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Exercise as a treatment for depression: A meta-analysis adjusting for publication bias

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ABSTRACT

The effects of exercise on depression have been a source of contentious debate. Meta-analyses have demonstrated a range of effect sizes. Both inclusion criteria and heterogeneity may influence the effect sizes reported. The extent and influence of publication bias is also unknown. Randomized controlled trials (RCTs) were identified from a recent Cochrane review and searches of major electronic databases from 01/2013 to 08/2015. We included RCTs of exercise interventions in people with depression (including those with a diagnosis of major depressive disorder (MDD) or ratings on depressive symptoms), comparing exercise versus control conditions. A random effects meta-analysis calculating the standardized mean difference (SMD, 95% confidence interval; CI), meta-regressions, trim and fill and fail-safe n analyses were conducted. Twenty-five RCTs were included comparing exercise versus control comparison groups, including 9 examining participants with MDD. Overall, exercise had a large and significant effect on depression (SMD adjusted for publication bias = 1.11 (95% CI 0.79–1.43)) with a fail-safe number of 1057. Most adjusted analyses suggested publication bias led to an underestimated SMD. Larger effects were found for interventions in MDD, utilising aerobic exercise, at moderate and vigorous intensities, in a supervised and unsupervised format. In MDD, larger effects were found for moderate intensity, aerobic exercise, and interventions supervised by exercise professionals. Exercise has a large and significant antidepressant effect in people with depression (including MDD). Previous meta-analyses may have underestimated the benefits of exercise due to publication bias. Our data strongly support the claim that exercise is an evidence-based treatment for depression.

1. Introduction

Depression is a prevalent condition, with a long-life prevalence ranging from 10% to about 20% in different countries (Andrade et al., 2003). Depression is a major cause of disability, responsible for 40.5% of total disability-adjusted life years (DALYs) caused by mental and substance-use disorders (Whiteford et al., 2013).

Physical activity and exercise are suggested as potential treatments for depression, and incorporated in guidelines as a complementary form for illness of mild to moderate severity (Cleare et al., 2015). Several meta-analyses have demonstrated that exercise is an effective treatment for depression, with a pooled standardized mean deviation (SMD) ranging from small (−0.4) (Krogh et al., 2011) to very large (−1.4) (Cooney et al., 2013; Craft and Landers, 1998; Daley, 2008; Danielsson et al., 2013; Josefsson et al., 2014; Krogh et al., 2011; Rethorst et al., 2009; Silveira et al., 2013; Stathopoulou et al., 2006). However, a number of different approaches have been undertaken in prior meta-analyses and

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uncertainty remains over the magnitude of the effects of exercise on depression.

The 2013 update of the Cochrane review on exercise for depression, provided new data for discussion, showing that when analysis was restricted to the six trials considered of low risk of bias only, the SMD was small and non-significant (Cooney et al., 2013). This review has been criticized, with a particular emphasis on the potential inappropriate selection criteria applied (Ekkekakis, 2015). For example, the review proposed excluding studies that had a control arm with any "active control comparison". However, some studies that compared different exercise arms were included (Krogh et al., 2009), thus clearly precluding a fair comparison. In addition, the review included studies that compared exercise plus well-established treatments versus other well-established forms of treatment, such as pharmacological antidepressants (Blumenthal et al., 1999). As a result, these limitations directly affected the effect size (ES), producing a "shrinkage" effect on the efficacy of exercise for depressive symptoms when compared to previous meta-analyses (Ekkekakis, 2015). In addition, separate subgroup analyses of studies that assessed the effects of exercise on Beck depression inventory (BDI) (Beck et al., 1961) scores were also criticized regarding the inclusion criteria (e.g. including a trial which used the Hamilton HAM-D (Hamilton, 1967) scale for depression and not the BDI (Blumenthal and Doraiswamy, 2014; Cooney et al., 2014)).

No recent (within the last decade) comprehensive meta-regression analyses have been conducted investigating exercise and depression. Previous meta-analyses (Craft and Landers, 1998; Rethorst et al., 2009) evaluated the moderating role of sample characteristics, such as a diagnosis of major depressive disorder (MDD), which were found to be significant moderators of the antidepressant effects of exercise. However, a number of additional eligible studies have since been published.

Another limitation within the available literature investigating the effects of exercise on depression is that no previous meta-analyses have adjusted for publication bias, which is a considerable threat to the validity of any such synthesis (Ioannidis et al., 2014). Previous studies of psychotherapy for depression have demonstrated that publication bias is evident in RCTs, and effect sizes have consequently been overstated (Cuijpers et al., 2010). It remains unclear, however, if publication bias threatens the validity and interpretation of the exercise as a treatment for depression literature.

The present review sets out to address these limitations. Specific aims were: (1) to establish the updated effects of exercise on depression comparing exercise versus non-active control groups, (2) to identify moderators through meta-regression analyses, including sample characteristics (sex, use of medication and severity of baseline symptoms) and exercise intervention variables (length of the trial, frequency) that could impact the effects of exercise on depression, (3) to investigate, through subgroup and sensitivity analyses, the magnitude of the effects of exercise considering study quality, group format, setting, intensity, type, supervision, presence of clinical co-morbidities, type of publication and diagnosis of MDD, (4) to assess the influence of publication bias on the reported effects of exercise on depression, and (5) to quantify the strength of the existing evidence by calculating the number of negative studies required to nullify the pooled ES of the analyses performed.

2. Methods

This systematic review is in line with the PRISMA statement (Moher et al., 2009) and the MOOSE guidelines (Stroup et al., 2000).

2.1. Inclusion criteria

Included in this meta-analysis were studies that: (1) Investigated adult participants with a primary diagnosis of MDD according to established criteria (e.g. Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), DSM-IV (American Psychiatric Association, 1994) or ICD-10 (World Health Organization, 1993)) or those with above-threshold depressive symptoms determined by a validated screening measure (e.g. Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1967), Beck Depression Inventory (BDI) (Beck et al., 1961) or (BDI-II) (Beck et al., 1996)). Studies included using this criterion were those that included participants with at least mild (or equivalent) scores on validated scales, or had the scale revised by a psychiatrist, confirming the presence of depression or, in cases where the scale did not have a validated cut-off, the cut-off used by the author was accepted. Only studies where all participants met criteria for depression were included in the analyses (e.g. studies that presented a subsample of depressed participants were not included). Studies including people with depressive disorders other than MDD, such as dysthymia, were also included. (2) Measured depressive symptoms pre- and post-intervention, or reported a mean change and standard deviation using a validated measure (e.g. HAM-D, BDI). (3) Were RCTs investigating exercise, as defined by Caspersen et al. (1985) as planned, structured, repetitive and purposive physical activity, in the sense that improvement or maintenance of one or more components of physical fitness was an objective, in the active arm of the trial. Trials that used yoga, tai chi or qi going, were not included since such mind-body activities also comprise a core set of behavioral techniques such as, but not limited to, deep breathing, meditation/mind-fullness and self-awareness (Larkey et al., 2009). These techniques are known to have an influence on depressive symptoms (Goyal et al., 2014). Moreover, previous studies found significant heterogeneity in trials incorporating these mind-body approaches when compared with conventional aerobic or strength exercises (Bridle et al., 2012). (4) Included a non-active control group such as: usual-care, wait-list control conditions, placebo pills or other social activities. Trials that included any other exercise intervention (such as stretching or low-dose exercise) for comparison were excluded. (5) Were published in peer-reviewed journal articles or as part of a dissertation.

