

Exercise for depression (Review)

Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE



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Exercise for depression (Review)

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[Intervention Review]

Exercise for depression

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ABSTRACT

Background

Depression is a common and important cause of morbidity and mortality worldwide. Depression is commonly treated with antidepressants and/or psychological therapy, but some people may prefer alternative approaches such as exercise. There are a number of theoretical reasons why exercise may improve depression. This is an update of an earlier review first published in 2009.

Objectives

To determine the effectiveness of exercise in the treatment of depression in adults compared with no treatment or a comparator intervention.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Review Group's Controlled Trials Register (CCDANCTR) to 13 July 2012. This register includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years); MEDLINE (1950 to date); EMBASE (1974 to date) and PsycINFO (1967 to date). We also searched www.controlled-trials.com, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. No date or language restrictions were applied to the search.

We conducted an additional search of the CCDANCTR up to 1st March 2013 and any potentially eligible trials not already included are listed as 'awaiting classification.'

Selection criteria

Randomised controlled trials in which exercise (defined according to American College of Sports Medicine criteria) was compared to standard treatment, no treatment or a placebo treatment, pharmacological treatment, psychological treatment or other active treatment in adults (aged 18 and over) with depression, as defined by trial authors. We included cluster trials and those that randomised individuals. We excluded trials of postnatal depression.

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Data collection and analysis

Two review authors extracted data on primary and secondary outcomes at the end of the trial and end of follow-up (if available). We calculated effect sizes for each trial using Hedges' *g* method and a standardised mean difference (SMD) for the overall pooled effect, using a random-effects model risk ratio for dichotomous data. Where trials used a number of different tools to assess depression, we included the main outcome measure only in the meta-analysis. Where trials provided several 'doses' of exercise, we used data from the biggest 'dose' of exercise, and performed sensitivity analyses using the lower 'dose'. We performed subgroup analyses to explore the influence of method of diagnosis of depression (diagnostic interview or cut-off point on scale), intensity of exercise and the number of sessions of exercise on effect sizes. Two authors performed the 'Risk of bias' assessments. Our sensitivity analyses explored the influence of study quality on outcome.

Main results

Thirty-nine trials (2326 participants) fulfilled our inclusion criteria, of which 37 provided data for meta-analyses. There were multiple sources of bias in many of the trials; randomisation was adequately concealed in 14 studies, 15 used intention-to-treat analyses and 12 used blinded outcome assessors.

For the 35 trials (1356 participants) comparing exercise with no treatment or a control intervention, the pooled SMD for the primary outcome of depression at the end of treatment was -0.62 (95% confidence interval (CI) -0.81 to -0.42), indicating a moderate clinical effect. There was moderate heterogeneity ($I^2 = 63\%$).

When we included only the six trials (464 participants) with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment, the pooled SMD for this outcome was not statistically significant (-0.18, 95% CI -0.47 to 0.11). Pooled data from the eight trials (377 participants) providing long-term follow-up data on mood found a small effect in favour of exercise (SMD -0.33, 95% CI -0.63 to -0.03).

Twenty-nine trials reported acceptability of treatment, three trials reported quality of life, none reported cost, and six reported adverse events.

For acceptability of treatment (assessed by number of drop-outs during the intervention), the risk ratio was 1.00 (95% CI 0.97 to 1.04).

Seven trials compared exercise with psychological therapy (189 participants), and found no significant difference (SMD -0.03, 95% CI -0.32 to 0.26). Four trials ($n = 300$) compared exercise with pharmacological treatment and found no significant difference (SMD -0.11, -0.34, 0.12). One trial ($n = 18$) reported that exercise was more effective than bright light therapy (MD -6.40, 95% CI -10.20 to -2.60).

For each trial that was included, two authors independently assessed for sources of bias in accordance with the Cochrane Collaboration 'Risk of bias' tool. In exercise trials, there are inherent difficulties in blinding both those receiving the intervention and those delivering the intervention. Many trials used participant self-report rating scales as a method for post-intervention analysis, which also has the potential to bias findings.

Authors' conclusions

Exercise is moderately more effective than a control intervention for reducing symptoms of depression, but analysis of methodologically robust trials only shows a smaller effect in favour of exercise. When compared to psychological or pharmacological therapies, exercise appears to be no more effective, though this conclusion is based on a few small trials.

PLAIN LANGUAGE SUMMARY

Exercise for depression

Why is this review important?

Depression is a common and disabling illness, affecting over 100 million people worldwide. Depression can have a significant impact on people's physical health, as well as reducing their quality of life. Research has shown that both pharmacological and psychological therapies can be effective in treating depression. However, many people prefer to try alternative treatments. Some NHS guidelines suggest that exercise could be used as a different treatment choice. However, it is not clear if research actually shows that exercise is an effective treatment for depression.

Who may be interested in this review?

Patients and families affected by depression.

General Practitioners.

Mental health policy makers.

Professionals working in mental health services.

What questions does this review aim to answer?

This review is an update of a previous Cochrane review from 2010 which suggested that exercise can reduce symptoms of depression, but the effect was small and did not seem to last after participants stopped exercising.

We wanted to find out if more trials of the effect of exercise as a treatment for depression have been conducted since our last review that allow us to answer the following questions:

Is exercise more effective than no therapy for reducing symptoms of depression?

Is exercise more effective than antidepressant medication for reducing symptoms of depression?

Is exercise more effective than psychological therapies or other non-medical treatments for depression?

How acceptable to patients is exercise as a treatment for depression?

Which studies were included in the review?

We used search databases to find all high-quality randomised controlled trials of how effective exercise is for treating depression in adults over 18 years of age. We searched for studies published up until March 2013. We also searched for ongoing studies to March 2013. All studies had to include adults with a diagnosis of depression, and the physical activity carried out had to fit criteria to ensure that it met with a definition of 'exercise'.

We included 39 studies with a total of 2326 participants in the review. The reviewers noted that the quality of some of the studies was low, which limits confidence in the findings. When only high-quality trials were included, exercise had only a small effect on mood that was not statistically significant.

What does the evidence from the review tell us?

Exercise is moderately more effective than no therapy for reducing symptoms of depression.

Exercise is no more effective than antidepressants for reducing symptoms of depression, although this conclusion is based on a small number of studies.

Exercise is no more effective than psychological therapies for reducing symptoms of depression, although this conclusion is based on small number of studies.

The reviewers also note that when only high-quality studies were included, the difference between exercise and no therapy is less conclusive.

Attendance rates for exercise treatments ranged from 50% to 100%.

The evidence about whether exercise for depression improves quality of life is inconclusive.

What should happen next?

The reviewers recommend that future research should look in more detail at what types of exercise could most benefit people with depression, and the number and duration of sessions which are of most benefit. Further larger trials are needed to find out whether exercise is as effective as antidepressants or psychological treatments.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise compared to no intervention or placebo for adults with depression					
Patient or population: adults with depression Settings: any setting Intervention: Exercise Comparison: no intervention or placebo					
Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	No intervention or placebo	Exercise			
Symptoms of depression Different scales Follow-up: post-treatment	The mean symptoms of depression in the control groups was 0	The mean symptoms of depression in the intervention groups was 0.62 standard deviations lower (0.81 to 0.42 lower) ¹	1353 (35 studies)	⊕⊕⊕○ moderate ^{2,3,4}	SMD -0.62 (95% CI: -0.81 to -0.42). The effect size was interpreted as 'moderate' (<i>using Cohen's rule of thumb</i>)
Symptoms of depression (long-term) different scales	The mean symptoms of depression (long-term) in the control groups was 0	The mean symptoms of depression (long-term) in the intervention groups was 0.33 standard deviations lower (0.63 to 0.03 lower)	377 (8 studies)	⊕⊕○○ low ^{4,5}	SMD -0.33 (95% CI: -0.63 to -0.03). The effect size was interpreted as 'small' (<i>using Cohen's rule of thumb</i>)
Adverse events	See comment	See comment	0 (6 studies)	⊕⊕⊕○ moderate	Seven trials reported no difference in adverse events between exercise and usual care groups. Dunn 2005 reported increased severity of depressive symptoms (n = 1), chest pain (n = 1) and joint pain/

swelling (n = 1); all these participants discontinued exercise. [Singh 1997](#) reported that 1 exerciser was referred to her psychologist at 6 weeks due to increasing suicidality; and musculoskeletal symptoms in 2 participants required adjustment of training regime. [Singh 2005](#) reported adverse events in detail (visits to a health professional, minor illness, muscular pain, chest pain, injuries requiring training adjustment, falls, deaths and hospital days) and found no difference between the groups. [Knubben 2007](#) reported ‘ ‘ no negative effects of exercise (muscle pain, tightness or fatigue)’ ’; after the training had finished, 1 person in the placebo group required gastric lavage and 1 person in the exercise group inflicted a superficial cut on her arm. [Sims 2009](#) reported no adverse events or falls in either the exercise or control group. [Blumenthal 2007](#) reported more side effects in the sertraline group (see comparison below) but there was no difference be-

					tween the exercise and control group. Blumenthal 2012a reported more fatigue and sexual dysfunction in the sertraline group than the exercise group
Acceptability of treatment	Study population		1363 (29 studies)	⊕⊕⊕○ moderate ²	RR 1 (95% CI: 0.97 to 1.04)
	865 per 1000	865 per 1000 (839 to 900)			
Quality of life		The mean quality of life in the intervention groups was 0 higher (0 to 0 higher)	0 (4 studies)	See comment	There was no statistically significant differences for the mental (SMD -0.24; 95% CI -0.76 to 0.29). psychological (SMD 0.28; 95% CI -0.29 to 0.86) and social domains (SMD 0.19; 95% CI -0.35 to 0.74). Two studies reported a statistically significant difference for the environment domain favouring exercise (SMD 0.62; 95% CI 0.06 to 1.18) and 4 studies reported a statistically significant difference for the physical domain favouring exercise (SMD 0.45; 95% CI 0.06 to 0.83)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

-
- 1 Effect estimate calculated by re-expressing the SMD on the Hamilton Depression Rating Scale using the control group SD (7) from [Blumenthal 2007](#) (study chosen for being most representative). The SD was multiplied by the pooled SMD to provide the effect estimate on the HDRS.
 - 2 Lack of blinding of outcome assessors probably increased effect sizes and drop-out rates were high. Also sequence generation was considered unclear in 23 studies.
 - 3 $I^2 = 63\%$ and $P < 0.00001$, indicated moderate levels of heterogeneity
 - 4 Population size is large, effect size is above 0.2 SD, and the 95% CI does not cross the line of no effect.
 - 5 Lack of blinding of outcome assessors probably increased effect sizes and drop-out rates were high. Also sequence generation was considered unclear in 4 studies.

BACKGROUND

Description of the condition

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), persistent low mood and a range of associated emotional, cognitive, physical and behavioural symptoms (NICE 2009).

Severity of depression is classified using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria as mild (five or more symptoms with minor functional impairment), moderate (symptoms or functional impairment are between 'mild' and 'severe') and severe (most symptoms present and interfere with functioning, with or without psychotic symptoms) (NICE 2009). Depression is common, affecting 121 million adults worldwide, and rated as the fourth leading cause of disease burden in 2000 (Moussavi 2007). Depression is an important cause of morbidity and mortality and produces the greatest decrement in health compared with other chronic diseases such as angina or arthritis (Moussavi 2007).

