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Association of Efficacy of Resistance Exercise Training With Depressive Symptoms: Meta-analysis and Meta-regression Analysis of Randomized Clinical Trials

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Abstract

Importance The physical benefits of resistance exercise training (RET) are well documented, but less is known regarding the association of RET with mental health outcomes. To date, no quantitative synthesis of the antidepressant effects of RET has been conducted.

Objectives To estimate the association of efficacy of RET with depressive symptoms and determine the extent to which logical, theoretical, and/or prior empirical variables are associated with depressive symptoms and whether the association of efficacy of RET with depressive symptoms accounts for variability in the overall effect size.

Data Sources Articles published before August 2017, located using Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science.

Study Selection Randomized clinical trials included randomization to RET (n = 947) or a nonactive control condition (n = 930).

Data Extraction and Synthesis Hedges *d* effect sizes were computed and random-effects models were used for all analyses. Meta-regression was conducted to quantify the potential moderating influence of participant and trial characteristics.

Main Outcomes and Measures Randomized clinical trials used validated measures of depressive symptoms assessed at baseline and midintervention and/or postintervention. Four primary moderators were selected a priori to provide focused research hypotheses about variation in effect size: total volume of prescribed RET, whether participants were healthy or physically or mentally ill, whether or not allocation and/or assessment were blinded, and whether or not the RET intervention resulted in a significant improvement in strength.

Results Fifty-four effects were derived from 33 randomized clinical trials involving 1877 participants. Resistance exercise training was associated with a significant reduction in depressive symptoms with a moderate-sized mean effect Δ of 0.66 (95% CI, 0.48-0.83; $z = 7.35$; $P < .001$). Significant heterogeneity was indicated (total $Q = 216.92$, $df = 53$; $P < .001$; $I^2 = 76.0\%$ [95% CI, 72.7%-79.0%]), and sampling error accounted for 32.9% of observed variance. The number needed to treat was 4. Total volume of prescribed RET, participant health status, and strength improvements were not significantly associated with the antidepressant effect of RET. However, smaller reductions in depressive symptoms were derived from randomized clinical trials with blinded allocation and/or assessment.

Conclusions and Relevance Resistance exercise training significantly reduced depressive symptoms among adults regardless of health status, total prescribed volume of RET, or significant improvements in strength. Better-quality randomized clinical trials blinding both allocation and assessment and comparing RET with other empirically supported treatments for depressive symptoms are needed.

Disciplines

Biomechanics | Exercise Science | Kinesiology | Kinesiotherapy

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The Effects of Resistance Exercise Training on Depressive Symptoms: A Meta-Analysis and Meta-Regression Analysis of Randomized Controlled Trials

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Key Points

Question: What is the overall effect of resistance exercise training (RET) on depressive symptoms, and what variables of logical, theoretical, and/or prior empirical relation to depressive symptoms and/or RET effects on depressive symptoms account for variability in the overall effect?

Findings: In this meta-analysis, RET significantly reduced depressive symptoms by a moderate-sized mean effect. Total volume of RET, health status, and strength improvements were not associated with the antidepressant effect. However, smaller depressive symptom reductions were derived from studies with blinded allocation and/or assessment.

Meaning: The available empirical evidence supports RET as an alternative and/or adjuvant therapy for depressive symptoms.

Abstract

Importance: The physical benefits of resistance exercise training (RET) are well documented, but less is known regarding the effect of RET on mental health outcomes. No quantitative synthesis of the antidepressant effects of RET has been conducted.

Objective: To estimate the effect of RET on depressive symptoms, and determine the extent to which variables of logical, theoretical, and/or prior empirical relation to depressive symptoms and/or RET effects on depressive symptoms account for variability in the overall effect.

Data Sources: Articles published before August 2017, located using Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science.

Study Selection: Randomized controlled trials (RCTs) included randomization to RET (n=947) or a non-active control condition (n=930).

Data Extraction and Synthesis: Hedges' *d* effect sizes were computed, and random effects models were used for all analyses. Meta-regression was conducted to quantify the potential moderating influence of participant and trial characteristics.

Main Outcome and Measure: RCTs utilized validated measures of depressive symptoms assessed at baseline, and mid- and/or post-intervention. Four primary moderators were selected *a priori* to provide focused research hypotheses about variation in effect size: total volume of prescribed RET, whether participants were healthy or physically/mentally ill, whether or not allocation and/or assessment were blinded, and whether or not the RET intervention resulted in a significant improvement in strength.

Results: Fifty-four effects were derived from 33 RCTs of 1,877 participants. RET significantly reduced depressive symptoms by a moderate-sized mean effect Δ of 0.66 (95%CI: 0.48-0.83; z=7.35; p<0.001). Significant heterogeneity was indicated ($Q_T(53)$=216.92, p<0.001; I^2=76.0%, 95%CI: 72.7%-79.0%), and sampling error accounted

for 32.9% of observed variance. The Number Needed to Treat (NNT) was 4. Total volume of prescribed RET, participant health status, and strength improvements were not significantly associated with the antidepressant effect of RET. However, smaller depressive symptom reductions were derived from RCTs with blinded allocation and/or assessment.