2.2. Information sources and searches

Articles were identified in a two-step strategy. First, three authors (BS, FS, SR) reviewed all articles identified (both included and excluded with reasons) by the recent Cochrane review on exercise for depression (Cooney et al., 2013). Second, three independent reviewers (BS, FS, SR) searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed without language restrictions from January 2013 until August 1st, 2015, using the key words: ((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, reference lists of all eligible articles of recent reviews investigating the effectiveness of exercise versus control were screened to identify potentially eligible articles (Cooney et al., 2013; Josefsson et al., 2014; Silveira et al., 2013). Dissertations and studies from the same center were identified to avoid sample overlap. In case of overlap the most recent and/or most extensively reported version of study was included.

2.3. Study selection

Three authors (BS, FS, SR) determined potentially eligible articles meeting the inclusion criteria. After removal of duplicates, two independent reviewers screened all potentially eligible articles using the titles and abstracts. These authors then applied the eligibility criteria, after obtaining the full texts, and generated a final list of included articles through consensus.

2.4. 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 of the control group, calculated as the SMD together with 95% confidence intervals (CIs). If an author reported the results of two outcome measures meeting our criteria (i.e. mean change/pre and posttest change in depressive symptoms according to two different measures), we used the primary outcome chosen by the author. If this was not clear, we used the HAMD or the BDI in order to increase homogeneity in our results. These outcome measures were also prioritized since they are commonly used in the exercise and depression literature (Cooney et al., 2013). 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.

2.5. Data extraction

Two authors (FS, SR) independently extracted data using a data extraction form, including: sample (number of participants, % of women, % of participants taking antidepressants, presence of clinical co-morbidities and severity of baseline symptoms), exercise (length of the trial, intensity of intervention [according to the American College of Sports Medicine (ACSM) (Garber et al., 2011) classification of intensity], weekly frequency, type and supervision [if exercise was supervised and if supervision was provided by exercise professionals, such as physiotherapists, physical educators, exercise physiologists etc.]) and methodological factors (study quality, instruments used for diagnosis and symptom assessment, clinical setting, and type of document). Finally, we extracted the pre- and post-test means and standard deviations (SD) of the depressive symptom rating scales for the exercise and the control group (primary outcome). If this was not available, we used the mean change and SD from pre- and post-test, if reported within the study.

2.6. Risk of bias and quality assessment

Three authors (FS, JR, BS) assessed studies on the presence of high, low or unclear risk of bias according to the Cochrane Handbook definition (Higgins and Green, 2011). The risk of bias was assessed by considering the following factors: random sequence generation, allocation concealment, blinding of participants, blinding of those delivering the intervention, blinding of outcome assessors, incomplete data outcome, selective reporting or others. To be considered a low risk of bias, studies had to involve adequate allocation concealment AND had to involve the analysis of outcome data according to intention-to-treat principles AND had to have blinding of outcome assessors. The criteria used for risk of bias assessment was modeled on that employed in a previous meta-analysis (Cooney et al., 2013).

2.7. Meta-analysis

We used a random effects meta-analysis due to expected heterogeneity. The SMD and 95% confidence intervals (CIs) were used as the ES measure. The meta-analysis was conducted using the following procedure. First, we calculated the SMD statistic, together with 95% CIs, to establish the effects of exercise on depression across all studies using Comprehensive Meta-Analysis software (CMA; Version 3, Biostat, Englewood, New Jersey). We subsequently conducted a sensitivity analysis computing the effects of exercise on depression in high quality studies only. Further, we conducted meta-regression analyses to investigate the potential moderators of the antidepressant effects of exercise. Potential moderators were chosen a-priori, according to the previous literature, and included: sex, age, use of medication, length of the trial weekly frequency and the rate of dropout. Next, we conducted subgroup analyses to compare exercise response according to depression diagnosis (MDD [studies that included only patients with MDD and used a diagnostic instrument based on Research Domain Criteria (RDC), DSM or ICD criteria] versus depressive symptoms), study setting (inpatient, outpatient, mixed), type of publication (peer review article or dissertation), high quality (low risk of bias) versus low quality, presence of other clinical comorbidities (yes or no), supervision (yes or no), the qualification of the professional supervising the exercise sessions, exercise type (aerobic, resistance, mixed) and exercise intensity. Heterogeneity was assessed with the Cochran Q and I^2 statistics for each analysis (Higgins et al., 2003). Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau (Begg and Mazumdar, 1994) and Egger bias test (Egger et al., 1997). In addition, we conducted a trim and fill adjusted analysis (Duval and Tweedie, 2000) 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. Finally, the fail safe number of negative studies that would be required to nullify (i.e. make $p > 0.05$) the ES was calculated (Rosenthal, 1979).

3. Results

3.1. Search results

In the first stage of the search strategy, 35 RCTs were identified from a previous review (Cooney et al., 2013). In the second stage, following the removal of duplicates, 819 potentially relevant articles were identified. At the full text review stage, we reviewed 76 articles (N = 35 from stage 1 and 41 from our stage 2 searches) and 45 were excluded with reasons (details summarized in Fig. 1). There were 30 full texts that met the eligibility criteria (Blumenthal et al., 2007; Brenes et al., 2007; Danielsson et al., 2014; Doyne et al., 1987; Epstein, 1986; Gary et al., 2010; Hallgren et al., 2015; Hemat-Far et al., 2012; Hess-Homeier, 1981, Hoffman et al., 2009; Huang et al., 2015; Kerling et al., 2015; Martinsen, 1987; Mather et al., 2002; McNeil et al., 1991; Mota-Pereira et al., 2011; Mutrie, 1989; Nabkasorn et al., 2006; Oertel-Knöchel et al., 2014; Orth, 1979; Pfaff et al., 2014; Pilu et al., 2007; Schuch et al., 2011; Setaro, 1985; Shahidi et al., 2011; Sims et al., 2009; Singh et al., 1997, 2005; Veale et al., 1992; Williams and Tappen, 2008). Of these, 25 (Blumenthal et al., 2007; Brenes et al., 2007; Danielsson et al., 2014; Doyne et al., 1987; Epstein, 1986; Gary et al., 2010; Hallgren et al., 2015; Hemat-Far et al., 2012; Huang et al., 2015; Kerling et al., 2015; McNeil et al., 1991; Mota-Pereira et al., 2011; Mutrie, 1989; Nabkasorn et al., 2006; Oertel-Knöchel et al., 2014; Orth, 1979; Pilu et al., 2007; Schuch et al., 2011; Setaro, 1985; Shahidi et al., 2011; Sims et al., 2009; Singh et al., 1997, 2005; Veale et al., 1992; Williams and

Tappen, 2008) provided complete data to enable inclusion within our meta-analysis. One of the studies included in the Cooney et al. (2013) review, reported preliminary data from a trial (Schuch et al., 2011) and this data was replaced with the final updated results from that trial (Schuch et al., 2015).