Description of the intervention

Depression is commonly treated with antidepressants or psychological therapies or a combination of both. Antidepressants are effective for the treatment of depression in primary care (Arroll 2009). However antidepressants may have adverse side effects, adherence can be poor, and there is a lag time between starting antidepressants and improvements in mood. Psychological treatments are generally free from side effects and are recommended in the UK National Institute for Health and Clinical Excellence (NICE) guidelines (NICE 2009) but some people may not wish to receive psychological therapy due to low expectations of positive outcome or perceived stigma. Psychological therapy also requires sustained motivation and a degree of psychological mindedness in order to be effective. Depression is a well-recognised reason for seeking alternative therapies (Astin 1998). Whilst this may reflect dissatisfaction with conventional treatments, another possibility is that alternative therapies may be more in line with people's own beliefs and philosophies (Astin 1998). There has been increasing interest in the potential role of alternative therapies such as music therapy, light therapy, acupuncture, family therapy, marital therapy, relaxation and exercise for the management of depression.

Exercise is defined as the "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness" (ACSM 2001). The effect of exercise on depression has been the subject of research for several decades and is believed by a number of researchers and clinicians to be effective in the treatment of depression (Beesley 1997). This reflects an historic perspective on the role of aerobic exercise prescription for

depression. For example, a report for the National Service Framework for Mental Health suggested that exercise should be included as a treatment option for people with depression (Donaghy 2000). The NICE guideline for depression recommended structured, supervised exercise programmes, three times a week (45 minutes to one hour) over 10 to 14 weeks, as a low-intensity Step 2 intervention for mild to moderate depression (NICE 2009). A recent guideline published by the Scottish Intercollegiate Guidelines Network (SIGN) for non-pharmaceutical management of depression in adults recommended that structured exercise may be considered as a treatment option for people with depression (graded 'B' relating to the strength of the evidence on which the recommendation was based) (SIGN 2010). Exercise programmes can be offered in the UK through Exercise Referral Systems (DOH 2001). These schemes direct someone to a service offering an assessment of need, development of a tailored physical activity programme, monitoring of progress and follow-up. However, a systematic review of exercise on prescription schemes found limited evidence about their effectiveness and recommended further research (Sorensen 2006), and a further more recent review found that there was still considerable uncertainty about the effectiveness of exercise referral schemes for increasing physical activity, fitness, or health indicators, or whether they are an efficient use of resources for sedentary people (Pavey 2011). A second recent review noted that most trials in this area that have previously been included in systematic reviews recruit participants from outside of health services, making it difficult to assess whether prescribing exercise in a clinical setting (i.e. when a health professional has made a diagnosis of depression) is effective (Krogh 2011). In that review, studies were restricted only to those trials in which participants with a clinical diagnosis of depression were included, and the authors found no evidence of an effect of exercise in these trials (Krogh 2011). NICE concluded that there was insufficient evidence to recommend Exercise Referral Schemes other than as part of research studies to evaluate their effectiveness. Thus, whilst the published guidelines recommend exercise for depression, NICE recommends that Exercise Referral Schemes, to which people with depression are referred, need further evaluation.

This review focuses on exercise defined according to American College of Sports Medicine (ACSM) criteria. Whilst accepting that other forms of bodily movement may be effective, some of these are the subjects of other reviews.

How the intervention might work

Observational studies have shown that depression is associated with low levels of physical activity (Smith 2013). Whilst an association between two variables does not necessarily imply causality, there are plausible reasons why physical activity and exercise may improve mood. Exercise may act as a diversion from negative thoughts, and the mastery of a new skill may be important (LePore 1997). Social contact may be part of the mechanism. Craft 2005

found support for self efficacy as the mechanism by which exercise might have an antidepressant effect; people who experienced an improvement in mood following exercise showed higher self efficacy levels at three weeks and nine weeks post-exercise. Self efficacy has been found to be intricately linked with self esteem, which in turn is considered to be one of the strongest predictors of overall, subjective well-being (Diener 1984). Low self esteem is also considered to be closely related to mental illness (Fox 2000). Physical activity may have physiological effects such as changes in endorphin and monoamine levels, or reduction in the levels of the stress hormone cortisol (Chen 2013), all of which may improve mood. Exercise stimulates growth of new nerve cells and release of proteins known to improve health and survival of nerve cells, e.g. brain-derived growth neurotrophic factor (Cotman 2002; Ernst 2005).

Why it is important to do this review

Several systematic reviews and meta-analyses (Blake 2009; Carlson 1991; Craft 2013; Krogh 2011; Lawlor 2001; North 1990; Pinquart 2007; Rethorst 2009; Sjosten 2006; Stathopoulou 2006; Sorensen 2006) have looked at the effect of exercise on depression. However, five of these reviews pooled data from a range of study types that included uncontrolled studies and randomised as well as non-randomised controlled trials, and pooled data from trials that compared exercise without treatment with data from trials that compared exercise and other forms of treatment (Blake 2009; Carlson 1991; Craft 2013; North 1990; Pinquart 2007). Two included trials predominantly of older people (Blake 2009; Sjosten 2006). One meta-analysis (Stathopoulou 2006) included only publications from peer-reviewed journals even though it is widely acknowledged that positive trials are more likely to be published than negative or inconclusive trials. The *Cochrane Handbook for Systematic Reviews of Interventions* recommends comprehensive searching for all trials, including unpublished ones, to avoid bias (Handbook 2011). Two meta-analyses which included assessments of study quality both cautiously concluded that exercise may be effective, but recommended that further well-designed trials are required (Lawlor 2001; Sjosten 2006). One meta-analysis (Rethorst 2009) concluded that exercise is effective as a treatment for depression, but suggested that further conclusive results are necessary for exercise to become a recommended form of treatment. When only studies recruiting participants from a clinical setting were included (i.e. those diagnosed by a health professional as having depression), there is no evidence that exercise is of benefit (Krogh 2011). Another review of walking for depression suggested that walking might be a useful adjunct for depression treatment, and recommended further trials (Robertson 2012). This review was published in 2001, in the *British Medical Journal* (Lawlor 2001). It was converted into a Cochrane review in 2009 (Mead 2009), and updated in 2012 (Rimer 2012). Since our last update, we had become aware of new trials that needed to be

considered for inclusion, some of which had received considerable press coverage. Furthermore, several suggestions were made by the Cochrane Depression, Anxiety and Neurosis Review Group (CC-DAN) editorial team about how to improve the review, e.g. inclusion of new subgroup analyses and summary of findings tables. The aim of this review is therefore to update the evidence in this area and to improve the methodology since the previous version (Rimer 2012). These changes are described below in [Differences between protocol and review](#).

OBJECTIVES

1. To determine the effectiveness of exercise compared with no treatment (no intervention or control) for depression in adults.
2. To determine the effectiveness of exercise compared with other interventions (psychological therapies, alternative interventions such as light therapy, pharmacological treatment) for depression in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) (including parallel, cluster, or individual, or the first phase of cross-over trials).

We defined a trial as a 'randomised controlled trial' if the allocation of participants to intervention and comparison groups is described as randomised (including terms such as 'randomly', 'random' and 'randomisation').

Types of participants

Adult men and women aged 18 and over (with no upper age limit) in any setting, including inpatients.

Studies were included if the participants were defined by the author of the trial as having depression (by any method of diagnosis and with any severity of depression). We excluded trials that randomised people both with and without depression, even if results from the subgroups of participants with depression were reported separately, as we had done in previous versions of the review (Mead 2009; Rimer 2012).

The effects of exercise on depressive symptoms in participants with emotional distress (but not fulfilling a diagnosis of depression) or those who are healthy were not included in this review. We acknowledge that it can sometimes be difficult to distinguish between depression and dysthymia in the 'real world', as there needs

to be only two weeks of decreased interest and enjoyment to define depression. However, we were primarily interested in the role of exercise in people with depression, for whom there is substantial morbidity, rather than people with mild, transient episodes of low mood.

Studies that investigated the effect of exercise on anxiety and neurotic disorders, dysthymia (i.e. low mood not fulfilling diagnostic criteria for depression) or postnatal depression were not included in the review.

Types of interventions

Exercise was defined as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (ACSM 2001). The reviews in 2001 (Lawlor 2001) and 2009 (Mead 2009) included any trial where the intervention was defined by the authors as exercise, irrespective of whether it fulfilled this standard definition. For subsequent updates, we agreed with the CCDAN Review Group editorial team that we would use the widely accepted and standardised definition instead (ACSM 2001). This meant that we excluded two trials (Chou 2004; Tsang 2006) that we had included in a previous review, and we also excluded studies that provided advice on how to increase physical activity, that did not fulfil the ACSM definition of exercise. We note however that studies are included irrespective of whether fitness gains were reported or not, and if they were reported, irrespective of whether fitness gains were achieved.

Experimental intervention

- Any type of exercise (as defined above). We excluded studies that measured outcomes immediately before and after a single exercise session, and trials which provided less than a week of exercise.

Comparator intervention

- A ‘control’ intervention. This included studies in which exercise was compared to no intervention; ‘waiting list control’, those in which it was compared to an intervention which the authors defined as a placebo; and those in which exercise was used as an adjunct to an established treatment which was received (in an identical way) by participants in both the exercising and non-exercising group, e.g. exercise plus cognitive behavioural therapy (CBT) versus CBT alone.

- Other type of active treatments, where the aim of the treatment was to improve mood. This includes pharmacological treatments, psychological therapies, or other alternative treatments.

Note that this strategy was the same as that included in the original review (Lawlor 2001).

We excluded studies comparing two different types of exercise with no non-exercising comparison group.

We excluded trials described by the authors as ‘combination treatments’, where exercise was one component of the ‘combination’, because we could not disentangle the effect of exercise from the effect of the other components of the intervention.

Types of outcome measures

Primary outcomes

1. Our primary outcome was a measure of depression or mood at the outcome assessment, either as a continuous measure or as a dichotomous outcome.

Continuous measures of depression were reported using a variety of depression scales, the most common of which were the Beck Depression Inventory (Beck 1961) and the Hamilton Rating Scale for Depression (Hamilton 1960).

In previous versions of the review, where trials used a number of different tools to assess depression, we included the main outcome measure only in the meta-analysis. The main outcome measure was defined using a hierarchy of criteria as follows: identified by the trial authors as the main outcome measure, outcome reported in the abstract, first outcome reported in the Results section.

Where trials used dichotomous data as primary outcomes, and also provided data on continuous outcome measures, we used the data provided in the trial reports for the continuous outcome measure in our meta-analysis. This was because we knew from previous updates that trials generally reported only continuous outcomes.

Secondary outcomes

2. Acceptability of treatment, assessed by a) attendance at exercise interventions, and b) the number of participants completing the interventions;
3. Quality of life;
4. Cost;
5. Adverse events, e.g. musculoskeletal pain, fatigue.

In order to better understand the generalisability of exercise for depression, we also extracted data on the number of people screened for inclusion and the number recruited (Table 1).

Timing of outcome assessment

We extracted data at the end of treatment, and also at the end of any longer-term follow-up after the intervention had been stopped.

Search methods for identification of studies

Electronic searches

We carried out the following electronic searches (Appendix 1; Appendix 2)

- The Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR) (all years to 1 March 2013);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (all years to 2010):
 - MEDLINE (1950 to February 2010);
 - EMBASE (1980 to February 2010);
 - PsycINFO (all years to February 2010);
 - Sports Discus (1975 to 2007).

We searched [Current Controlled Trials](#) (May 2008, November 2010 and March 2013) to identify any ongoing trials. We performed an electronic search of [ClinicalTrials.gov](#) and WHO International Clinical Trials Registry Platform (ICTRP) in March 2013.

Because the searches for the CCDANCTR register are up-to-date and comprehensive, we were advised by the CCDAN editorial team that it was not necessary to search the other databases.

For a previous version of this review ([Mead 2009](#)) we conducted a cited reference search in the Web of Science using the references to all included studies, excluded studies and studies awaiting assessment. This cited reference search was not repeated for subsequent updates.

In order to ensure that the review was as up-to-date as possible when it was submitted for editorial review, we searched the CCDANCTR (up to 1st March 2013) again on 2nd May 2013, so that we could list potentially eligible studies as 'Studies awaiting classification'.

