore, the likelihood that the Egger and Begg tests would detect publication bias was decreased.[48,49] Considering this limitation, the preliminary subgroup analysis provides only initial directions for future research, and should be interpreted with caution.

In conclusion, exercise can be considered an effective non-pharmacological treatment for depression in older adults. This result is especially relevant because late-life depression is a major societal burden, resulting in increased health care costs, increased risk of morbidity, suicide, cognitive and functional decline, as well as increased mortality. Some results might be sensitive to publication bias, and previous meta-analyses may have inadvertently presented conservative ESs for the impact of exercise on depression in older adults. To ensure optimal effectiveness, moderate-intensity, mixed aerobic and anaerobic exercise sessions in a group format appear to have the greatest impact on reduction of depressive symptoms.

Acknowledgements

This study received financial support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Disclosure

The authors report no conflicts of interest.

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