3.1.1. Characteristics of included trials and participants

Across the 25 studies, 1487 adults with depression were included, of whom 757 and 730 were randomised to exercise and control conditions respectively. The mean age ranged from 18.4 to 76.4 years and the percentage of females ranged from 17% to 100%. Overall, 9 studies contained patients with a confirmed diagnosis of MDD, and a further three included participants with depression and participants with additional co-morbid diagnoses, such as, cardiovascular or neurological diseases (Gary et al., 2010; Sims et al., 2009; Williams and Tappen, 2008). There were two studies (Singh et al., 1997, 2005) that included participants with MDD and other mood disorders (MDD and dysthymia). The majority of included studies involved outpatients with depression (N = 22), were published in peer-reviewed journals (N = 21), and included people without reported clinical co-morbidities (N = 21). The most commonly used measures of depressive symptoms were the HAM-D (N = 7), BDI (N = 7), or MADRS (N = 3). Participant details and symptom measures are presented in Table 1. Full details of other characteristics can be found in supplementary table 1.

3.1.2. Risk of bias

Four studies were judged to be of good methodological quality and at low risk of bias (Blumenthal et al., 2007; Danielsson et al., 2014; Hallgren et al., 2015; Schuch et al., 2015) and the remaining 21 were low quality (high risk of bias). Full details of the risk of bias are presented in supplementary table 2.

3.2. Main analysis

Data pooled from 25 studies showed a large significant improvement favoring exercise (SMD = 0.98, 95% CI 0.68 to 1.28, $p < 0.001$, $Q = 135$, $p < 0.01$) (Fig. 2). The Begg–Mazumdar Kendall's Tau" (=-0.41, $p = 0.001$) and the Egger tests indicated publication bias (intercept = 2.21, $p = 0.004$). Therefore, the ES was recalculated using Duval and Tweedie's trim and fill method with nine studies being adjusted and a new ES of 1.11 (95% CI 0.79 to 1.43, $p < 0.001$). The fail-safe number of additional negative studies required to nullify the significance of the main analysis was of 1057 studies with negative results. Means, standard deviations and sample sizes of each study are summarized in the supplementary table 3.

All of the subgroup analyses are presented in Table 2. Briefly, studies including people with MDD presented a larger decrease in symptoms when compared to studies in samples without a clinical diagnosis of MDD (SMD = 1.135, 95% CI 0.46 to 1.81, $p < 0.001$). Studies using aerobic exercise (SMD = 1.04, 95% CI 0.65 to 1.43, $p < 0.001$), with moderate (SMD = 1.33, 95% CI 0.46 to 2.19, $p = 0.003$) or vigorous intensities (SMD = 1.34, 95% CI 0.43 to 2.24, $p = 0.004$), with a mixed supervised/unsupervised format (SMD = 3.01, 95% CI -0.61 to 1.97, $p<0.0001$) and supervised by qualified physical exercise professionals (SMD = 1.26, 95% CI 0.54 to 1.97, $p < 0.001$) were associated with larger antidepressant effects.

3.2.1. Adjustment of publication bias and fail safe number of studies

Several of the meta-analyses were adjusted for publication bias, with most original analyses being underestimates due to publication bias. For instance, studies in MDD, study quality (both low and high) and group exercise all had an increased ES after adjustment (see Table 2). The fail safe number of studies provided further evidence of magnitude of exercise ES, with a higher number of

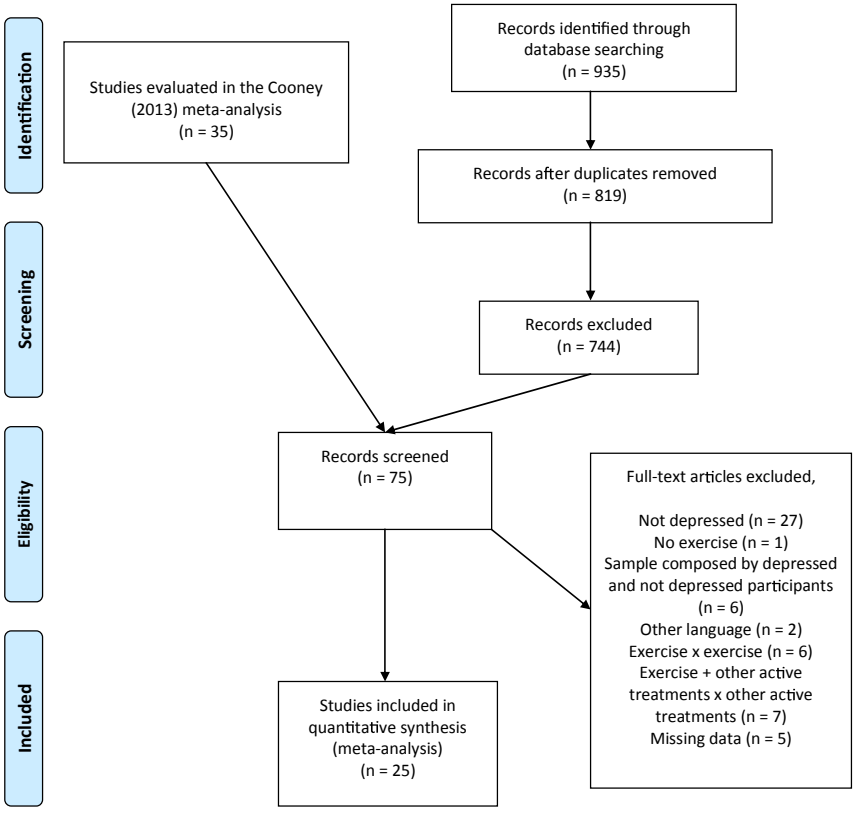

Fig. 1. Flowchart of studies selection.

Table 1
Summary of included studies.