Searching other resources

For the initial review ([Lawlor 2001](#)), the following journals were searched: *BMJ*, *JAMA*, *Archives of Internal Medicine*, *New England Journal of Medicine*, *Journal of the Royal Society of Medicine*, *Comprehensive Psychiatry*, *British Journal of Psychiatry*, *Acta Psychiatrica Scandinavica* and *British Journal of Sports Medicine*.

For the update in 2009 ([Mead 2009](#)), we contacted experts, including authors of all included studies and those with at least two publications amongst the excluded studies, to identify any additional unpublished or ongoing studies, authors of significant papers and other experts in the field to ensure identification of all randomised controlled trials (published, unpublished or ongoing). Due to limitations in available resources for this current update, we did not repeat these handsearches. We limited our contact with authors to those whose trials had been 'ongoing' in the previous version, to enquire whether they had subsequently been published. We also contacted authors to obtain any missing information about trial details. We had planned to do this should any data be missing e.g. standard deviations, although this was not necessary.

We screened the bibliographies of all included articles for additional references.

Data collection and analysis

Selection of studies

Two review authors (GC and GM) independently screened the citations from the searches, and decided which full texts should be retrieved. They then independently applied inclusion and exclusion criteria, resolving any differences in opinion through discussion. If they could not reach agreement, a third author was available (CG) to decide whether a study should be included or excluded.

For the searches of the CCDANCTR up to 1st March 2013, the Trials Search Co-ordinator checked abstracts, excluded obviously irrelevant ones, and then sent a list of the remaining citations to GM for scrutiny, to be included as 'studies awaiting classification'. We created a PRISMA flow diagram to detail the study selection process.

Data extraction and management

We extracted data, when available, at the end of treatment and at the end of follow-up.

For this update, two review authors (GC, FW) independently extracted data for our primary and secondary outcomes for each new trial identified. A third review author (GM) extracted data on type of exercise from all the included trials, to enable a fourth author (CG) to categorise intensity of exercise according to ACSM criteria.

Data extracted were participants, interventions, outcome measures, results, the number of people screened, the number randomised, the number allocated to exercise, the number who dropped out of the exercise arm ([Table 1](#)), secondary clinical outcomes, cost and adverse events, and main conclusions. All the review authors used the same structured paper extraction form that had been piloted on two studies. We resolved any discrepancies by referring to the original papers and by discussion.

Main comparisons

We undertook the following analyses.

1. Exercise versus 'control' (as defined above).
2. Exercise versus psychological therapies.
3. Exercise versus alternative treatments.
4. Exercise versus pharmacological treatments.

Assessment of risk of bias in included studies

The Cochrane Collaboration 'Risk of bias' tool was used to assess risks of bias, according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Handbook 2011](#)). Two review authors independently extracted data on random sequence generation, allocation concealment, blinding of participants, blinding of those delivering the intervention, blinding of outcome assessors,

incomplete outcome data, selective reporting and other potential biases. Each of these domains was categorised as being at high risk of bias, unclear risk of bias or low risk of bias. We resolved any disagreements through discussion.

For concealment of allocation we distinguished between trials that were adequately concealed (central randomisation at a site remote from the study; computerised allocation in which records are in a locked, unreadable file that can be assessed only after entering participant details; the drawing of non-opaque envelopes), inadequately concealed (open lists or tables of random numbers; open computer systems; drawing of non-opaque envelopes) and unclear (no information in report, and the authors either did not respond to requests for information or were unable to provide information).

Trials could only be defined as 'intention-to-treat' if participants were analysed according to the allocated treatment AND if all participants either completed allocated treatments or if missing outcome data were replaced using a recognised statistical method, e.g. last observation carried forward (LOCF).

For blinding we distinguished between trials in which the main outcome was measured by an assessor who was blind to treatment allocation (blind) and those in which the main outcome was measured either by the participants themselves (i.e. self report) or by a non-blinded assessor (not blind).

Measures of treatment effect

We undertook a narrative review of all studies and a meta-analysis of those studies with appropriate data. Where trials used a number of different tools to assess depression we included the main outcome measure only in the meta-analysis. The main outcome measure was defined using a hierarchy of criteria as follows: identified by the authors as the main outcome measure; outcome reported in the abstract; first outcome reported in the Results section.

For continuous data where different scales were used, the standardised mean difference (SMD) was calculated and reported with a 95% confidence interval (CI). For dichotomous data the risk ratio was calculated and reported with a 95% CI.

We interpreted the SMDs using the following 'rule of thumb': 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Schünemann 2008).

We pooled long-term follow-up data from those trials that reassessed participants long after the interventions had been completed. 'Long after' could mean an assessment at any period of time after the intervention had been completed.

Unit of analysis issues

Studies with multiple treatment groups

Where trials included a control arm, an exercise arm and an 'established treatment' arm (e.g. CBT, antidepressants), we extracted

data on control versus exercise, and exercise versus established treatment. This meant that data from the exercise arm were included in two separate comparisons, in separate univariate analyses.

Where trials compared an established treatment (e.g. CBT, antidepressants) versus exercise versus both the established treatment and exercise, we made two comparisons: (i) established treatment plus exercise versus established treatment alone, and included this in the meta-analysis of treatment versus control; (ii) exercise versus established treatment (e.g. CBT, antidepressants). This means that data from the 'established treatment alone' arm were used in two separate comparisons.

In the review versions in 2001 (Lawlor 2001), 2009 (Mead 2009) and 2012 (Rimer 2012), for trials which included more than one intensity of exercise, we used the exercise arm with the greatest clinical effect in the review. Similarly, when trials provided more than one type of exercise, we used the type of exercise with the greatest clinical effect. However, because this may overestimate the effect of exercise, we now use the exercise arm which provides the biggest 'dose' of exercise, and performed a sensitivity analysis to explore the effect of using the smallest 'dose'.

Cross-over trials

For cross-over trials, we intended to use the first phase of the trial only due to the potential 'carry-over' effect of exercise. To date, we have not included any cross-over trials.

Cluster-randomised trials

If cluster-randomised trials were identified and incorrectly analysed using individuals as the unit of analysis, we intended to make corrections using the intraclass correlation coefficient (ICC). If this had not been available, we would have imputed the ICC from similar studies. In fact, we did not find any cluster-RCTs to include.

Dealing with missing data

For two previous versions of this review (Lawlor 2001; Mead 2009) we found current contact details of all authors through correspondence addresses in study reports and by searching websites. We contacted all authors by email or post (sending three reminders to non-responders) to establish missing details in the methods and results sections of the written reports and to determine authors' knowledge of, or involvement in, any current work in the area. For the previous update (Rimer 2012) and this current update, we contacted authors only if there were missing data items, or if we needed more detail to decide on whether or not to include the study.

Some trials, in which participants dropped out, reported data from only the remaining participants, so we used these data in our meta-analyses. For trials which attempted to impute data from missing

participants (e.g. LOCF for continuous data) we used the imputed values and categorised the trial as 'intention-to-treat.' When we could not obtain information either from the publication or from the authors, we classified the trial as 'not intention-to-treat', and used the data from the available cases in the meta-analysis.

Assessment of heterogeneity

We used the Chi² test, together with the I² statistic, to assess heterogeneity.

A P value of 0.1 or less indicates significant heterogeneity when considering Chi². The ranges for I² are:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Note that the importance of the observed value of I² depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g. P value from the Chi² test, or a confidence interval for I²) ([Handbook 2011](#)).

Assessment of reporting biases

We used a funnel plot to explore reporting biases when 10 or more studies were included in the meta-analysis. However, other reasons such as heterogeneity and small study effects also cause asymmetrical funnel plots.

Data synthesis

We used a random-effects model based on DerSimonian and Laird's method to calculate the pooled effect size ([DerSimonian 1986](#)). We synthesised data from trials where outcome data were collected as soon as the intervention ended, and performed a separate synthesis of data collected weeks or months after the intervention ended, to explore whether any benefits were retained after the intervention had been completed. When performing meta-analyses of complex interventions, decisions need to be made about whether the interventions are sufficiently similar to be combined into a meta-analysis. We included trials that fulfilled the ACSM definition of exercise ([ACSM 2001](#)), and combined these data in a meta-analysis.

We created 'Summary of findings' tables for outcomes and graded them accordingly using the GRADE approach ([gradepro.org/aboutus.html](#)).

Subgroup analysis and investigation of heterogeneity

1. We explored the effect of different types of exercise (aerobic, resistance exercise or mixed aerobic and resistance) for those trials comparing exercise versus control on outcome, by performing subgroup analyses for the different types of exercise.

2. This update has for the first time explored the impact of intensity of exercise on outcome, dividing intensity into hard/vigorous or moderate, using ACSM criteria ([ACSM 1998](#)). The combination (where possible) of authors' description, compendium of physical activities classification and the ACSM intensity/metabolic equations (MET) cut-offs (in particular the most recent ones which take age into account) were used to categorise intensity (<https://sites.google.com/site/compendiumofphysicalactivities/Activity>).

3. This update has for the first time explored the effect of the number of exercise sessions, by extracting data on the length of the exercise programme and the frequency of exercise sessions. We categorised studies by the total number of sessions and then grouped the total number as 0 - 12, 13 - 24, 25 - 36, at least 37.

4. This update has for the first time explored how the diagnosis of depression at baseline (using a cut-point on a scale, or by psychiatric interview) influenced the effect of exercise on mood at the end of treatment.

Sensitivity analysis

We undertook sensitivity analyses to explore how much of the variation between studies comparing exercise to no exercise is explained by between-study differences in:

1. publication type (peer-reviewed journal, conference abstract/proceedings, doctoral dissertation).
2. allocation concealment.
3. intention-to-treat analysis (as defined above).
4. blinding.

We included only trials at low risk of bias for each of these outcomes in the sensitivity analysis. We then performed a sensitivity analysis, as we had done previously, including trials that were at low risk of bias for three key quality criteria: Allocation concealment, AND intention-to-treat AND blinding.

We also performed a sensitivity analysis using those trials that had several arms, for which we had included the arm with the biggest 'dose' of exercise in the initial analysis. Here we include the arm with the smallest 'dose'.

RESULTS

Description of studies

Results of the search

The results of searches for the previous updates have already been described in detail ([Lawlor 2001](#); [Mead 2009](#); [Rimer 2012](#)).

The 2012 review update ([Rimer 2012](#)) included studies identified from searches performed in 2010 and 2011. In 2010 ([Rimer](#)

2012), we had identified three ongoing trials (Blumenthal 2012a; McClure 2008; Underwood 2013). Of these, one has been included (Blumenthal 2012a) in this update. One of these was excluded because the intervention was not exercise alone (McClure 2008). The other was excluded because participants did not have to have depression to enter the trial (Underwood 2013); although the trialists reported results from the subgroup with depression at entry, we had previously excluded trials reporting our main outcomes as subgroup analyses. In June 2011, our search of the Cochrane Depression, Anxiety and Neurosis Group Clinical Trials Register (CCDANCTR) identified 45 citations; of which we retrieved full texts for 10 studies. Of these 10 full-text studies, we excluded five (Lolak 2008; Mailey 2010; Oeland 2010; Sneider 2008; Thomson 2010) and five studies (Annesi 2010; Ciocon 2003; Gary 2010; Shahidi 2011; Chalder 2012) were listed as 'awaiting classification' (Rimer 2012); in this current update, two of these have been included (Gary 2010; Shahidi 2011), one has been excluded because further scrutiny led us to conclude that the intervention did not fulfil the definition of 'exercise' (Ciocon 2003), one was excluded because it was a trial of advice to increase physical activity that did not fulfil the ACSM definition of exercise (Chalder 2012) and one was excluded because it was a subgroup analysis from a trial of people with obesity (Annesi 2010).