Conclusions and Relevance: RET significantly reduced depressive symptoms among adults regardless of health status, total prescribed volume of RET, or significant improvements in strength. Better quality RCTs blinding both allocation and assessment and comparing RET to other empirically-supported treatments for depressive symptoms are needed.

Key words: mental health; resistance training; strength; depression

1 Introduction

Depression is a highly prevalent global burden, affecting over 300 million people worldwide,[1] is a significant source of absenteeism and disability in the work force,[2] has an economic burden of approximately $118 billion annually,[3] and is the most costly mental health disorder in Europe, accounting for 1% of the total gross domestic product.[4] Depressive symptoms are highly comorbid and significantly associated with poor health,[5] including an increased risk of cardiovascular diseases,[6,7] Alzheimer's disease,[8] type 2 diabetes,[9] mortality,[10] and non-compliance with medical treatment.[10]

Current frontline treatments for depression include medication and psychotherapy. However, for those with mild-to-moderate or severe depression, medication can be expensive, with limited efficacy (d <0.20).[12,13] Psychotherapy can be expensive, inaccessible, and previously reported effects may be overestimated due to publication bias.[14] Moreover, among treatment-seeking individuals with depression, symptoms persist in approximately 67% after first-line treatment of up to 14 weeks, and at least 30% remain depressed after four rounds of distinct 12-week treatments.[15] Thus, there is continued interest in alternative treatments for depression and continued need to compare potential alternative treatments to established treatments.

Exercise interventions are promising treatments for depressive symptoms free from the negative side effects and costs associated with antidepressant medications and psychotherapy.[16,17] Exercise interventions also have established benefits for cardiovascular diseases, the leading cause of death in Major Depressive Disorder.[6] Exercise training improves depressive symptoms among otherwise healthy adults,[18] chronically-ill adults[19] and adults with a depressive disorder.[17] However, the magnitude of the effect remains unclear, as publication bias and flawed inclusion criteria may have resulted in underestimations of the magnitude of exercise effects.[17,20] The benefits of acute aerobic exercise and aerobic exercise

training (AET) for depressive symptoms among otherwise healthy and chronically-ill adults are well-established,[18,19,21,22] but less is known regarding the effects of resistance exercise training (RET) on depressive symptoms. Additionally, few trials have included both an RET and AET arm in the same investigation, limiting direct comparisons between modalities.

RET interventions are generally designed to increase strength, skeletal muscle mass, endurance and/or power.[23] Evidence has supported significant anxiolytic effects of RET among adults regardless of health status,[24] and a previous narrative review supported the antidepressant effects of RET.[25] However, no quantitative synthesis of randomized controlled trials (RCTs) of the antidepressant effect of RET has been conducted. Further, there is a need to identify potential sources of variability in the antidepressant effect of RET, particularly modifiable participant and trial characteristics, to better inform the prescription of RET and future RET interventions.

The key objectives of this meta-analysis and meta-regression analysis were to: (a) estimate the overall effect of RET on depressive symptoms, (b) determine the extent to which the overall effect varies based on variables of logical, theoretical, and/or prior empirical relation to depressive symptoms and/or RET effects on depressive symptoms, and (c) compare the effect of different exercise modes derived from RCTs in which participants were randomized to RET, AET, or a non-active control condition.

2 Methods

2.1 Evidence Acquisition

This systematic review was conducted in accordance with the PRISMA guidelines.[26]

2.2 Data Sources and Searches

Articles published before August 2017 were identified using Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science. Keywords utilized included combinations of “strength training,” “resistance training,” and “weight training,” with

"depress*." Supplementary searches of relevant systematic reviews[17,18,24,25,27] and references within included articles were performed manually.

2.3 Study Selection/Inclusion Criteria

Inclusion criteria were: (i) peer-reviewed publication, (ii) randomized allocation to either a RET intervention or a non-active control condition, and (iii) a validated self-report/clinician-rated measure of depressive symptoms assessed at baseline, and at mid- and/or post-intervention. Investigations were excluded that (i) included exercise as part of a multicomponent intervention but did not include the additional component in comparison conditions, and/or (ii) compared RET only with an active treatment for depression, including cognitive therapy, pharmacotherapy, relaxation/meditation, flexibility training, etc. One article[28] was excluded as the depressive outcomes were previously reported in an earlier included manuscript.[29] eFigure 1 provides a flowchart of article inclusion and exclusion.

2.4 Data Extraction

Data were extracted from included RCTs into an SPSS file by three authors (BRG, CMcD, and MPH). Data extracted included participant and trial characteristics, and exercise effects on outcomes of logical, theoretical, and/or prior empirical relation to depressive symptoms and/or RET effects on depressive symptoms; these included age, sex, physical and mental health status, type of control condition, whether allocation and/or assessment were blinded, exercise program duration, frequency, session duration, RET intensity, whether or not RET sessions were supervised, whether or not the trial primary outcome was depressive symptoms, depressive symptom measure utilized, and whether or not there was a significant improvement in strength. To calculate total volume of RET prescribed, intervention duration (weeks), weekly frequency (days), and session duration (minutes) were multiplied together.