Study	Sample size		Age		Gender		Antidepressant use		Outcome	Length of the trial	Diagnosis	Thesis or peer-reviewed article
	Exercise (n =)	Control (n =)	Exercise (mean or range)	Control (mean or range)	Exercise (% females)	Control (% females)	Exercise (% taking)	Control (% taking)				
Blumenthal, 2007	51	49	52	52	75	77	0	0	HAM-D	16	MDD	Peer-reviewed
Brenes, 2007	14	12	73.5	73.9	64	50	0	0	HAM-D	16	Depressive symptoms	Peer-reviewed
Danielsson, 2014	22	20	44.7	46.3	73	80	100	100	MADRS	10	MDD	Peer-reviewed
Doyne 1987	14	11	28.58	29.46	100	100	0	0	BDI	8	Depressive symptoms	Peer-reviewed
Epstein 1986	7	10	24–60	24–60	?	?	?	?	BDI	8	MDD	Thesis
Gary 2010	20	15	?	?	?	?	?	?	HAM-D	12	Depressive symptoms	Peer-reviewed
Hallgreen 2015	317	312	18–71	18–71	?	?	31	24	MADRS	12	Depressive symptoms	Peer-reviewed
Hemat-far 2012	10	10	18–25	18–25	100	100	?	?	BDI	8	Depressive symptoms	Peer-reviewed
Huang 2015	19	20	76.42	75.85	57.9	55	0	0	GDS-15	12	Depressive symptoms	Peer-reviewed
Kerling 2015	22	20	44.2	40.9	45	30	77	75	MADRS	6	MDD	Peer-reviewed
Mcneil 1991	10	10	?	?	?	?	0	0	BDI	6	Depressive symptoms	Peer-reviewed
Mota-pereira 2011	19	11	48.68	45.33	57.9	80	100	100	HAM-D	12	MDD	Peer-reviewed
Mutrie 1988	9	7	?	?	?	?	0	0	BDI	4	Depressive symptoms	Thesis
Nabkasorn 2005	21	28	18.7	18.8	100	100	0	0	CES-D	8	Depressive symptoms	Peer-reviewed
Oertel-Knoechel 2014	4	4	36.6	42.2	50	37.5	100	100	BDI-II	4	MDD	Peer-reviewed
Orth 1979	3	2	17–56	17–56	?	?	?	?	DACL	4	Depressive symptoms	Thesis
Pilu 2007	10	20	40–60	40–60	100	100	100	100	HAM-D	32	MDD	Peer-reviewed
Schuch 2015	25	25	38.8	41.76	72	76	Change during the trial	Change during the trial	HAM-D	3	MDD	Peer-reviewed
Setaro 1985	25	25	18–35	18–35	?	?	0	0	MMPI	10	Depressive symptoms	Thesis
Shahidi 2011	20	20	65.7	68.4	100	100	?	?	GDS	?	Depressive symptoms	Peer-reviewed
Sims 2009	23	21	67.95	66.27	39	41	?	?	PHQ-9	10	Depressive symptoms	Peer-reviewed
Singh 1997	17	15	70	72	70.5	53.3	0	0	BDI	10	MDD + dysthimia	Peer-reviewed
Singh 2005	18	19	69	69	55	50	0	42	HAM-D	8	MDD + dysthimia	Peer-reviewed
Veale 1992	36	29	?	?	?	?	45	34	BDI	12	MDD	Peer-reviewed
Williams 2008	17	12	71–101	71–101	?	?	?	?	CSDD	16	Depressive symptoms	Peer-reviewed

BDI = Beck Depression Inventory, CSDD = Cornel Scale for Depression in Dementia, GDS = Geriatric Depression Scale, HAM-D = Hamilton Depressive Disorder, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = Major Depressive Disorder, MMPI = Minnesota Multhipasic Personality Inventory, PHQ-9 = Patient Health Questionnaire, SCL = Symptom Checklist.

negative studies required to nullify the ES in outpatients (N = 911), low quality studies (N = 589), aerobic exercise (N = 543) and supervised exercise (N = 450). Full details are summarised in Table 2.

3.3. Meta-regression of antidepressant effects in main analysis

Mean age, gender, dropout, use of antidepressant medications, baseline depressive symptoms, frequency of exercise sessions and length of the trial did not moderate the antidepressant effect of exercise. A summary of all meta-regression analyses is presented in Table 3.

3.4. Sensitivity analyses

3.4.1. Exercise effects on people with MDD only

All analyses investigating exercise in MDD are presented in Table 4. Briefly, a larger pooled SMD was evident in low quality studies (SMD = 1.32, 95% CI 0.22 to 2.42, p = 0.001), for RCTS without a group format (SMD = 2.58, 95% CI 0.54 to 4.62, p = 0.013), in outpatients (SMD = 1.51, 95% CI 0.45 to 1.57, p = 0.005), and when the intervention was supervised by qualified exercise professionals (SMD = 1.53, 95% CI 0.51 to 2.59, p = 0.003). There were no studies using strength or mixed interventions. No studies were conducted in a sample with major clinical comorbidities.

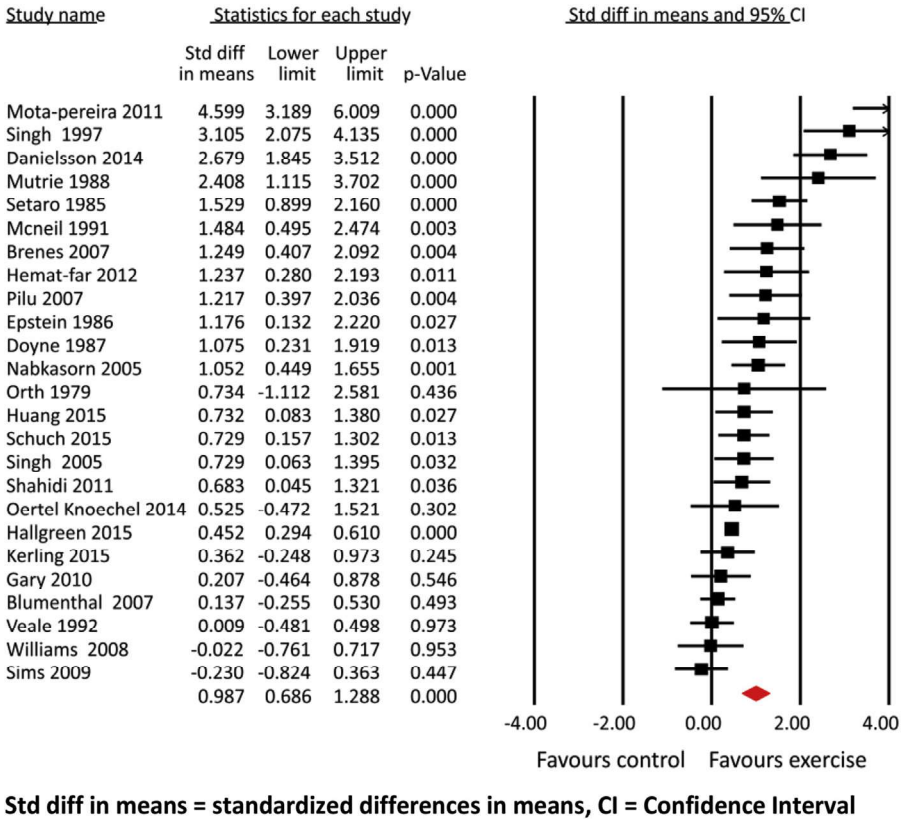

Fig. 2. Meta-analysis of overall studies.