In September 2012, the searches of the CCDANCTR identified a further 290 citations. Of these, we retrieved full texts for 43 studies: 39 were excluded (Akandere 2011; Arcos-Carmona 2011; Attia 2012; Aylin 2009; Bowden 2012; Chalder 2012; Chan 2011; Chow 2012; Christensen 2012; Clegg 2011; Demiralp 2011; Deslandes 2010; Gutierrez 2012; Hedayati 2012; Immink 2011; Jacobsen 2012; Johansson 2011; Lavretsky 2011; Leibold 2010; Levendoglu 2004; Lvinger 2011; Littbrand 2011; Matthews 2011; Midtgaard 2011; Mudge 2008; O'Neil 2011; Ouzouni 2009; Penttinen 2011; Perna 2010; Piette 2011; Robledo Colonia 2012; Roshan 2011; Ruunsunen 2012; Schwarz 2012; Silveira 2010; Songoygard 2012; Trivedi 2011; Whitham 2011; Wipfli 2011); three were included (Hemat-Far 2012; Mota-Pereira 2011; Schuch 2011) and one trial is not yet complete (EFFORT D).

In March 2013, a search of the WHO Clinical Trials Registry Platform identified 188 citations. We sought full texts for 29; of these 29 studies, 23 are listed as ongoing

trials (ACTRN12605000475640; ACTRN12612000094875; ACTRN12612000094875; CTR/2012/09/002985; EFFORT D; IRCT201205159763; IRCT2012061910003N1; ISRCTN05673017; NCT00103415; NCT00643695; NCT00931814; NCT01024790; NCT01383811; NCT01401569; NCT01464463; NCT01573130; NCT01573728; NCT01619930; NCT01696201; NCT01763983; NCT01787201; NCT01805479; UMIN000001488). One trial has been completed and is included (Hoffman 2010). Four trials were excluded (Bromby 2010; Lever-van Milligen 2012; NCT00964054; NCT00416221) and one awaits assessment (DEMO II 2012)

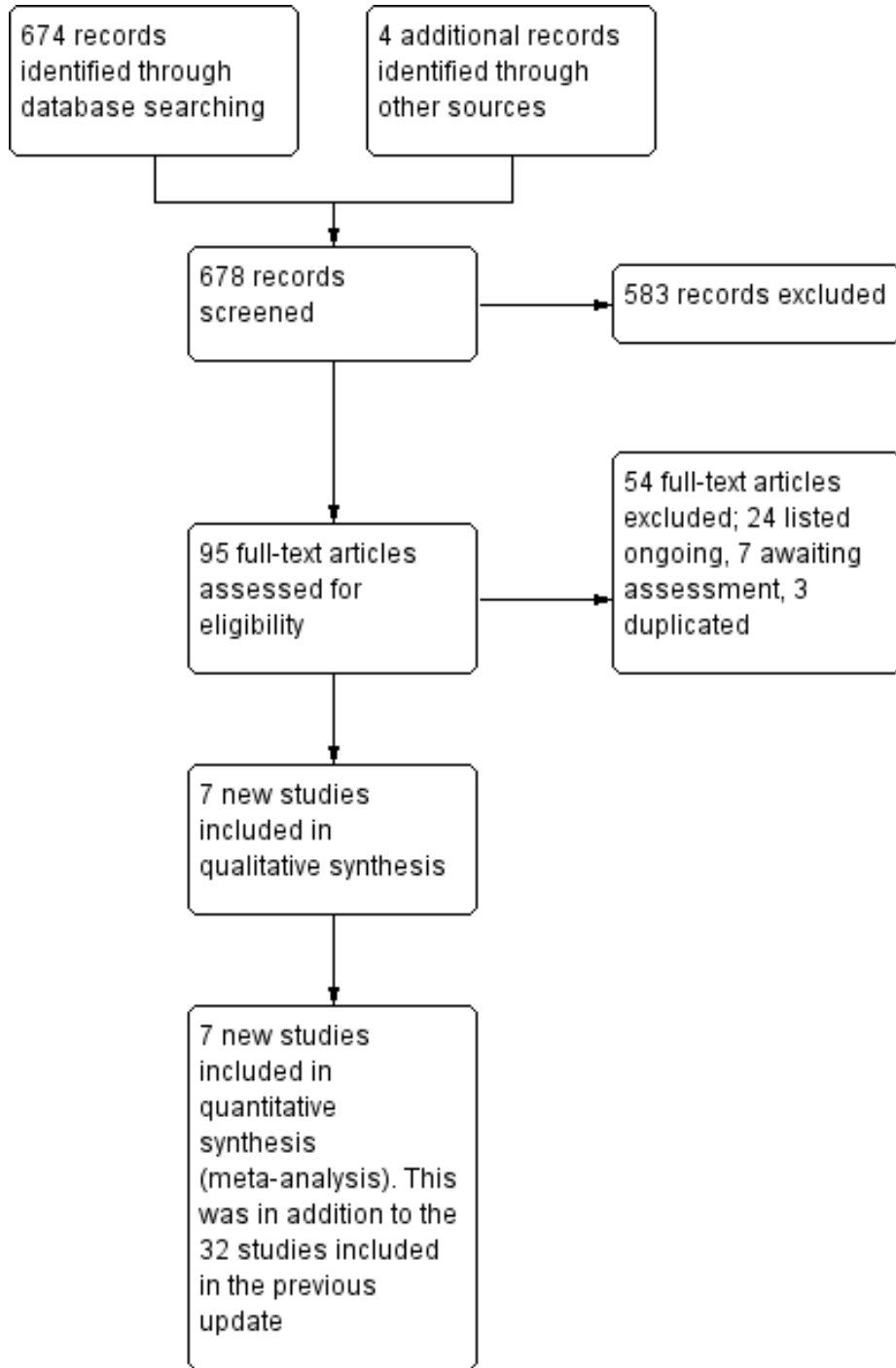
Through correspondence with the authors of one study (Blumenthal 2012a), another study by the same group was identified (Blumenthal 2012b); however this reported data from a subgroup with depression and was excluded (as we did for previous trials reporting subgroups).

The search of CCDANCTR up to 1st March 2013 identified 151 records (titles and abstracts). The Trials Search Co-ordinator excluded 89 obviously irrelevant citations. Of the remaining 62 studies, seven were already listed as included or excluded or awaiting assessment, one review author (GM) excluded 46 were excluded as they were obviously irrelevant, and the full text of nine articles were retrieved; one of these was a subsidiary publication for an included study (Hoffman 2010), one had already been excluded (Silveira 2010) and the other seven are listed as 'awaiting classification' (Aghakhani 2011; DEMO II 2012; Gotta 2012; Murphy 2012; Pinniger 2012; Sturm 2012; Martiny 2012).

For this current update, we are therefore including seven new studies (Hemat-Far 2012; Hoffman 2010; Gary 2010; Mota-Pereira 2011; Shahidi 2011; Schuch 2011; Blumenthal 2012a), making a total of 39 included studies (Characteristics of included studies table). For this update, we have excluded a further 54 studies (Characteristics of excluded studies table), giving a total of 175 excluded, listed 23 as ongoing studies (Characteristics of ongoing studies table), and listed seven as awaiting classification (Characteristics of studies awaiting classification table).

See the PRISMA flow diagram for details of the study selection process for this current update (Figure 1).

Figure 1. Study flow diagram, showing the results of the searches for this current update.



Included studies

In our previous update, we identified 32 completed trials.

For this update, we include seven additional trials, recruiting a total of 408 additional participants at randomisation. Of these, 374 participants remained in the trials by the time of outcome analysis (Blumenthal 2012a; Gary 2010; Hemat-Far 2012; Hoffman 2010; Mota-Pereira 2011; Shahidi 2011; Schuch 2011) (see *Characteristics of included studies* table).

Of the 39 included trials (recruiting 2326 people), 22 were from the USA (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Bonnet 2005; Brenes 2007; Chu 2008; Dunn 2005; Doyne 1987; Epstein 1986; Fetsch 1979; Fremont 1987; Gary 2010; Greist 1979; Hess-Homeier 1981; Hoffman 2010; Klein 1985; McCann 1984; Orth 1979; Reuter 1984; Setaro 1985; Singh 1997; Williams 2008); one was from Canada (McNeil 1991), three from the UK (Mather 2002; Mutrie 1988; Veale 1992), two from Australia (Sims 2009; Singh 2005), two from Iran (Hemat-Far 2012; Shahidi 2011), one from New Zealand (Foley 2008), one from Norway (Martinsen 1985), one from Denmark (Krogh 2009), one from Germany (Knubben 2007), one from Italy (Pilu 2007), one from Russia (Pinchasov 2000), one from Brazil (Schuch 2011), one from Portugal (Mota-Pereira 2011) and one from Thailand (Nabkasorn 2005).

Of these 39 trials, 30 were peer-reviewed papers (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Brenes 2007; Dunn 2005; Doyne 1987; Foley 2008; Fremont 1987; Gary 2010; Greist 1979; Hemat-Far 2012; Hoffman 2010; Klein 1985; Krogh 2009; Knubben 2007; Martinsen 1985; Mather 2002; McCann 1984; McNeil 1991; Mota-Pereira 2011; Nabkasorn 2005; Pilu 2007; Pinchasov 2000; Schuch 2011; Shahidi 2011; Sims 2009; Singh 1997; Singh 2005; Veale 1992; Williams 2008). Seven were doctoral dissertations (Bonnet 2005; Chu 2008; Epstein 1986; Fetsch 1979; Hess-Homeier 1981; Orth 1979; Setaro 1985) and two were published in abstract form only (Mutrie 1988; Reuter 1984). Of these 39 trials, data from two studies were unsuitable for statistical pooling because they were provided in graphical form only (McCann 1984) or provided no numerical data at all (Greist 1979). One trial (Nabkasorn 2005) provided data in graphical form only which we were able to include after manually converting the graph into mean and standard deviation (SD) values by drawing a horizontal line from the mean and SD on the graph to the vertical axis. Hence, we used data from 37 trials in the meta-analyses.

Five trials (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Krogh 2009; Mather 2002) provided data on whether participants fulfilled diagnostic criteria for depression at the end of the study, as well as depression scales. We used the scale results described in the paper rather than using formulae to convert the

dichotomous outcomes to continuous outcomes, to allow inclusion of these trials in the meta-analysis.

Five authors provided further data on their studies (Blumenthal 2012a; Gary 2010; Hoffman 2010; Mota-Pereira 2011; Sims 2009).

Design

All included studies were randomised controlled trials (RCTs); further details are provided in the *Characteristics of included studies* table. There were no cluster-RCTs that fulfilled our inclusion criteria.

Seventeen studies had two arms (Bonnet 2005; Fetsch 1979; Foley 2008; Knubben 2007; Hemat-Far 2012; Hoffman 2010; Martinsen 1985; Mather 2002; Mota-Pereira 2011; Nabkasorn 2005; Pilu 2007; Pinchasov 2000; Reuter 1984; Schuch 2011; Sims 2009; Singh 1997; Veale 1992), 17 had three arms (Blumenthal 1999; Blumenthal 2012a; Brenes 2007; Chu 2008; Doyne 1987; Epstein 1986; Fremont 1987; Greist 1979; Hess-Homeier 1981; Klein 1985; Krogh 2009; McCann 1984; McNeil 1991; Mutrie 1988; Shahidi 2011; Singh 2005; Williams 2008), three had four arms (Blumenthal 2007; Gary 2010; Orth 1979), one had five arms (four intensities of exercise and control; (Dunn 2005) and one had six arms (cognitive behavioural therapy (CBT) plus aerobic exercise, aerobic exercise only, CBT only, CBT plus non-aerobic exercise, non-aerobic exercise only or no intervention; Setaro 1985).