2.5 Study Quality Assessment

Two authors (BRG, MPH) independently assessed study quality (scored 0-13) utilizing the Detsky Scale.[30] This scale was amended to include research design, control condition, randomization and blinding methods, outcome measures, adherence, and exercise intervention characteristics. Higher scores indicated better study quality. Individual scores of included RCTs are presented in eTable 1.

2.6 Effect Size Calculation

To calculate Hedges' *d* effect sizes, the mean change for the control was subtracted from the mean change for RET, and the difference was divided by the pooled baseline standard deviation.[31] Larger reductions in depressive symptoms for RET resulted in positive effect sizes. eTable 2 presents values utilized to calculate Hedges' *d*, and primary moderator values. Inter-rater reliability for effect size calculations was examined by calculating two-way (effects x raters) intraclass correlation coefficients (ICC) for absolute agreement. The initial ICCs were >0.90. When means and standard deviations were not reported, authors were contacted. When these values could not be provided, (k=5), they were estimated from exact p values reported in the manuscript,[32] included graphs,[33,34] or from the largest other study of the same population sample that used the same measure of depressive symptoms,[35,36] in accordance with common meta-analytic protocols.[37] Discrepancies (e.g., values of standard deviations estimated from included graphs) were resolved by consensus among the investigators involved in data extraction (BRG, CMcD, and MPH).

2.7 Data Synthesis and Analysis

Meta-regression was used for moderator analyses because it reduces the probability of type I error by computing concurrent estimates of independent effects by multiple moderators on the variation in effect size across trials. Random effects models were used with macros (MeanES, MetaReg)[38] to aggregate mean effect size delta (Δ) and test variation in effects according to moderator variables.[31,38] Heterogeneity and consistency were evaluated with

Cochrane's Q and I^2, respectively.[37] If sampling error accounted for less than 75% of the observed variance, heterogeneity was indicated.[31] The mean reduction in depressive symptoms among RET participants, expressed as a function of absolute risk reduction, was calculated to determine the number needed to treat (NNT).[39] The number of unretrieved or unpublished studies of null effect that would diminish the significance of observed effects of $p>0.05$ was estimated as fail-safe N+.[40]

As a sensitivity analysis, the mean effect was recalculated extracting single effects from included RCTs determined by 1) the effect with the maximum dose of RET, and 2) the effect in which the Beck Depression Inventory was utilized,[41] for homogeneity of results. There were three exceptions in which two effects remained extracted from single RCTs, as these RCTs each contained two treatment groups and two control groups.[33,42,43]

To examine publication bias, funnel plot symmetry was examined, Egger's regression[44] and Begg's rank correlation tests were calculated,[45] and trim and fill analysis adjusting to the left of the mean was performed.[46] Potential outliers, effects substantially larger than most, were also removed, and the mean effect size Δ was recalculated for additional sensitivity analysis.

2.8 Primary Moderators

Four primary moderators were selected *a priori* to provide focused research hypotheses about variation in effect size: total volume of prescribed RET, participant health status, whether or not allocation and/or assessment were blinded, and whether or not the RET intervention resulted in a significant improvement in strength. Definitions for each primary and secondary moderator and associated levels are presented in eTable 3.

2.8 Primary Moderator Analysis

Each of the four primary moderators were coded according to the planned contrasts ($p\leq0.05$) among its levels.[47] Primary moderators were included in the mixed-effects multiple

linear regression analyses with maximum likelihood estimation, adjusting for non-independence of multiple effects contributed by single studies, baseline depressive symptoms, and the depressive symptom measure.[31,38] Tests of the regression model (Q_R) and its residual error (Q_E) are reported.

3.0 Univariate Meta-Regression Analyses

Secondary moderators were selected for exploratory univariate analyses. Random effects models were used to calculate the mean effect sizes (Δ) and 95%CIs for moderator variables.[38] Each secondary moderator was included in random effects univariate meta-regression analysis with maximum-likelihood estimation.[31,38]

3 Results

3.1 Study Characteristics

Fifty-four effects were derived from 33 RCTs of 1,877 participants (RET=947, control=930) (See eReferences). Table 1 presents relevant characteristics for each of the included RCTs. Depressive symptoms were the primary outcome in 18 RCTs (*k*=37). The mean sample age was (52±18 years), and 67% of participants were female. The average prescribed RET program duration was 16 weeks (range=6-52 weeks). RET session frequency ranged from 2-7 days per week; the most common frequency was 3 days per week (20 RCTs, *k*=30). Twenty-five RCTs (*k*=39) evaluated participants with a physical or mental illness. Twenty-five RET interventions (*k*=44) were fully supervised by various health professionals. Seven RET interventions (*k*=9) included a combination of supervised and unsupervised sessions, and one RET intervention was unsupervised. Adherence or compliance was reported in 15 of the 33 RCTs. Mean adherence rate was 78%±18%. Of the 18 remaining RCTs that did not report adherence or compliance, two reported attendance rates, which ranged from 87.5%[e12] to 94%.[e13] The Beck Depression Inventory[41] was the most frequently used measure of depressive symptoms (*k*=21).