3.4.2. Adjustment of publication bias and fail safe number of studies

Adjusting for publication bias, studies of high methodological quality, in inpatients, and that used aerobic exercise interventions had larger effects sizes. The fail-safe number of studies in RCTs composed exclusively of people with diagnosed MDD was 84 for RCTs in outpatient settings and 132 in RCTs using aerobic exercise RCTs. Full details are summarised in Table 4.

3.4.3. Meta regression of moderators of control group response in MDD

Mean age, gender, dropout, use of antidepressant, baseline depressive symptoms, frequency of exercise and length of the trial did not moderate the antidepressant effect of exercise. The full meta-regression data can be found in Table 3.

3.5. Mean change in depressive symptoms

Data from 25 studies found an improvement of −4.52 points (95% CI 2.03 to 7.01, $p < 0.001$) and of −6.46 (95% CI 4.18 to 8.41, $p < 0.001$) points on the HAM-D and the BDI scales, respectively. A sensitivity analysis including only studies in MDD established a mean improvement in depressive symptoms of −5.07 points (95% CI 1.37 to 8.78, $p = 0.007$) in the HAM-D.

4. Discussion

This meta-analysis found large antidepressant effects of exercise on depression when compared to non-active control conditions (e.g. studies that did not compare exercise versus alternative treatments). The anti-depressant effect of exercise was higher for studies that included participants diagnosed with MDD. Moreover, our adjusted analyses demonstrate that publication bias generally resulted in an underestimation of the positive effects of exercise. Larger effect sizes were found for outpatients, in samples without other clinical co-morbidities, and when supervised by qualified exercise professionals, both in the main analysis and when restricted to MDD participants alone.

Overall, our results provide robust evidence that exercise can be considered an evidence-based treatment for the management of depression. The fail safe assessment suggests that more than a thousand studies with negative results would be needed to nullify the effects of exercise on depression. The large effect of exercise on depression found in our meta-analysis differs in magnitude, being larger than the effects found in a recent Cochrane review (Cooney et al., 2013). The differences in the magnitudes of the effects are mainly due to three factors: (1) the inclusion criteria, (2) the statistical test used to evaluate the ES, and (3) the inclusion of more recent trials. In the present review, we removed the studies without true control groups that were included in Cooney review (Blumenthal et al., 1999; Fremont and Craighead, 1987). These studies compared exercise plus an established treatment versus an established treatment and were included by Cooney et al. (2013) using the prerogative that one can add and subtract therapeutic efficacies in an algebraic fashion (e.g. exercise + selective serotonin reuptake inhibitor (SSRI)/cognitive behavioural therapy (CBT)—SSRI/CBT = exercise) (Ekkekakis, 2015). However, this argument is flawed since exercise may potentially overlap, at least in part, with some of the potential mechanisms of SSRI (e.g. increase on neurotrophic markers) and CBT (e.g. improved perceived coping ability and self-appraisal) (Ekkekakis, 2015). Second, we calculated the ES based on the mean change (baseline to endpoint) of symptoms of control and exercise groups, not only the endpoint measure (Cooney et al., 2013). This approach is particularly important when pooling studies that have different baseline values for the main

Table 2
Subgroup meta-analysis in all studies.

Analysis	Number of RCTs	Meta-analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]	Classic fail safe N
		SMD	95% CI		P value			
Main analysis								
Exercise x control	25	0.987	0.686	1.281	< **0.0001**	82.10	1.11 (0.79–1.43) [2]	1057
Depression classification								
MDD	9	1.139	0.464	1.814	= **0.0001**	88.54	1.23 (0.569–2.08) [1]	132
Depressive symptoms	14	0.801	0.489	1.112	< **0.0001**	68.47	Unchanged	145
Study quality								
High quality	4	0.882	0.221	1.544	= **0.009**	90.15	1.21 (0.35–2.08) [1]	56
Low quality	21	1.033	0.657	1.408	< **0.0001**	79.25	1.40 (0.95–1.84) [5]	614
Study setting								
Outpatient/community	21	1.123	0.770	1.473	< **0.0001**	84.65	Unchanged	911
Inpatient	3	0.553	0.167	0.938	**0.005**	0	0.72 (0.41–1.03) [2]	3
Nursing homes	1	−0.022	−0.761	0.717	0.953	0	N/A	N/A
Intensity of exercise								
Light to moderate	3	0.586	−0.019	1.190	0.058	32.96	Unchanged	2
Moderate	6	1.330	0.463	2.197	**0.003**	83.37	1.86 (0.86–2.68)[2]	63
Vigorous	7	1.342	0.437	2.246	**0.004**	91.09	Unchanged	102
Exercise type								
Aerobic only	19	1.045	0.653	1.437	< **0.0001**	80.97	1.11 (0.71–1.52) [1]	543
Resistance only	3	1.152	−0.50	2.801	=0.174	93.40	Unchanged	11
Mixed	3	0.659	0.248	1.069	= **0.002**	48.39	Unchanged	27
Group exercise								
Yes	13	0.924	0.513	1.336	< **0.0001**	76.10	Unchanged	227
No	8	1.531	0.775	2.288	< **0.0001**	90.38	Unchanged	23
Supervised								
Supervised	18	0.906	0.054	1.271	< **0.0001**	80.34	0.98 (0.60–1.36) [1]	450
Unsupervised	3	1.074	−0.400	2.549	=0.153	77.20	Unchanged	4
Supervised and unsupervised	2	3.000	−0.061	6.093	=0.05	92.34	N/A	N/A
Professional who supervised								
Physical exercise professional/physiotherapists/ exercise physiologists	11	1.261	0.549	1.972	< **0.0001**	87.21	1.50 (0.80–2.21) [2]	262
Other	6	1.094	0.452	1.734	< **0.0001**	16.13	Unchanged	73
Comorbidities								
No major comorbidities	22	1.142	0.815	1.469	< **0.0001**	82.65	1.37 (.96–1.77) [3]	1067
Included participants with comorbidities	3	−0.034	−0.415	0.347	=0.861	0.00	Unchanged	0
Type of publication								
Thesis	4	1.514	0.690	2.339	< **0.0001**	2.92	Unchanged	30
Peer review journal	21	0.909	0.593	1.225	< **0.0001**	82.88	1.12 (0.76–1.47) [3]	712

Key: MDD = Major depressive Disorder, Randomized Clinical Trials, SMD = Standardised mean difference.