Of the 17 trials with two arms, exercise was compared with waiting list or usual care in eight trials (Hemat-Far 2012; Hoffman 2010; Mota-Pereira 2011; Nabkasorn 2005; Pilu 2007; Schuch 2011; Sims 2009; Veale 1992), exercise was compared with a placebo intervention (e.g. social activity) in four trials (Knubben 2007; Martinsen 1985; Mather 2002; Singh 1997), exercise was compared with CBT in one trial (Fetsch 1979), two trials compared CBT plus exercise versus CBT alone (Bonnet 2005; Reuter 1984), one trial compared exercise with stretching (Foley 2008) and one trial compared exercise with bright light therapy (Pinchasov 2000). Of the 17 trials with three arms, one trial compared exercise versus exercise plus sertraline versus sertraline (Blumenthal 1999), one compared exercise versus sertraline versus usual care (Brenes 2007), one compared exercise versus antidepressant (sertraline) versus placebo (Blumenthal 2012a), one compared exercise versus walking versus social conversation (Williams 2008) and three compared exercise versus waiting list versus a placebo intervention (e.g. social activity) (McCann 1984; McNeil 1991; Mutrie 1988). Two compared exercise versus usual care versus CBT (Epstein 1986; Hess-Homeier 1981), one compared exercise versus CBT versus both exercise and CBT (Fremont 1987), one compared exercise versus low-intensity CBT versus high-intensity CBT (Greist

1979), and one compared exercise versus a placebo versus CBT (Klein 1985). One trial compared high-intensity versus low-intensity aerobic exercise versus stretching (Chu 2008), one compared strength versus aerobic versus relaxation training (Krogh 2009), one compared high-intensity resistance training versus low-intensity resistance training versus usual care (Singh 2005), one compared exercise versus yoga versus control (Shahidi 2011) and one compared running versus weight-lifting versus waiting list (Doyne 1987).

Of the three trials with four arms, one compared exercise to three types of control (Orth 1979), one compared home-based exercise versus supervised exercise versus sertraline versus placebo (Blumenthal 2007), and one compared exercise versus combined exercise and CBT versus CBT alone versus usual care (Gary 2010).

Participants

Twenty-three trials recruited participants from non-clinical populations (Blumenthal 1999; Blumenthal 2007; Bonnet 2005; Brenes 2007; Dunn 2005; Doyne 1987; Epstein 1986; Fetsch 1979; Fremont 1987; Greist 1979; Hemat-Far 2012; Hess-Homeier 1981; Klein 1985; McCann 1984; McNeil 1991; Nabkasorn 2005; Orth 1979; Pinchasov 2000; Setaro 1985; Shahidi 2011; Singh 1997; Singh 2005; Williams 2008) with most involving recruitment of participants through the media.

Nine trials recruited participants from clinical populations, i.e. hospital inpatients or outpatients (Gary 2010; Knubben 2007; Martinsen 1985; Mota-Pereira 2011; ; Mutrie 1988; Pilu 2007; Reuter 1984; Schuch 2011; Veale 1992).

Seven trials recruited participants from both clinical and non-clinical populations (Blumenthal 2012a; Chu 2008; Foley 2008; Hoffman 2010; Krogh 2009; Mather 2002; Sims 2009).

Of the 23 trials recruiting people from non-clinical populations, diagnosis of depression was by a clinical interview in ten studies (Blumenthal 1999; Blumenthal 2007; Bonnet 2005; Doyne 1987; Dunn 2005; Hemat-Far 2012; Klein 1985; Pinchasov 2000; Singh 1997; Singh 2005). The other 13 studies used a cut-off point on one of several depression scales: Beck Depression Inventory: (Epstein 1986; Fremont 1987; Fetsch 1979; Hess-Homeier 1981; McCann 1984; McNeil 1991); Centre for Epidemiologic Studies Depression Scale (Nabkasorn 2005); Cornell Scale for Depression in Dementia (Williams 2008); Depression Adjective Checklist (Orth 1979); Minnesota Multiple Personality Inventory (Setaro 1985); Patient Health Questionnaire-9 (Brenes 2007); Geriatric Depression Scale (Shahidi 2011); or Symptom Checklist Score (Greist 1979).

There were more women than men (see [Characteristics of included studies](#) table) and mean age ranged from 22 years (Orth 1979) to 87.9 years (Williams 2008).

Interventions

Thirty-three trials provided aerobic exercise, of which 16 trials provided running (Blumenthal 1999; Blumenthal 2012a; Doyne 1987; Epstein 1986; Fetsch 1979; Fremont 1987; Greist 1979; Hess-Homeier 1981; Hemat-Far 2012; Klein 1985; McCann 1984; Nabkasorn 2005; Orth 1979; Reuter 1984; Shahidi 2011; Veale 1992), three provided treadmill walking (Blumenthal 2007; Bonnet 2005; Dunn 2005), four provided walking (Gary 2010; Knubben 2007; McNeil 1991; Mota-Pereira 2011), one provided aerobic training with an instructor (Martinsen 1985), one provided aerobic dance (Setaro 1985) and one provided cycling on a stationary bicycle (Pinchasov 2000).

Three studies provided aerobic exercises according to preference (Chu 2008; Hoffman 2010; Schuch 2011) and another provided mixed aerobic and resistance training (Brenes 2007). One study did not specify the type of aerobic exercise provided (Foley 2008). Two trials compared two different exercise interventions versus control: Krogh 2009 compared resistance training with combination aerobic exercises (including cycling, running, stepping and rowing) and Williams 2008 compared combination walking and strength training and walking alone.

Two trials provided mixed exercise, i.e. endurance, muscle strengthening and stretching (Mather 2002; Mutrie 1988), and four provided resistance training (Pilu 2007; Sims 2009; Singh 1997; Singh 2005).

Seventeen trials (Blumenthal 2007; Blumenthal 2012a; Bonnet 2005; Brenes 2007; Doyne 1987; Dunn 2005; Fremont 1987; Hoffman 2010; Knubben 2007; Mather 2002; McCann 1984; Mutrie 1988; Schuch 2011; Setaro 1985; Sims 2009; Singh 1997; Singh 2005) provided indoor exercise, two trials provided outdoor exercise (Gary 2010; McNeil 1991) and the remaining trials did not report whether the exercise was indoors or outdoors.

Only one trial stated that unsupervised exercise was provided (Orth 1979). Two trials included both supervised and home-based exercise arms (Blumenthal 2007; Chu 2008). The other trials provided supervised exercise or did not report this information.

Twelve trials provided individual exercises (Blumenthal 2007; Chu 2008; Doyne 1987; Dunn 2005; Greist 1979; Klein 1985; McNeil 1991; Mota-Pereira 2011; Mutrie 1988; Orth 1979; Schuch 2011; Williams 2008), 16 provided group exercises (Blumenthal 1999; Blumenthal 2012a; Brenes 2007; Fetsch 1979; Fremont 1987; Krogh 2009; Mather 2002; McCann 1984; Nabkasorn 2005; Pilu 2007; Setaro 1985; Shahidi 2011; Sims 2009; Singh 1997; Singh 2005; Veale 1992) and the remaining trials did not report this information.

The duration of the intervention ranged from 10 days (Knubben 2007) to 16 weeks (Blumenthal 1999; Blumenthal 2007). Two trials did not state duration: one performed assessments at the end of the intervention at eight months (Pilu 2007) and the other at time of discharge from hospital (Schuch 2011).

The 'control' groups of 'no treatment' or 'placebo' comprised heterogeneous interventions including social conversation, telephone conversations to discuss their general health and relaxation (avoid-

ing muscular contraction). For exercise versus control, there were different types of comparator arm (see [Analysis 5.5](#)). Two compared with a placebo; 17 with no treatment, waiting list, usual care or self management; six compared exercise plus treatment vs treatment; six compared exercise with stretching, meditation or relaxation; and four with 'occupational intervention', health education or casual conversation.

Outcomes

Depression measurement

Of the 39 trials, 12 reported Beck Depression Inventory (BDI) scores, and 13 reported Hamilton Rating Scale for Depression (HAM-D) scores. A variety of other scales were also used.

Other clinical endpoints and adverse effects

Several recorded clinical endpoints as well as mood: [Blumenthal 2012a](#), [Brenes 2007](#) and [Gary 2010](#) (physical functioning); [Chu 2008](#) (self efficacy), [Foley 2008](#) (self efficacy, episodic memory and cortisol awakening response), [Knubben 2007](#) (length of hospital stay), [Krogh 2009](#) (absence from work and effect on cognitive ability), [Mather 2002](#) (participant and clinical global impression), [Pilu 2007](#) and [Mota-Pereira 2011](#) (clinical global impression and global assessment of functioning), [Sims 2009](#) (quality of life, stroke impact scale, psychosocial health status and adverse events), [Singh 1997](#) (sickness impact profile), [Gary 2010](#), [Hoffman 2010](#), [Schuch 2011](#), [Singh 2005](#), [Pilu 2007](#) and [Brenes 2007](#) (quality of life), [Shahidi 2011](#) (Life satisfaction scale) and [Blumenthal 2012a](#) (cardiovascular biomarkers).

Seven trials systematically recorded and reported adverse events ([Blumenthal 2007](#); [Blumenthal 2012a](#); [Dunn 2005](#); [Knubben 2007](#); [Singh 1997](#); [Singh 2005](#); [Sims 2009](#)). No trial provided data on costs.

Timing of outcome measures

All our included trials reported mood as a continuous outcome at the end of treatment. Long-term follow-up data beyond the end of the interventions are described for eight trials (ranging from 4 months to 26 months). [Fremont 1987](#) (follow-up at four months), [Sims 2009](#) (follow-up at six months), [Klein 1985](#) (follow-up for nine months), [Blumenthal 1999](#) (follow-up at 10 months [Babyak 2000](#)), [Krogh 2009](#) (follow-up at 12 months), [Singh 1997](#) (follow-up at 26 months, reported in [Singh 2001](#)), [Mather 2002](#) (follow-up at 34 weeks) and [Gary 2010](#) (follow-up at six months). [Hoffman 2010](#) reported long-term follow-up but we were unable to include this in the meta-analysis due to the way it was reported. The author has been contacted for data.

Excluded studies

In this update, a further 54 studies were excluded following review of full text.

In this update, we decided not to list reviews as excluded studies. Additionally some references that were previously classified as excluded studies have been re-classified as additional reports of included studies. As a result there are now a total of 174 excluded studies.

One hundred and twenty-nine publications described randomised trials of exercise; the reasons for excluding these are listed in more detail below:

In 93 trials, participants did not have to have depression (as defined by the authors of the trial) to be eligible for the trial ([Abascal 2008](#); [Akandere 2011](#); [Arcos-Carmona 2011](#); [Asbury 2009](#); [Aylin 2009](#); [Badger 2007](#); [Baker 2006](#); [Berke 2007](#); [Blumenthal 2012b](#); [Bosch 2009](#); [Brittle 2009](#); [Burton 2009](#); [Carney 1987](#); [Chen 2009](#); [Christensen 2012](#); [Clegg 2011](#); [Courneya 2007](#); [Demiralp 2011](#); [Dalton 1980](#); [Eby 1985](#); [Elavsky 2007](#); [Ersek 2008](#); [Fox 2007](#); [Gary 2007](#); [Ghroubi 2009](#); [Gottlieb 2009](#); [Gusi 2008](#); [Gutierrez 2012](#); [Haffmans 2006](#); [Hannaford 1988](#); [Haugen 2007](#); [Hembree 2000](#); [Herrera 1994](#); [Hughes 1986](#); [Jacobsen 2012](#); [Johansson 2011](#); [Karlsson 2007](#); [Kerr 2008](#); [Kerse 2010](#); [Kim 2004](#); [Knapen 2006](#); [Kulcu 2007](#); [Kupecz 2001](#); [Lai 2006](#); [Latimer 2004](#); [Lautenschlager 2008](#); [Leppämäki 2002](#); [Levendoglu 2004](#); [Lever-van Milligen 2012](#); [Levinger 2011](#); [Lin 2007](#); [Littbrand 2011](#); [Lolak 2008](#); [Machado 2007](#); [Mailey 2010](#); [Martin 2009](#); [Matthews 2011](#); [Midtgaard 2011](#); [Morey 2003](#); [Motl 2004](#); [Mudge 2008](#); [Mutrie 2007](#); [Neidig 1998](#); [Neuberger 2007](#); [Nguyen 2001](#); [Oeland 2010](#); [Ouzouni 2009](#); [Pakkala 2008](#); [Penttinen 2011](#); [Perna 2010](#); [Rhodes 1980](#); [Robledo Colonia 2012](#); [Ruunsunen 2012](#); [Salminen 2005](#); [Sarsan 2006](#); [Sims 2006](#); [Smith 2008](#); [Songoygard 2012](#); [Stein 1992](#); [Stern 1983](#); [Strömbeck 2007](#); [Sung 2009](#); [Tapps 2009](#); [Thomson 2010](#); [Tomas-Carus 2008](#); [Tsang 2003](#); [Tenorio 1986](#); [Underwood 2013](#); [Weinstein 2007](#); [White 2007](#); [Wilbur 2009](#); [Wipfli 2008](#); [Wipfli 2011](#)).