3.2 Mean Effect Delta, Heterogeneity, and Publication Bias

A forest plot of the distribution of effects is presented in Figure 1. Forty-eight of the 54 effects (89%) were larger than zero, indicating a reduction in depressive symptoms favouring RET. Twenty effects significantly favoured RET. The mean effect size Δ was 0.66 (95%CI: 0.48-0.83; z=7.35, p<0.001). The effect was heterogeneous (Q_T(53)=216.92, p<0.001; I^2=76.0%, [95%CI: 72.7%-79.0%]), and sampling error accounted for 32.9% of observed variance. The mean quality score was 10.5 with a range of 7-13. The fail-safe number of effects was 1,358, indicating that 1,358 null effects would be needed to diminish the overall effect to p>0.05. Significant Begg's rank correlation (Kendall's tau=0.45, p<0.001) and Egger's regression tests (intercept=-1.34, SE=0.52, p=0.01) indicated significant funnel plot asymmetry (eFigure 2). Trim and fill analyses did not change the overall effect (Δ=0.66, 95%CI: 0.48-0.83, 0 RCTs trimmed). The mean reduction in depressive symptoms among RET participants resulted in a NNT of 4.

Three effects substantially larger than most were derived from one RCT.[48] The magnitude of these effects appeared to be due partly to greater depressive symptoms among participants randomized to the intervention group compared to controls. The mean effect was recalculated with this RCT removed, and the effect remained moderate and significant (Δ=0.53, 95%CI: 0.38-0.68; z=7.00; p<0.001). Similarly, a non-significant reduction in the overall effect was observed when calculated with single effects derived from each study (Δ=0.48, 95%CI: 0.30-0.67, z=5.08, p<0.001).

3.3 Primary Moderator Analyses

The overall meta-regression model was significant (Q_{R7}=17.97; p=0.012; R^2=0.30; Q_{31}=42.57;p=0.08; I^2=38.88% [95%CI: 25.63%-49.77%]). Blinded allocation and/or assessment of outcomes accounted for significant variation in the antidepressant effects of RET (β=-0.39; z=-2.50, p=0.012). Effects were significantly smaller when outcome allocation

and/or assessment were blinded (Δ=0.56, 95%CI: 0.40-0.71), compared to when outcome allocation and/or assessment were not blinded (Δ=1.07, 95%CI: 0.36-1.78). Total volume of prescribed exercise (β=-0.28), significant improvements in strength (β=0.32), and participant health status (β=-0.23) were not significantly related to effect size (all p>0.08) (Table 2).

3.4 Univariate Meta-Regression Analyses

Univariate moderator analyses results for the primary and secondary moderators are presented in Table 3.

3.5 Sub-analysis Between RET and AET

To facilitate sub-analyses between RET and AET, data were extracted from nine RCTs (k=17) in which participants were randomized to RET, AET, or non-active control condition.[e4,e6,e10,e15-e21] Effects were not significantly different for the RET interventions (Δ=0.64, 95%CI: 0.34-0.93) than the AET interventions (Δ=0.46, 95%CI: 0.22-0.70) in comparison to the control groups (p=0.48). When directly comparing the effects of RET to AET (positive effects favouring RET), a small, non-significant mean effect Δ favouring RET was found (Δ=0.15, 95%CI: -0.004-0.30, z=1.91, p=0.056).

4.0 Discussion

This is the first meta-analysis to examine the antidepressant effects of RET derived from RCTs. Across 33 RCTs, RET significantly reduced depressive symptoms regardless of participant characteristics (i.e., age, sex, health status) or features of the RET stimulus (i.e., program duration, session duration, intensity, frequency, or total prescribed volume). However, while simultaneously considering potential variation associated with baseline depressive scores, multiple effects from single RCTs, whether or not strength was significantly improved, total prescribed RET volume, and participant health status, blinded allocation and/or assessment was significantly associated with the overall effect of RET, such

that significantly smaller reductions in depressive symptoms were found when investigators were blinded to allocation and/or assessment.

Univariate analyses showed that significantly larger reductions in depressive symptoms were derived from RCTs of participants with scores indicative of mild-to-moderate depression compared to RCTs of participants without scores indicating mild-to-moderate depression, and from RCTs of shorter duration RET sessions (<45 minutes) compared to RCTs featuring longer session durations. Additionally, significantly larger reductions were found in fully supervised RCTs compared to RCTs that used combinations of supervised and unsupervised RET, and from RCTs in which the primary outcome was depressive symptoms (Table 3).