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

	Moderator	Number RCTs	β	95% CI		P value	R^2
Main exercise response							
	Mean age control	14	−0.0092	−0.0398	0.0214	0.5560	0.03
	Mean age exercisers	14	−0.0119	−0.0426	0.0188	0.4460	0.03
	% females exercise	16	0.0142	−0.0376	0.0092	0.2336	0.08
	% females control	16	0.0002	−0.0199	0.0203	0.9849	0.10
	% taking antidepressants exercise	18	0.0076	−0.0010	0.0163	0.0838	0.02
	% taking antidepressants control	18	0.0067	−0.0021	0.0155	0.1382	0.02
	Baseline depressive symptoms exercise	25	0.0178	−0.0133	0.0438	0.1791	0.05
	Baseline depressive symptoms control	25	0.0041	−0.0226	0.0308	0.7635	0.02
	% drop out exercise group	20	−0.0023	−0.0234	0.0346	0.5834	0.01
	% drop out control group	20	−0.0010	−0.0423	0.0354	0.8453	0.00
	Duration of trial	24	−0.177	−0.0857	0.0503	0.6098	0.02
	Weekly frequency	23	0.1164	−0.3252	0.5579	0.6056	0.00
MDD only							
	Mean age control	6	0.0251	−0.2903	0.3405	0.8761	0.00
	Mean age exercisers	6	0.0756	−0.1485	0.2998	0.5084	0.01
	% females exercise	7	0.0007	−0.0530	0.0545	0.9783	0.01
	% females control	7	0.0233	−0.0152	0.0618	0.2363	0.00
	% taking antidepressants exercise	7	0.0223	−0.0024	0.0234	0.0709	0.34
	% taking antidepressants control	7	0.0225	−0.005	0.0444	0.0671	0.14
	Baseline depressive symptoms exercise	9	−0.0360	−0.2599	0.1880	0.7531	0.04
	Baseline depressive symptoms control	9	−0.1377	−0.3487	0.0013	0.0517	0.31
	% drop out exercise group	8	−0.0063	−0.3764	0.0434	0.4183	0.02
	% drop out control group	8	−0.0256	−0.0892	0.5304	0.6420	0.00
	Duration of trial	9	−0.1241	−0.8476	0.4511	0.3425	0.01
	Weekly frequency	9	0.1535	−0.2039	1.9812	0.5352	0.04

Table 4
Subgroup meta-analysis in MDD studies.

Analysis	Number of RCTs	Meta-analysis				Heterogeneity	Trim and fill effect size (95% CI) [adjusted studies]	Classic fail safe N
		SMD	95% CI		P value	I2		
Study quality								
High quality	3	1.133	−0.140	2.406	=0.08	93.19	Unchanged	21
Low quality	6	1.176	0.244	2.109	= **0.013**	87.64	1.81 (0.59–3.02) [2]	44
Study setting								
Outpatient/community	6	1.517	0.458	2.576	= **0.005**	92.73	1.89 (0.53–3.25) [1]	84
Inpatient	3	0.553	0.167	0.938	=0.005	0.00	0.72 (0.41–1.03) [2]	3
Intensity								
Ligth to moderate	1	0.525	−0.472	1.521	=**0.302**	0.00	N/A	N/A
Moderate	3	1.965	−0.211	4.142	=**0.077**	93.16	Unchanged	22
Vigorous	2	1.380	−1.110	3.870	=**0.277**	96.7	N/A	N/A
Exercise type								
Aerobic only	9	1.139	0.464	1.814	= **0.001**	88.54	1.32 (0.56–2.08) [1]	132
Group exercise								
No	3	2.585	0.549	4.62207	= **0.013**	93.86	Unchanged	158
Yes	4	0.677	0.061	1.294	= **0.031**	60.91	Unchanged	9
Supervised								
Supervised	8	0.798	0.257	1.339	= **0.004**	81.89	0.93 (0.36–1.51) [1]	66
Supervised and unsupervised	1	4.599	3.189	6.009	< **0.001**	0.00	N/A	N/A
Professional who supervised								
Qualified exercise professional	6	1.537	0.514	2.599	= **0.003**	91.619	Unchanged	97
Other	2	0.655	−0.011	1.420	=0.094	6.11	N/A	N/A
Comorbidities								
No major comorbidities	9	1.139	0.464	1.814	= **0.001**	88.54	1.32 (0.56–2.08) [1]	132
Type of publication								
Peer review journal	8	1.14	0.411	1.871	= **0.002**	89.81	1.35 (0.52–2.18)[1]	107
Thesis	1	1.176	0.132	2.220	= **0.027**	0.00	N/A	N/A

Key: MDD = Major depressive Disorder, SMD = Standardised mean difference.

outcome (Mota-Pereira et al., 2011; Sims et al., 2009; Veale et al., 1992). Third, one trial that was included in the Cooney et al. (2013) review contained preliminary results from one RCT, which were replaced by the published final results in our updated meta-analysis (Schuch et al., 2015) and a further five new trials were included. The inclusion of these recent trials may have influenced our findings, particularly our analyses of high quality studies, since three of the new studies were classified as being of high quality (Danielsson et al., 2014; Hallgren et al., 2015; Schuch et al., 2015). The inclusion of these recent trials led to the change from "small and non-significant" effects of high quality trials in Cooney review (Cooney et al., 2013) to large and significant effects in the present review. The magnitude of those effects was larger in studies in MDD than in samples where clinical diagnoses were not stated. It should be noted that samples with clinical diagnoses have greater baseline depression scores and consequently more potential to achieve greater reductions in symptoms. Unlike the larger effects in samples diagnosed with MDD, the effect of exercise in samples without a clinical diagnosis of MDD was moderate.

Both aerobic and mixed exercises were associated with large effects across all studies. In clinical samples, only aerobic exercises had large and significant effects on depression, while mixed interventions had non-significant effects. This finding deserves further investigation since no RCT investigating the effects of resistance exercise in samples comprised entirely of participants with MDD was identified. Moderate and vigorous intensity exercises where shown to be more effective than light to moderate intensity exercises. However, this finding needs to be interpreted with caution, since it is based on a small number of studies.

Supervised interventions had the largest effects, in our main analysis. This is in line with previous reviews on exercise and lifestyle interventions (Ward et al., 2015). Exercise supervised by professionals with relevant training, including physical educators, physiotherapists and exercise physiologists, was associated with the greatest improvements. Additionally, exercise supervised by other health professionals appears to have a large effect although this did not reach statistical significance. This result, added to previous findings of lower drop-out rate in interventions delivered by exercise professionals in people with depression (Stubbs et al., 2016) highlighting the importance of adequately trained professionals providing exercise interventions. Therefore, this finding has a practical implication in the design of further trials, as well as providing evidence for policy makers to consider including competent exercise professionals in mental health care treatment teams (NICE, 2009).

Unlike psychotherapy RCTs for depression (Cuijpers et al., 2010), the effects of exercise studies in depression appear to have been underestimated due to publication bias. Previous meta-analyses have largely ignored the potential impact of publication bias, and none to our knowledge have re-calculated the effect sizes accounting for publication bias. These analyses confirm and strengthen the evidence-base regarding the benefits of exercise in people with depression.