Ten trials compared two types of exercise with no non-exercising control ([Bosscher 1993](#); [NCT00546221](#); [NCT01152086](#); [Legrand 2009](#); [Passmore 2006](#); [Sexton 1989](#); [TREAD 2003](#); [Trivedi 2011](#); [Wieman 1980](#); [Williams 1992](#)).

Three trials reported subgroup analyses of depressed patients, one from a randomised trial of exercise for osteoarthritis ([Penninx 2002](#)), one from a cohort of participants enrolled in cardiac rehabilitation following major cardiac events ([Milani 2007](#)) and one from a cluster-RCT of exercise in nursing homes ([Underwood 2013](#)).

Three trials included only a single bout of exercise ([Bartholomew 2005](#); [Bodin 2004](#); [Gustafsson 2009](#)) and one trial provided exercise for only four days ([Berlin 2003](#)).

Two trials that recruited women with postnatal depression were excluded ([Armstrong 2003](#); [Armstrong 2004](#)).

Five trials provided exercise interventions that did not fulfil the

ACSM definition of exercise (Tai-Chi (Chou 2004); Qigong (Tsang 2006; Chow 2012); and yoga (Oretzky 2006; Immink 2011) to waiting list controls.

Seven trials involving adolescents (Beffert 1993; Brown 1992; NCT00964054; Hughes 2009; MacMahon 1988; Rofey 2008; Roshan 2011) were excluded.

Two trials were excluded as they provided exercise counselling, not exercise (Vickers 2009; Chalder 2012).

Three trials were excluded as the intervention was multifaceted (McClure 2008; O'Neil 2011; Sneider 2008).

Ongoing studies

There are 23 ongoing studies (IRCT201205159763; NCT01805479; CTR/2012/09/002985; NCT01787201; NCT01619930; NCT01573130; NCT01573728; EFFORT D; NCT01464463; ACTRN12605000475640; UMIN000001488; NCT01763983; ACTRN12612000094875; NCT00103415; ACTRN12609000150246; NCT01696201; ISRCTN05673017; NCT01401569; IRCT2012061910003N1; NCT01024790; NCT01383811; NCT00643695; NCT00931814). One trial (EFFORT D) was identified from the September 2012 search of the CCDANCTR and the remaining 23 were identified from the March 2013 search of the WHO Clinical Trials Registry Platform.

Studies awaiting classification

This is a fast-moving field and our searches of CCDANCTR in March 2013 identified seven studies that are awaiting further assessment (Aghakhani 2011; DEMO II 2012; Martiny 2012; Murphy 2012; Pinniger 2012; Sturm 2012; Gotta 2012). Initial screening of these studies indicated three of these studies (Martiny 2012; Pinniger 2012; Sturm 2012) could be eligible for inclusion in this review. We plan to update the review, ideally within the year, to include the constantly growing number of relevant studies. See [Characteristics of studies awaiting classification](#) for full details.

New studies found for this update

We are including seven additional trials, recruiting a total of 408 participants at randomisation. Of these, 374 participants remained in the trials by the time of outcome analysis (Blumenthal 2012a; Hemat-Far 2012; Hoffman 2010; Gary 2010; Mota-Pereira 2011; Shahidi 2011; Schuch 2011). See [Characteristics of included studies](#).

Risk of bias in included studies

Sequence generation

We categorised 11 trials as being at low risk of bias, one as being at high risk of bias (Hemat-Far 2012), and the rest as being at unclear risk of bias. A graphical representation of the 'Risk of bias' assessment can be seen in [Figure 2](#) and [Figure 3](#). Please see the [Characteristics of included studies](#) for the full 'Risk of bias' assessment for each study.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

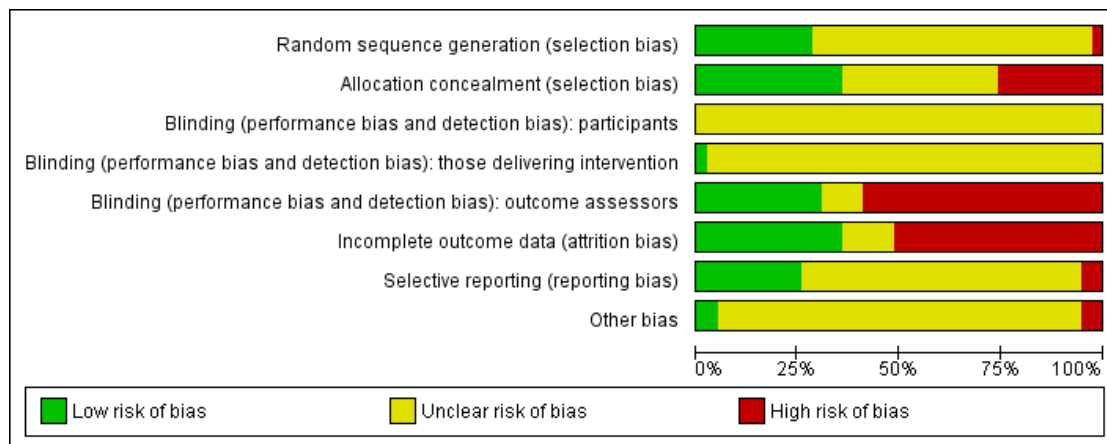


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): participants	Blinding (performance bias and detection bias): those delivering intervention	Blinding (performance bias and detection bias): outcome assessors	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blumenthal 1999	?	?	?	?	?	?	?	?
Blumenthal 2007	?	?	?	?	?	?	?	?
Blumenthal 2012a	?	?	?	?	?	?	?	?
Bonnet 2005	?	?	?	?	?	?	?	?
Brenes 2007	?	?	?	?	?	?	?	?
Chu 2008	?	?	?	?	?	?	?	?
Doyle 1987	?	?	?	?	?	?	?	?
Dunn 2005	?	?	?	?	?	?	?	?
Epstein 1986	?	?	?	?	?	?	?	?
Fetsch 1979	?	?	?	?	?	?	?	?
Foley 2008	?	?	?	?	?	?	?	?
Fremont 1987	?	?	?	?	?	?	?	?
Gary 2010	?	?	?	?	?	?	?	?
Greist 1979	?	?	?	?	?	?	?	?
Hemat-Far 2012	?	?	?	?	?	?	?	?
Hess-Homeier 1981	?	?	?	?	?	?	?	?
Hoffman 2010	?	?	?	?	?	?	?	?
Klein 1985	?	?	?	?	?	?	?	?
Knubben 2007	?	?	?	?	?	?	?	?
Krogh 2009	?	?	?	?	?	?	?	?
Martinsen 1985	?	?	?	?	?	?	?	?
Mather 2002	?	?	?	?	?	?	?	?
McCann 1984	?	?	?	?	?	?	?	?
McNeil 1991	?	?	?	?	?	?	?	?
Mota-Pereira 2011	?	?	?	?	?	?	?	?
Nutrie 1980	?	?	?	?	?	?	?	?
Nabkasorn 2005	?	?	?	?	?	?	?	?
Orth 1979	?	?	?	?	?	?	?	?
Pilu 2007	?	?	?	?	?	?	?	?
Pinchasov 2000	?	?	?	?	?	?	?	?
Reuter 1984	?	?	?	?	?	?	?	?
Schuch 2011	?	?	?	?	?	?	?	?
Setaro 1985	?	?	?	?	?	?	?	?
Shahidi 2011	?	?	?	?	?	?	?	?
Sims 2008	?	?	?	?	?	?	?	?
Singh 1997	?	?	?	?	?	?	?	?
Singh 2005	?	?	?	?	?	?	?	?
Veale 1992	?	?	?	?	?	?	?	?
Williams 2008	?	?	?	?	?	?	?	?

Allocation

Allocation concealment was adequate and therefore at low risk of bias in 14 trials (Blumenthal 2007; Blumenthal 2007; Blumenthal 2012a; Dunn 2005; Hoffman 2010; Knubben 2007; Krogh 2009; Martinsen 1985; Mather 2002; Sims 2009; Singh 1997; Singh 2005; Veale 1992; Williams 2008). For the remaining trials, the risk of bias was rated as unclear or high.

Blinding

Twelve trials included blinding of the outcome assessor so were rated as being at low risk of bias (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Brenes 2007; Dunn 2005; Gary 2010; Knubben 2007; Krogh 2009; Mather 2002; Mota-Pereira 2011; Singh 2005; Williams 2008). The rest were categorised as being at unclear or high risk because they used self-reported outcomes. In exercise trials, participants cannot be blind to the treatment allocation. We were uncertain what effect this would have on bias, so we classified all trials as being at 'unclear' risk of bias. Similarly, for those trials where supervised exercise was provided, the person delivering the intervention could not be blind, so we classified all trials as being at 'unclear' risk of bias (note that not all reported whether exercise was performed with or without supervision).

Incomplete outcome data

Fifteen trials performed 'intention-to-treat' (ITT) analyses (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Dunn 2005; Hemat-Far 2012; Hoffman 2010; Krogh 2009; Mather 2002; McNeil 1991; Mota-Pereira 2011; Mutrie 1988; Orth 1979; Pilu 2007; Singh 1997; Schuch 2011), i.e. complete outcome data were reported or, if there were missing outcome data, these were replaced using a recognised statistical method, e.g. last observation carried forward, and participants remained in the group to which they had been allocated. One trial reported data for individual participants (Orth 1979), so by using last observation carried forward we replaced data from the participants who did not complete the trial and included these data in the meta-analysis of ITT trials. One trial reported that the analysis was ITT, because it used a 'worse-case' scenario assumption to replace data from participants who did not complete the trial, but only included 38 of the 39

randomised participants in the analyses, so we classified it as 'not ITT' (Knubben 2007). The remaining studies were classified as being at unclear or high risk of bias. Most trials did not report data from participants who dropped out.

Selective reporting

We attempted to identify whether a protocol was available by screening the reference list of the publications. We identified protocols for three trials and checked that all prespecified outcome events were reported, and rated these as being at low risk of bias (Blumenthal 2012a; Dunn 2005; Krogh 2009). We categorised four others trials (Hemat-Far 2012; Hoffman 2010; Mota-Pereira 2011; Shahidi 2011) as being at low risk of bias as we judged that there was sufficient information in the methods to be sure that the trials had reported all their planned outcomes.

