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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.