Lastly, we found a reduction of about 5 points in HAM-D scale, and greater than 6 points in the BDI scale, in the overall sample and in MDD patients considered separately. This reduction is above the clinically significant reduction of three points in the HAM-D as formulated in the NICE guidelines (NICE, 2009).

In summary, compared to non-active interventions, exercise has a large and significant antidepressant effect, and it would require over 1000 negative studies to nullify this result. Publication bias is evident in exercise RCTs, but this has largely resulted in an underestimation of the ES of exercise. Our novel ES, calculated adjusting for publication bias, confirms and strengthen the case that exercise is an evidence-based treatment for depression.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2016.02.023.

Conflict of interest

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Contributors

Felipe Schuch - Participated in the conception and design of the study, reviewed studies, extracted data, performed the analysis and wrote the manuscript.

Davy Vancampfort - Participated in the design of the study, reviewed studies and wrote the manuscript.

Justin Richards - Reviewed studies, extracted data and wrote the manuscript.

Simon Rosenbaum - Reviewed studies, extracted data and wrote the manuscript.

Philip Ward - Reviewed studies and wrote the manuscript.

Brendon Stubbs - Participated in the conception and design of the study, reviewed studies, extracted data, performed the analysis and wrote the manuscript.

All authors revised the article critically for important intellectual content and approved the final manuscript.

Role of the founding source

The present study have received no specific founding.

References

Andrade, L., Caraveo-Anduaga, J.J., Berglund, P., Bijl, R.V., De Graaf, R., Vollebergh, W., et al., 2003. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int. J. Methods Psychiatr. Res. 12, 3–21.

Association AP, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. Washington D.C.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.

Beck, A.T., Steer, R.A., Brown, G.K., 1996. Beck Depression Inventory-II. San Antonio.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101.

Blumenthal, J.A., Doraiswamy, P., 2014. EXercise to combat depression. JAMA 312, 2166–2167.

Blumenthal, J.A., Babyak, M.A., Moore, K.A., Craighead, W.E., Herman, S., Khatri, P., et al., 1999. Effects of exercise training on older patients with major depression. Arch. Intern Med. 159, 2349–2356.

Blumenthal, J.A., Babyak, M.A., Doraiswamy, P.M., Watkins, L., Hoffman, B.M., Barbour, K.A., et al., 2007. Exercise and pharmacotherapy in the treatment of major depressive disorder. Psychosom. Med. 69, 587–596.

Brenes, G.A., Williamson, J.D., Messier, S.P., Rejeski, W.J., Pahor, M., Ip, E., et al., 2007. Treatment of minor depression in older adults: a pilot study comparing sertraline and exercise. Aging Ment. Health 11, 61–68.

Bridle, C., Spanjers, K., Patel, S., Atherton, N.M., Lamb, S.E., 2012. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. Br. J. Psychiatry 201, 180–185.

Caspersen, C.J., Powell, K.E., Christenson, G.M., 1985. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 100, 126.

Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., et al., 2015 May. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J. Psychopharmacol. 29 (5), 459–525. http://dx.doi.org/10.1177/0269881115581093 (Epub 2015 May 12).

Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., et al., 2013. Exercise for depression. Cochrane Database Syst. Rev. 9. CD004366.

Cooney, G., Dwan, K., Mead, G., 2014. Exercise for depression. JAMA 311, 2432–2433.

Craft, L.L., Landers, D.M., 1998. The effects of exercise on clinical depression and depression resulting from mental illness: a meta-regression analysis. J. Sport & Exerc. Psychol. 20, 339–357.

Cuijpers, P., Smit, F., Bohlmeijer, E., Hollon, S.D., Andersson, G., 2010. Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. Br. J. Psychiatry 196, 173–178.

Daley, A., 2008. Exercise and depression: a review of reviews. J. Clin. Psychol. Med. Settings 15, 140–147.

Danielsson, L., Noras, A.M., Waern, M., Carlsson, J., 2013. Exercise in the treatment of major depression: a systematic review grading the quality of evidence. Physiother. Theory Pract. 29, 573–585.

Danielsson, L., Papoulias, I., Petersson, E.L., Carlsson, J., Waern, M., 2014. Exercise or basic body awareness therapy as add-on treatment for major depression: a controlled study. J. Affect. Disord. 168, 98–106.

Doyne, E.J., Ossip-Klein, D.J., Bowman, E.D., Osborn, K.M., McDougall-Wilson, I.B., Neimeyer, R.A., 1987. Running versus weight lifting in the treatment of depression. J. Consult. Clin. Psychol. 55, 748.

Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56, 455–463.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634 (Clinical Research Ed).

Ekkekakis, P., 2015. Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. Ment. Health Phys. Act 8, 21–36.

Epstein, D., 1986. Aerobic Activity versus Group Cognitive Therapy: an Evaluative Study of Contrasting Interventions for the Alleviation of Clinical Depression. University of Nevada, Reno.

Fremont, J., Craighead, L.W., 1987. Aerobic exercise and cognitive therapy in the treatment of dysphoric moods. Cognitive Ther. Res. 11, 241–251.

Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.-M., et al., 2011. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med. Sci. Sports Exerc. 43, 1334–1359. http://dx.doi.org/10.249/MSS.0b013e318213fefb.

Gary, R.A., Dunbar, S.B., Higgins, M.K., Musselman, D.L., Smith, A.L., 2010. Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. J. Psychosom. Res. 69, 119–131.

Goyal, M., Singh, S., Sibinga, E.M., Gould, N.F., Rowland-Seymour, A., Sharma, R., et al., 2014. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern. Med. 174, 357–368.

Hallgren, M., Kraepelien, M., Öjehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., et al., 2015. Physical exercise and internet-based cognitive behavioural therapy in the treatment of depression: randomised controlled trial. Br. J. Psychiatry bjp. bp.114.160101.

Hamilton, M.A.X., 1967. Development of a rating scale for primary depressive illness. Br. J. Soc. Clin. Psychol. 6, 278–296.

Hemat-Far, A., Shahsavari, A., Roholla Mousavi, S., 2012. Effects of selected aerobic exercises on the depression and concentrations of plasma serotonin in the depressed female students aged 18 to 25. J. Appl. Res. Clin. Exp. Ther. 12, 47.

Hess-Homeier, M.J., 1981. A comparison of Beck's cognitive therapy and jogging as treatments for depression.

Higgins, J., Green, S., 2011. Cochrane Handbook for systematic reviews of interventions version. In: Collaboration TC.

Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560 (Clinical Research Ed).

Hoffman, B.M., Babyak, M.A., Sherwood, A., Hill, E.E., Patidar, S.M., Doraiswamy, P.M., et al., 2009. Effects of aerobic exercise on sexual functioning in depressed adults. Ment. Health Phys. Act 2, 23–28.