Other potential sources of bias

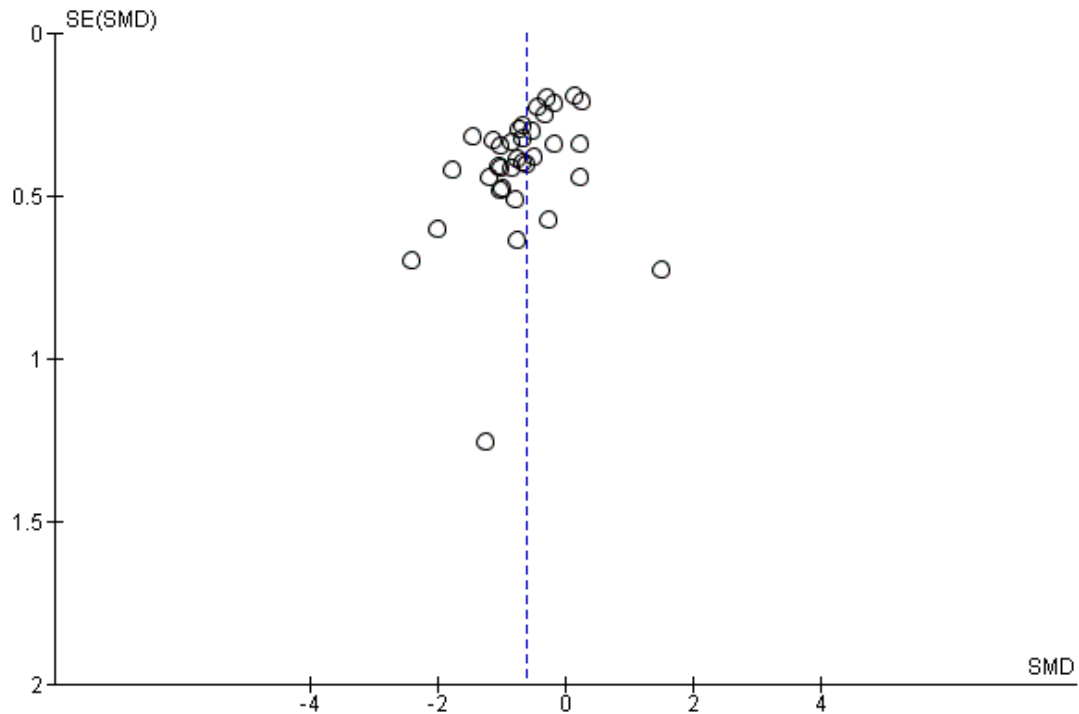
On the basis of the first 50 participants, one study (Krogh 2009) changed their sample size calculation based on the observed standard deviation (they had initially calculated they needed a minimum of 186 participants (SD = 6), but for the first 50 participants the SD was 3.9 so they adjusted their sample size calculation to 135 participants). Hemat-Far 2012 told the control group to reduce their activity.

We decided to include data on continuous depression scores in our meta-analysis, rather than depression measured as a dichotomous outcome. This is because we knew from previous updates that very few trials had reported depression as a dichotomous outcome, and we wished to include as many trials as possible in our meta-analysis. For future updates, we will consider whether to perform a separate meta-analysis for trials that measured depression as a dichotomous outcome.

Publication bias

Visually our funnel plot appeared to be asymmetrical. There is evidence of bias (Begg P value = 0.02, Egger P value = 0.002) (funnel plot for Analysis 1.1, exercise versus control, Figure 4) that might be due to publication bias, to outcome reporting bias or to heterogeneity.

Figure 4. Funnel plot of comparison: I Exercise versus control, outcome: I.1 Reduction in depression symptoms post-treatment.



Effects of interventions

See: [Summary of findings for the main comparison](#) Exercise compared to control for adults with depression; [Summary of findings 2](#) Exercise compared to psychological treatments for adults with depression; [Summary of findings 3](#) Exercise compared to bright light therapy for adults with depression; [Summary of findings 4](#) Exercise compared to pharmacological treatments for adults with depression

We included 37 trials in our meta-analyses. The remaining two trials could not be included for the reasons stated above ([Greist 1979](#); [McCann 1984](#)).

Comparison I: Exercise versus 'control'

Thirty-five trials (1356 participants) included a comparison of exercise with a 'control' intervention.

Primary outcome measure

1.1 Reduction in depression symptom severity

Post-treatment

The pooled standardised mean difference (SMD), for the 35 trials, calculated using the random-effects model was -0.62 (95% confidence interval (CI) -0.81 to -0.42) ([Analysis 1.1](#)), indicating a moderate clinical effect in favour of exercise. There was substantial heterogeneity ($I^2 = 63\%$).

End of long-term follow-up

The pooled SMD from the eight trials ([Blumenthal 1999](#); [Fremont 1987](#); [Gary 2010](#); [Klein 1985](#); [Krogh 2009](#); [Mather 2002](#); [Sims 2009](#); [Singh 1997](#)) (377 participants) that provided long-term follow-up data found only a small effect in favour of exercise (SMD -0.33, 95% CI -0.63 to -0.03) ([Analysis 1.2](#)). The long-term follow-up data from [Blumenthal 1999](#) were reported in a separate publication ([Babyak 2000](#)), and from [Singh 1997](#) in a separate publication ([Singh 2001](#)). There was moderate statistical heterogeneity ($I^2 = 49\%$). Follow-up data from [Blumenthal 2007](#) have been reported according to the proportion who had fully or partially remitted from depression, but continuous mood scores were

not reported so we could not include these data in the meta-analysis.

Secondary outcome measures

1.2a Acceptability of treatment: attendance at exercise

Fourteen trials reported attendance rates for exercise; these were 50.6% for aerobic and 56.2% for strength arm (Krogh 2009), 59% (Mather 2002), 70% (Doynes 1987), 72% (Dunn 2005), 78% (Nabkasorn 2005), 82% (Gary 2010), 91% (Mota-Pereira 2011) 92% (Blumenthal 1999; Blumenthal 2007), 93% (Singh 1997), 94% (Blumenthal 2012a), 97.3% for high-intensity and 99.1% for low-intensity (Chu 2008) and 95% to 100% (Singh 2005). One trial reported the mean number of exercise sessions attended as 5.88 (Hoffman 2010). One trial rescheduled missed visits (McNeil 1991) so participants attended the full course of exercise. As with intensity of exercise, it is difficult to attribute any differences in outcome to differences in attendance rates, because there were other sources of variation in the type of interventions (e.g. duration of intervention, type of exercise) and differences in the methodological quality between trials which might account for differences in outcome.

1.2b Acceptability of treatment: completing the intervention or control

We extracted data on the number randomised and completing each trial (see Table 1). This ranged from 100% completion (Hemat-Far 2012; Mather 2002; McNeil 1991; Mutrie 1988; Pilu 2007; Singh 1997; Schuch 2011) to 42% completion (Doynes 1987). For the exercise intervention, this ranged from 100% completion (Gary 2010; Hemat-Far 2012; Mather 2002; McNeil 1991; Mutrie 1988; Pilu 2007; Singh 1997; Schuch 2011) to 55% completion (Klein 1985).

Twenty-nine studies (1363 participants) reported how many completed the exercise and control arms (Analysis 1.3). The risk ratio (RR) was 1.00 (95% CI 0.97 to 1.04).

1.3. Quality of life

Five trials reported quality of life at the end of treatment (Gary 2010; Hoffman 2010; Schuch 2011; Singh 2005; Pilu 2007). One author provided data regarding the different domains (Gary 2010). One trial reported quality of life at baseline but not at follow-up (Sims 2009).

There were no statistically significant differences for the mental (SMD -0.24; 95% CI -0.76 to 0.29), psychological (SMD 0.28; 95% CI -0.29 to 0.86) and social domains (SMD 0.19; 95% CI -0.35 to 0.74) (Analysis 1.4). Two studies reported a statistically significant difference for the environment domain favouring exercise (SMD 0.62; 95% CI 0.06 to 1.18) and four studies reported a

statistically significant difference for the physical domain favouring exercise (SMD 0.45; 95% CI 0.06 to 0.83).

1.4 Cost

No trial reported costs.

1.5 Adverse events

Seven trials reported no difference in adverse events between the exercise and usual care groups (Blumenthal 2007; Blumenthal 2012a; Dunn 2005; Knubben 2007; Singh 1997; Singh 2005; Sims 2009). Dunn 2005 reported increased severity of depressive symptoms (n = 1), chest pain (n = 1) and joint pain/swelling (n = 1); all these participants discontinued exercise. Singh 1997 reported that one exerciser was referred to her psychologist at six weeks due to increasing suicidality; and musculoskeletal symptoms in two participants required adjustment of training regime. Singh 2005 reported adverse events in detail (visits to a health professional, minor illness, muscular pain, chest pain, injuries requiring training adjustment, falls, deaths and hospital days) and found no difference between the groups. Knubben 2007 reported “no negative effects of exercise (muscle pain, tightness or fatigue)”; after the training had finished, one person in the placebo group required gastric lavage and one person in the exercise group inflicted a superficial cut in her arm. Sims 2009 reported no adverse events or falls in either the exercise or control groups. Blumenthal 2007 reported more side effects in the sertraline group (see comparison below) but there was no difference between the exercise and control group. Blumenthal 2012a reported more fatigue and sexual dysfunction in the sertraline group than in the exercise group. Because of the diversity of different adverse events reported, we decided not to do a meta-analysis of these data.

Comparison 2: Exercise versus psychological therapies

Primary outcome

2.1 Reduction in depression symptom severity

Post-treatment

Seven trials (189 participants) provided data comparing exercise with psychological therapies; the SMD was -0.03 (95% CI -0.32 to 0.26) (Analysis 2.1) indicating no significant difference between the two interventions. No statistical heterogeneity was indicated.

End of long-term follow-up

There were insufficient data available for long-term follow-up.

Secondary outcomes

2.2a Acceptability of treatment: attendance at exercise sessions

One trial reported adherence scores that were calculated based on the number of sessions attended of those prescribed. This trial reported that the adherence rates were 82% for exercise and 72% for CBT (Gary 2010).

2.2b Acceptability of treatment: completing the intervention or psychological therapies

For staying in the trial, there were data from four trials (172 participants) (Analysis 2.2). The risk ratio was 1.08 (95% CI 0.95 to 1.24).

2.3. Quality of life

One trial reported changes in the Minnesota Living with Heart Failure Questionnaire, a quality of life measure (Gary 2010). There was no statistically significant difference for the physical domain (MD 0.15; 95% CI: -7.40 to 7.70) or the mental domain (MD -0.09; 95% CI: -9.51 to 9.33) (Analysis 2.3).

2.4 Cost

No trial reported costs.

2.5 Adverse events

No data available.

Comparison 3: Exercise versus alternative treatments

Primary outcome

3.1 Reduction in depression symptom severity

Post-treatment

One trial found that exercise was superior to bright light therapy in reducing depression symptoms (Pinchasov 2000) (MD -6.40, 95% CI -10.20 to -2.60) (Analysis 3.1).

End of long-term follow-up

There were no data with regard to long-term follow-up.

Secondary outcomes

This trial did not report on any of the following outcomes.

3.2a Acceptability of treatment: attendance at exercise

3.2b Acceptability of treatment: completing the intervention or control

3.3. Quality of life

3.4 Cost

3.5 Adverse events

Comparison 4: Exercise versus pharmacological treatments

Primary outcome

4.1 Reduction in depression symptom severity

Post-treatment

For the four trials (298 participants) that compared exercise with pharmacological treatments (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Brenes 2007) the SMD was -0.11 (95% CI -0.34 to 0.12) (Analysis 4.1), indicating no significant difference between the two interventions. No statistical heterogeneity was indicated.

End of long-term follow-up

There were insufficient data available for long-term follow-up.

Secondary outcomes

4.2a Acceptability of treatment: attendance at exercise

Blumenthal 1999 reported that of those allocated exercise alone, the median number of sessions attended was 89.6%. Of those allocated medication, no participant deviated by more than 5% from the prescribed dose.