The magnitude of the overall mean effect (Δ=0.66; 95%CI: 0.48-0.83) is consistent with the effect of all/diverse types of exercise training on depression (pooled SMD=-0.62 95%CI: -0.81-0.42, negative scores favouring exercise),[18] and larger than the recently reported effect of RET on anxiety (Δ=0.31).[24] Additionally, the magnitude of the overall mean effect, and effects among important sub-samples, are consistent with previously reported effects. Specifically, the mean effect for individuals with a physical illness (Δ=0.34, 95%CI: 0.17-0.52) is consistent with previous evidence of the effects of all types of exercise training on depressive symptoms among chronically-ill adults (Δ=0.30, 95%CI: 0.25-0.36)[19] and adults with neurologic disorders (Δ=0.28, 95%CI: 0.15-0.41).[49]

The large effect of RET found among adults with depressive symptoms indicative of mild-to-moderate depression (Δ=0.90, 95%CI: 0.68-1.11) is consistent with previously reported effects of all exercise modes among people with Major Depressive Disorder (SMD=1.11, 95%CI: 0.79-1.43).[17] Twelve RCTs (*k*=25) included samples that reported clinically significant elevations in depressive symptoms, based on cut-off scores commonly used for clinical screening.[50-53] Mean scores for 10 of the 25 effects (40%) suggested

potential remission based on a frequently used response threshold of ≥50% reduction in baseline scores.[54] The mean percentage reduction from baseline scores for all 25 of these effects was 45%. Moreover, the mean effect for RCTs in which baseline scores were indicative of mild-to-moderate depression (Δ=0.90, 95%CI: 0.68-1.12, z=8.12, p<0.001) was significantly larger than effects from RCTs in which baseline scores were below suggested clinical cut-scores (Δ=0.45, 95%CI: 0.23-0.67, z=4.02, p=0.026) (Table 3). The larger percentage reduction found from RCTs of participants with elevated depressive symptoms, coupled with the significant difference based on initial depressive symptom severity, suggests that RET may be particularly helpful for reducing depressive symptoms in people with greater depressive symptoms. These findings support potentially different mechanisms of action and/or unique interactions in participants with clinical depression that may not be present in participants with sub-clinical depressive symptoms.

4.1 Primary Moderators of the Effect

Blinded allocation and/or assessment was independently and significantly associated with reductions in depressive symptoms; smaller reductions occurred in RCTs with blinded allocation and/or assessment (Δ=0.56, 95%CI: 0.40-0.71). Blinded allocation and assessment of outcomes can limit biases associated with self-report measures in exercise interventions.[55-57] Previous reports have demonstrated a reduction in the overall effect of exercise on depression following exclusion of trials which do not adequately blind allocation and/or assessment.[18]

Blinded allocation and/or assessment are also indications of intervention quality.[30,58] Based on the study quality assessment used here, the overall quality of RCTs was high, with a mean score of 10.5 (range: 7-13) on a 13-point scale. When blinding was removed from the overall quality score, such that the maximum total score was 11, RCTs that reported blinded allocation and/or assessment had significantly higher quality scores (10.0±1.0) compared to

those without blinded allocation and/or assessment (8.0±0.9) ($t_{(31)}$=5.82, p<0.001). Blinded allocation and/or assessment may indicate higher quality research design, which may have resulted in smaller effects by providing a more rigorous estimation of the "true" effect of RET on depressive symptoms.

Participant health status, volume of prescribed RET, and whether or not strength was significantly improved were not independently associated with the overall mean reduction in depressive symptoms. These findings are consistent with previous evidence showing that the antidepressant effects of exercise training were not dependent on a significant improvement in fitness.[19] These findings are also consistent with recently reported effects of RET on anxiety.[24]

Although RET significantly reduced depressive symptoms independent of total prescribed volume of RET, this measure of total volume (intervention length x frequency x session duration) could not be extracted for all RCTs, as 8 RCTs (k=14) did not report RET session duration. Additionally, this measure of total volume did not include the intensity of prescribed RET. Heterogeneous reporting of prescribed intensity did not allow differentiation between low intensity RET and moderate intensity RET, necessitating their merger and comparison with vigorous intensity RET. Only four interventions (k=9)[e1,e5,e30,e31] were of vigorous intensity. The relationship between RET intensity and strength gains is moderated by participant training status, as moderate intensity RET improves strength most in untrained participants, and vigorous intensity RET improves strength most in trained participants.[59] There is a paucity of within-study comparisons of RET dose, multi-arm RCTs comparing RET and other strictly matched exercise modalities, and investigations of the influence of exercise volume, exercise intensity, and their interaction. For example, more frequently completed vigorous RET may afford the possibility of shorter exercise sessions while

meeting recommended guidelines,[60] potentially increasing feasibility while maintaining positive mental health benefits.

There is continued interest in the comparative effects of different exercise modes on mental health outcomes. However, with one notable exception,[61,62] few RCTs have directly compared the antidepressant effects of different exercise modes in a single study sample. Nine RCTs included here directly compared RET with AET and a non-active control condition.[e4,e6,e10,e15-e21] Although the magnitude of improvement for AET and RET did not differ significantly, consistent with recent results of the comparative effects of AET and RET on anxiety symptoms,[24] only two RCTs attempted to match AET and RET interventions in any capacity. One trial matched AET and RET based on energy expenditure,[63] and one trial more thoroughly matched AET and RET based on body region, positive work, time actively engaged in exercise, and load progression.[64] Future trials, matching different exercise modes on relevant features of the exercise stimulus, will allow more rigorous and controlled comparisons between exercise modalities, and the examination of interactions between factors such as frequency, intensity, duration, and exercise modality.