Huang, T.-T., Liu, C.-B., Tsai, Y.-H., Chin, Y.-F., Wong, C.-H., 2015. Physical fitness exercise versus cognitive behavior therapy on reducing the depressive symptoms among community-dwelling elderly adults: a randomized controlled trial. Int. J. Nurs. Stud.

Ioannidis, J.P., Munafo, M.R., Fusar-Poli, P., Nosek, B.A., David, S.P., 2014. Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. Trends Cognitive Sci. 18, 235–241.

Josefsson, T., Lindwall, M., Archer, T., 2014. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. Scand. J. Med. Sci. Sports 24, 259–272.

Kerling, A., Tegtbur, U., Gützlaff, E., Kück, M., Borchert, L., Ates, Z., et al., 2015. Effects of adjunctive exercise on physiological and psychological parameters in depression: a randomized pilot trial. J. Affect. Disord. 177, 1–6.

Krogh, J., Saltin, B., Gluud, C., Nordentoft, M., 2009. The DEMO trial: a randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. J. Clin. Psychiatry 70, 790–800.

Krogh, J., Nordentoft, M., Sterne, J.A., Lawlor, D.A., 2011. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. J. Clin. Psychiatry 72, 529–538.

Larkey, L., Jahnke, R., Etnier, J., Gonzalez, J., 2009. Meditative movement as a category of exercise: implications for research. J. Phys. Act. Health 6, 230–238.

Martinsen, E.W., 1987. The role of aerobic exercise in the treatment of depression. Stress Med. 3, 93–100.

Mather, A.S., Rodriguez, C., Guthrie, M.F., McHARG, A.M., Reid, I.C., McMURDO, M.E., 2002. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder randomised controlled trial. Br. J. Psychiatry 180, 411–415.

McNeil, J.K., LeBlanc, E.M., Joyner, M., 1991. The effect of exercise on depressive symptoms in the moderately depressed elderly. Psychol. Aging 6, 487.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.
Mota-Pereira, J., Silverio, J., Carvalho, S., Ribeiro, J.C., Fonte, D., Ramos, J., 2011. Moderate exercise improves depression parameters in treatment-resistant patients with major depressive disorder. J. Psychiatr. Res. 45, 1005–1011.
Mutrie, N., 1989. Exercise as a Treatment for Depression within a National Health Service. Microform Publications, College of Human Development and Performance, University of Oregon.
Nabkasorn, C., Miyai, N., Sootmongkol, A., Junprasert, S., Yamamoto, H., Arita, M., et al., 2006. Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. Eur. J. Public Health 16, 179–184.
NICE, 2009. Depression: the treatment and management of depression in adults.
Oertel-Knöchel, V., Mehler, P., Thiel, C., Steinbrecher, K., Malchow, B., Tesky, V., et al., 2014. Effects of aerobic exercise on cognitive performance and individual psychopathology in depressive and schizophrenia patients. Eur. Arch Psychiatry Clin. Neurosci. 264, 589–604.
organisation Wh, 1993. The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research.
Orth, D.K., 1979. Clinical Treatments for Depression. West Virginia University, Morgantown.
Pfaff, J.J., Alfonso, H., Newton, R.U., Sim, M., Flicker, L., Almeida, O.P., 2014. ACTIVEDEP: a randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. Br. J. Sports Med. 48, 226–232.
Pilu, A., Sorba, M., Hardoy, M.C., Floris, A.L., Mannu, F., Seruis, M.L., et al., 2007. Efficacy of physical activity in the adjunctive treatment of major depressive disorders: preliminary results. Clin. Pract. Epidemiol. Ment. Health 3, 8.
Rethorst, C.D., Wipfli, B.M., Landers, D.M., 2009. The antidepressive effects of exercise: a meta-analysis of randomized trials. Sports Med. 39, 491–511.
Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638.
Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Fleck, M.P., 2011. Exercise and severe depression: preliminary results of an add-on study. J. Affect Disord. 133, 615–618.
Schuch, F.B., Vasconcelos-Moreno, M.P., Borowsky, C., Zimmermann, A.B., Rocha, N.S., Fleck, M.P., 2015. Exercise and severe major depression: effect on symptom severity and quality of life at discharge in an inpatient cohort. J. Psychiatr. Res. 61, 25–32.
Setaro, J.L., 1985. Aerobic Exercise and Group Counseling in the Treatment of Anxiety and Depression. University Microfilms International/UMI.
Shahidi, M., Mojtahed, A., Modabbernia, A., Mojtahed, M., Shafiabady, A., Delavar, A., et al., 2011. Laughter yoga versus group exercise program in elderly depressed women: a randomized controlled trial. Int. J. Geriatr Psychiatry 26, 322–327.
Silveira, H., Moraes, H., Oliveira, N., Coutinho, E.S., Laks, J., Deslandes, A., 2013. Physical exercise and clinically depressed patients: a systematic review and meta-analysis. Neuropsychobiology 67, 61–68.
Sims, J., Galea, M., Taylor, N., Dodd, K., Jespersen, S., Joubert, L., et al., 2009. Regenerate: assessing the feasibility of a strength-training program to enhance the physical and mental health of chronic post stroke patients with depression. Int. J. Geriatr Psychiatry 24, 76–83.
Singh, N.A., Clements, K.M., Fiatarone, M.A., 1997. A randomized controlled trial of progressive resistance training in depressed elders. J. Gerontol. A Biol. Sci. Med. Sci. 52, M27–M35.
Singh, N.A., Stavrinos, T.M., Scarbek, Y., Galambos, G., Liber, C., Fiatarone Singh, M.A., 2005. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. J. Gerontol. A Biol. Sci. Med. Sci. 60, 768–776.
Spitzer, R.L., Endicott, J., Robins, E., 1978. Research diagnostic criteria: rationale and reliability. Arch General Psychiatry 35, 773–782.
Stathopoulou, G., Powers, M.B., Berry, A.C., Smits, J.A.J., Otto, M.W., 2006. Exercise interventions for mental health: a quantitative and qualitative review. Clin. Psychol. Sci. Pract. 13, 179–193.
Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., et al., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. Jama 283, 2008–2012.
Stubbs, B., Vancampfort, D., Rosenbaum, S., Ward, P.B., Richards, J., Soundy, A., et al., 2016. Dropout from exercise randomized controlled trials among people with depression: a meta-analysis and meta regression. J. Affect. Disord. 190, 457–466.
Veale, D., Le Fevre, K., Pantelis, C., de Souza, V., Mann, A., Sargeant, A., 1992. Aerobic exercise in the adjunctive treatment of depression: a randomized controlled trial. J. R. Soc. Med. 85, 541–544.
Ward, M.C., White, D.T., Druss, B.G., 2015. A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness. J. Clin. Psychiatry 76, e477–e486.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., et al., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–1586.
Williams, C., Tappen, R., 2008. Exercise training for depressed older adults with Alzheimer's disease. Aging Ment. Health 12, 72–80.