4.1 Future Research

There was a notable lack of clear and complete reporting of intervention design, protocol, data analyses, participant information, medication use, adherence and compliance, which should be emphasized in future trial reporting. Medication use was insufficiently reported to allow comparisons between RCTs; 12 out of the 33 RCTs (36%) did not report information regarding medication use. Twenty-one out of 33 RCTs (64%) did not report adherence or compliance to the interventions. Prescribed antidepressant medication use is associated with poor adherence rates to exercise programs among patients;[65] making this omission particularly problematic. Additionally, authors should report average session duration, numbers of sets, numbers of repetitions, rest period lengths between sets, and

intensity (e.g., percentages of one-repetition max and RPE), to more thoroughly assess the total volume of exercise prescribed. Authors should report whether interventions were performed in groups or individually. Where exercise sessions are supervised, efforts made to control for social interaction during sessions should be reported. Future trials should blind allocation, blind assessors from group assignment, explicitly report this process, and state how missing data/dropouts were handled, including explicitly stating if intention-to-treat analyses were conducted.

Six RCTs assessed the effects of RET on depressive symptoms in participants with a clinical diagnosis of depression or anxiety, and eight RCTs assessed depressive symptoms in participants that had scores indicative of moderate depression without an actual diagnosis. Importantly, individuals that display elevated subclinical depressive or anxiety symptoms are at increased risk of developing clinically significant psychopathology.[66] As participants with baseline scores indicative of mild-to-moderate depression had significantly larger improvements than those who did not, investigating RET interventions among individuals at different points on the severity spectrum may be particularly interesting.

5.0 Conclusion

The available empirical evidence supports RET as an alternative or adjuvant therapy for depressive symptoms. Future trials should include thorough reporting of trial and RET design, specifically blinded allocation, assessment, and adherence. Additionally, future trials should compare RET to other empirically supported therapies for depressive symptoms.

Author Contributions: Brett R. Gordon had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: Gordon, McDowell, Herring. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Gordon, McDowell Herring. Critical revision of the manuscript: All authors. Statistical analysis: Gordon, McDowell, Herring.

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Table 1. Characteristics of Included Randomized Controlled Trials

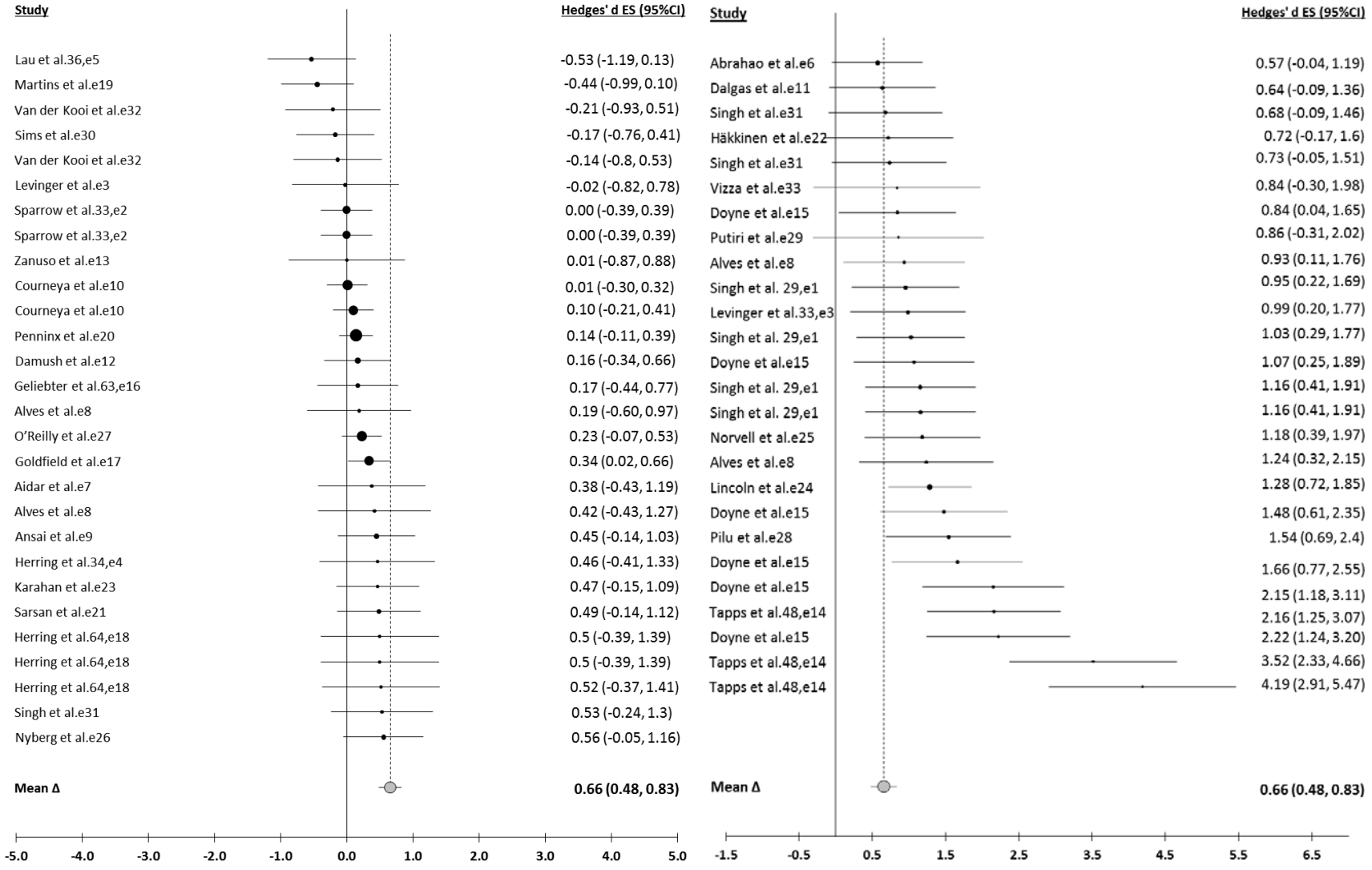
Study	Measure	Intensity	Intervention length (wk)	Age(y)*	Control	Sex	Participant characteristics
Abrahao et al.[e6]	BDI	Low to moderate	12	39±14	Wait-list	Mixed	Systemic lupus erythematosus
Aidar et al.[e7]	BDI	Low to moderate	12	53±8	No treatment	Mixed	Survivors of ischemic stroke
Alves et al.[e8]	GDS	Low to moderate	24	64±4	No treatment + Placebo supplement	Female	Elderly
Ansai et al.[e9]	GDS	Low to moderate	16	>80	No treatment	Mixed	Elderly
Courneya et al.[e10]	CESD	Low to moderate	Duration of treatment	25-76	Wait-list	Female	Breast cancer
Dalgas et al.[e11]	MDI	Low to moderate	12	48±10	Wait-list	Mixed	Multiple sclerosis
Damush et al.[e12]	MHFI	Low to moderate	8	68±6	Wait-list	Female	Elderly
Doyne et al.[e15]	BDI, DACL, HRSD	Low to moderate	8	28±5	Wait-list	Female	Major or minor depressive disorder
Geliebter et al.[63,e16]	BDI	Low to moderate	8	35±6	No training	Mixed	Obesity
Goldfield et al.[e17]	BRUMS-D	Low to moderate	22	16±2	Wait-list	Mixed	Obesity
Häkkinen et al.[e22]	BDI	Low to moderate	21	36±6	No treatment	Female	Fibromyalgia
Herring et al.[64,e18]	BDI	Low to moderate	6	24±6	Wait-list	Female	Generalized anxiety disorder
Herring et al.[35,e4]	HADS	Low to moderate	6	24-68	Patient education	Mixed	Obesity
Karahan et al.[e23]	BDI	Low to moderate	8	40±8	Patient education	Mixed	Failed back surgery syndrome
Lau et al.[36,e5]	HADS	Vigorous	6	10-17	No treatment	Mixed	Obesity
Levinger et al.[e3]	CDS	Low to moderate	10	51±7	No treatment	Mixed	Type 2 diabetes
Lincoln et al.[e24]	GDS	Low to moderate	16	66±8	No treatment	Mixed	Type 2 diabetes
Martins et al.[e19]	POMS-D	Low to moderate	16	76±8	No treatment	Mixed	Elderly
Norvell et al.[e25]	SCL-90-D	Low to moderate	16	33±8	Wait-list	Male	Law enforcement personnel
Nyberg et al.[e26]	HADS	Low to moderate	8	69±5	Patient education	Mixed	Chronic obstructive pulmonary disorder
O'Reilly et al.[e27]	HADS	Low to moderate	24	62±10	No treatment	Mixed	Knee osteoarthritis
Penninx et al.[32,e20]	CESD	Low to moderate	12	69±6	Patient education	Mixed	Knee osteoarthritis
Pilu et al.[e28]	HRSD	Not Reported	32	40-60	Usual care	Female	Major depressive disorder
Putiri et al.[e29]	BDI	Not Reported	12	58±7	Usual care	Mixed	Type 2 diabetes
Sarsan et al.[e21]	BDI	Low to moderate	12	43±10	No treatment	Female	Obesity
Sims et al.[e30]	CESD	Vigorous	10	68±15	Wait-list	Mixed	Chronic post stroke patients
Singh et al. [28,e1]	BDI, DSM, GDS, HRSD	Vigorous	10	71±7	Patient education	Mixed	Major or minor depression
Singh et al.[e31]	BDI, GDS, HRSD	Vigorous	6	71±7	Patient education	Mixed	Major or minor depression

Sparrow et al.[34,e2]	BDI	Low to moderate	24	70±8	Patient education	Mixed	Elderly
Tapps et al.[48,e14]	BDI	Low to moderate	12	75±3	No treatment	Mixed	Elderly
van der Kooi et al.[43,e32]	BDI	Low to moderate	52	38±10	No treatment	Mixed	Facioscapulohumeral muscular dystrophy
Vizza et al.[e33]	DASS-21	Low to moderate	12	26±7	Usual care	Female	Polycystic ovary syndrome
Zanuso et al.[e13]	POMS-D	Low to moderate	12	74±4	Wait-list	Mixed	Elderly

Study	**Measure**	**Intensity**	**Intervention length (wk)**	**Age(y)***	**Control**	**Sex**	**Participant characteristics**

Abbreviations: BDI, Beck Depression Inventory; BRUMS-D, Brunel Mood Scale Questionnaire-depression; CDS, Cardiac Depression Scale; CESD, Center for Epidemiologic Studies Depression Scale; DACL, Depression Adjective Checklist; DASS-21, Depression, Anxiety and Stress Scale; DSM, Diagnostic Statistics Manual-IV symptoms; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; SCL-90-D, Hopkins Symptom Checklist-depression; HRSD, Hamilton Rating Scale for Depression; MDI, Major Depression Inventory; MHFI, Mental Health Functioning Index-depression; POMS-D, Profile of Mood States-depression, wk, weeks.
*Age presented as mean ± SD if reported, if not, age range is presented

Figure 1. Forest plot of distribution of Hedges' *d* effect sizes



Abbreviations: 95%CI, 95 percent confidence interval.

Table 2. Summary of Primary Moderator Analysis

Primary Moderator	β	*p*-value	B	Standard Error	95%CI
Blinded allocation and/or assessment	-0.39	0.01	-.036	0.14	-0.63 to -0.08
Significant improvement in strength	-0.32	0.09	0.35	0.21	-0.76 to 0.06
Total volume of RET prescribed	-0.28	0.09	-0.0002	0.0001	-0.0004 to 0
Participant health status	-0.23	0.17	-0.19	0.14	-0.46 to 0.08

Abbreviations: 95%CI: 95 percent confidence interval; Adjusted for non-independence of multiple effects contributed by single studies, baseline depressive symptoms, and the depressive symptom measure.

Table 3. Summary of Univariate Analyses

Effect moderator	Contrast weights	Effects (k)	Δ	95%CI	Moderator *p*-value	Contrast *p*-value
Sex						
Female	1	20	0.81	0.51-1.10	<0.001	0.28
Mixed	-1	34	0.58	0.36-0.80	<0.001	
Age						
<25	-0.5	2	-0.04	-0.89-0.80	0.92	
25-54	-0.5	26	0.67	0.43-0.91	<0.001	0.63
55+	1	26	0.72	0.45-1.00	<0.001	
Health						
Healthy	1	15	0.81	0.33-1.29	<0.001	
Physical Illness	-0.5	20	0.34	0.17-0.52	<0.001	0.63
Mental Illness (MDD, GAD)	-0.5	18	1.00	0.69-1.31	<0.001	
Baseline Depression						
Indicative of mild- moderate depression	1	25	0.90	0.68-1.11	<0.001	0.02
Not indicative	-1	29	0.45	0.23-0.67	<0.001	
Control condition						
Attention placebo control	1	15	0.98	0.56-1.41	<0.001	0.09
No attention placebo control	-1	39	0.54	0.36-0.73	<0.001	
Comparison type						
Wait list	…	17	0.71	0.39-1.02	<0.001	
Patient education	…	13	0.51	0.27-0.75	<0.001	
No treatment	…	11	0.33	0.02-0.64	0.039	…
Usual care	…	5	2.30	1.05-3.55	<0.001	
Placebo or second treatment	…	8	0.48	0.07-0.88	0.022	
Program length						
<12 weeks	-1	26	0.88	0.58-1.18	<0.001	0.70
12 + weeks	1	26	0.51	0.28-0.73	<0.001	
Session						
<45 minutes	-1	12	1.10	0.49-1.70	<0.001	0.049
45+ minutes	1	28	0.48	0.29-0.68	<0.001	
Frequency						
2 days per week	-0.5	12	0.53	0.25-0.81	<0.001	
3 days per week	-0.5	32	0.60	0.37-0.84	<0.001	0.19
4+ days per week	1	10	1.00	0.55-1.46	<0.001	
Intensity						
Low to moderate	-1	45	0.67	0.49-0.87	<0.001	0.72
Vigorous	1	9	0.59	0.17-1.01	0.006	
Blinded assessment						
Yes	1	42	0.56	0.40-0.71	<0.001	0.15
No	-1	12	1.07	0.36-1.78	0.003	
Supervision						
Combination of supervised and unsupervised	-1	9	0.14	0-0.29	0.0501	0.02
Fully supervised	1	44	0.79	0.57-1.02	<0.001	
Primary Outcome Depression						
Yes	1	38	0.88	0.63-1.13	<0.001	0.002
No	-1	16	0.19	0.06-0.32	0.006	
Significant improvement in strength						
Yes	1	19	0.50	0.32-0.68	<0.001	
No	-0.5	7	0.09	-0.08-0.27	0.304	0.45
Not reported	-0.5	28	0.94	0.62-1.26	<0.001	

Abbreviations: 95%CI, 95 percent confidence interval; MDD, Major/minor depressive disorder; GAD, Generalized Anxiety Disorder. The moderator *p*-value indicates the *p*-value for the mean effect of the individual moderator. The contrast p-value indicates the p-value of the comparison between the moderator levels.