4.2b Acceptability of treatment: completing the intervention or pharmacological intervention

For remaining in the trial, there were data from three trials (278 participants). The risk ratio was 0.98 (95% CI 0.86 to 1.12) (Analysis 4.2).

4.3. Quality of life

One trial Brenes 2007 reported no difference in change in SF-36 mental health and physical health components between medication and exercise groups (Analysis 4.3).

4.4 Cost

No trial reported costs.

4.5 Adverse events

Blumenthal 1999 reported that 3/53 in the exercise group suffered musculoskeletal injuries; injuries in the medication group were not reported.

Blumenthal 2007 collected data on side effects by asking participants to rate a 36-item somatic symptom checklist and reported that "a few patients reported worsening of symptoms"; of the 36 side effects assessed, only one showed a statistically significant group difference ($P = 0.03$), i.e. that the sertraline group reported worse post-treatment diarrhoea and loose stools.

Blumenthal 2012a assessed 36 side effects; only two showed a significant group difference: 20% of participants receiving sertraline reported worse post-treatment fatigue compared with 2.4% in the exercise group and 26% reported increased sexual problems compared with 2.4% in the exercise group.

Subgroup analyses

Type of exercise

We explored the influence of the type of exercise (aerobic, mixed or resistance) on outcomes for those trials comparing exercise versus control (Analysis 5.1). The SMD for aerobic exercise indicated a moderate clinical effect (SMD -0.55, 95% CI -0.77 to -0.34), whilst the SMDs for both mixed exercise (SMD -0.85, 95% CI -

1.85 to 0.15) and resistance exercise (SMD -1.03, 95% CI -1.52 to -0.53) indicated large effect sizes, but with wide confidence intervals.

Intensity of exercise

We explored the influence of intensity (light/moderate, moderate, moderate/hard, hard, moderate/vigorous, vigorous) on the reduction of depression for those trials comparing exercise versus control (Analysis 5.2). The SMD for moderate/vigorous intensity (SMD -0.38, 95% CI -1.61 to 0.85) indicated a small effect size, whilst for moderate (SMD -0.64, 95% CI -1.01 to -0.28), moderate/hard (SMD -0.63, 95% CI -1.13 to -0.13) and hard intensity (SMD -0.56, 95% CI -0.93 to -0.20) there was a moderate clinical effect. A large effect size was indicated for vigorous intensity (SMD -0.77, 95% CI -1.30 to -0.24) and light/moderate intensity (SMD -0.83, 95% CI -1.32 to -0.34).

Duration and frequency of exercise

We explored the influence of the total number of prescribed exercise sessions (0 - 12, 13 - 24, 25 - 36, 37+ sessions) on the reduction of depression for those trials comparing exercise versus control (Analysis 5.3). A moderate effect size was observed for 0 - 12 sessions (SMD -0.42, 95% CI -1.26 to 0.43), and 37+ sessions (SMD -0.46, 95% CI -0.69 to -0.23). A large effect size was observed for 13 - 24 sessions (SMD -0.70, 95% CI -1.09 to -0.31) and 25 - 36 sessions (SMD -0.80, 95% CI -1.30 to -0.29).

Type of diagnosis

We performed subgroup analyses according to how the diagnosis of depression was made (cut-point on a scale, or clinical interview and proper psychiatric diagnosis) (Analysis 5.4). There was a moderate effect size for clinical diagnosis of depression (SMD -0.57, 95% CI -0.81 to -0.32) and a cut-point on a scale (SMD -0.67, 95% CI -0.95 to -0.39).

Type of control

We categorised controls as a) placebo; b) no treatment (including waiting list); c) exercise plus treatment versus treatment alone; d) stretching, meditation or relaxation; e) 'occupational', including education, occupational therapy. These categorisations were made by one author (KD) on the basis of data extracted at the initial stage of data extraction, and were checked by a second author (GM) (Analysis 5.5). The largest effect size was when exercise was compared with 'occupational' (SMD -3.67, 95% CI -4.94 to -2.41), and there was no statistically significant effect of exercise when it was compared with 'stretching, meditation or relaxation' (SMD -0.09 (95% CI -0.65 to 0.48).

We considered whether to perform additional subgroup analyses according to supervised versus unsupervised, indoor versus outdoor and individual versus group, and according to the type of control group (in the no-treatment comparison) but we wanted to focus on the main subgroups of interest. Multiple subgroup analyses are generally considered inadvisable.

Sensitivity analyses

We conducted sensitivity analyses for the first comparison of exercise versus control to explore the impact of study quality on effect sizes. We have commented on how these sensitivity analyses influence pooled SMD, compared with the pooled SMD for the 35 trials comparing exercise with control (-0.62 (95% CI) -0.81 to -0.42) (Analysis 1.1).

Peer-reviewed journal publications

For the 34 trials (1335 participants) that were reported in peer-reviewed journal publications or doctoral theses, the SMD was -0.59 (95% CI -0.78 to -0.40) (Analysis 6.1), showing a moderate clinical effect in favour of exercise, which is similar to the pooled SMD for all 35 trials.

Published as abstracts/conference proceedings only

The pooled SMD for the one study published as conference abstracts only was -2.00 (95% CI -3.19 to -0.82) (Analysis 6.2), showing a large effect size in favour of exercise i.e. larger than the pooled SMD for all 35 trials.

Allocation concealment

For the 14 trials (829 participants) with adequate allocation concealment and therefore at low risk of bias, the SMD was -0.49 (95% CI -0.75 to -0.24) (Analysis 6.3), showing a moderate clinical effect in favour of exercise, similar to the pooled SMD for all 35 trials.

Use of intention-to-treat analysis

For the 11 trials (567 participants) with intention-to-treat analyses, the SMD was -0.61 (95% CI -1.00 to -0.22) (Analysis 6.4), showing a moderate clinical effect in favour of exercise, similar to the pooled SMD for all 35 trials.

Blinded outcome assessment

For the 12 trials (658 participants) with blinded outcome assessments and therefore at low risk of bias, the SMD was -0.36 (95% CI -0.60 to -0.12) (Analysis 6.5), showing a small clinical effect in favour of exercise, which is smaller than the pooled SMD for all 35 trials.

Allocation concealment and intention-to-treat analysis and blinded outcome assessment

For the six trials (Blumenthal 1999; Blumenthal 2007; Blumenthal 2012a; Dunn 2005; Krogh 2009; Mather 2002) (464 participants) with adequate allocation concealment and intention-to-treat analyses and blinded outcome assessment and therefore at low risk of bias, the SMD was -0.18 (95% CI -0.47 to 0.11) (Analysis 6.6), i.e. there was a small clinical effect in favour of exercise, which did not reach statistical significance. This is smaller than the pooled SMD for all 35 trials.

Sensitivity analyses: including the arm with the smallest dose of exercise for those trials for which we used the arm with the largest dose of exercise in comparison 1

We included the arm with the smallest dose of exercise for 10 trials (Blumenthal 2007; Chu 2008; Doyne 1987; Dunn 2005; Krogh 2009; Mutrie 1988; Orth 1979; Setaro 1985; Singh 2005; Williams 2008) for which we had used the arm with the largest clinical effect in comparison 1 (Analysis 1.1). The SMD was -0.44 (95% CI -0.55 to -0.33) (Analysis 6.7), showing a moderate clinical effect in favour of exercise. This is similar to the pooled SMD for all 35 trials.

Recruitment and retention of participants

Table 1 presents data about the feasibility of recruiting and retaining participants both in the trial as a whole and in the exercise intervention in particular. We extracted data, when available, about the number of participants who were considered for inclusion in each trial, although this information was not available for all trials. The trials that did provide these data used different recruitment techniques (ranging from screening of people responding to advertisements to inclusion of those patients who were considered eligible by a referring doctor).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Exercise compared to cognitive therapy for adults with depression					
Patient or population: adults with depression Settings: Intervention: Exercise Comparison: cognitive therapy					
Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Cognitive therapy	Exercise			
Symptoms of depression		The mean symptoms of depression in the intervention groups was 0.03 standard deviations lower (0.32 lower to 0.26 higher)	189 (7 studies)	⊕⊕⊕○ moderate ^{1,2,3}	SMD -0.03 (95% CI: -0.32 to 0.26)
Acceptability of treatment	Study population		172 (4 studies)	⊕⊕⊕○ moderate ¹	RR 1.08 (95% CI: 0.95 to 1.24)
		766 per 1000			
Quality of Life		The mean quality of life in the intervention groups was 0 higher (0 to 0 higher)	0 (1 study)	⊕⊕⊕○ moderate ¹	One trial reported changes in the Minnesota Living with Heart Failure Questionnaire, a quality of life measure (Gary 2010). There was no statistically significant difference for the physical domain (MD 0.15; 95% CI: -7.40 to 7.70) or the mental domain (MD -0.09;

95% CI: -9.51 to 9.33)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 Lack of blinding of outcome assessors probably increased effect sizes and drop-out rates were high. Also sequence generation was considered unclear in 7 studies.

2 $I^2 = 0\%$ and $P = 0.62$, indicated no heterogeneity

3 The studies included were all relevant to the review question, particularly given that all studies had to meet the criteria of the ACSM definition of exercise.

Exercise compared to bright light therapy for adults with depression					
Patient or population: adults with depression Settings: Intervention: Exercise Comparison: bright light therapy					
Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Bright light therapy	Exercise			
Symptoms of depression		The mean symptoms of depression in the intervention groups was 6.4 lower (10.2 to 2.6 lower)	18 (1 study)	⊕○○○ very low ^{1,2,3}	MD -6.40 (95% CI: -10.20 to -2.60). Although this trial suggests a benefit of exercise, it is too small to draw firm conclusions

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- 1 Lack of blinding of outcome assessors probably increased effect sizes and drop-out rates were not reported. Also sequence generation and concealment was considered unclear.
- 2 The study included was relevant to the review question, particularly given that all studies had to meet the criteria of the ACSM definition of exercise.
- 3 Based on 18 people

Exercise compared to antidepressants for adults with depression					
Patient or population: adults with depression Settings: Intervention: Exercise Comparison: antidepressants					
Outcomes	Illustrative comparative risks* (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Antidepressants	Exercise			
Symptoms of depression		The mean symptoms of depression in the intervention groups was 0.11 standard deviations lower (0.34 lower to 0.12 higher)	300 (4 studies)	⊕⊕⊕○ moderate ^{1,2,3}	SMD -0.11 (95% CI: -0.34 to 0.12)
Acceptability of treatment	Study population		278 (3 studies)	⊕⊕⊕○ moderate ¹	RR 0.98 (95% CI: 0.86 to 1.12)
		891 per 1000			
Quality of life		The mean quality of life in the intervention groups was 0 higher (0 to 0 higher)	0 (1 study)	⊕⊕⊕○ moderate ¹	One trial, Brenes 2007 , reported no difference in change in SF-36 mental health and physical health components between medication and exercise groups

<p>Adverse events</p>	<p>See comment</p>	<p>See comment</p>	<p>0 (3 studies)</p>	<p>⊕⊕⊕○ moderate¹</p>	<p>Blumenthal 1999 reported that 3/53 in exercise group suffered musculoskeletal injuries; injuries in the medication group were not reported Blumenthal 2007 collected data on side effects by asking participants to rate a 36-item somatic symptom checklist and reported that ‘ ‘ a few patients reported worsening of symptoms’; of the 36 side effects assessed, only 1 showed a statistically significant group difference (P = 0.03), i.e. that the sertraline group reported worse post-treatment diarrhoea and loose stools Blumenthal 2012a assessed 36 side effects; only 2 showed a significant group difference: 20% of participants receiving sertraline reported worse post-treatment fatigue compared with 2.4% in the exercise group and 26% reported increased sexual problems compared with 2.4% in the exercise group</p>
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Lack of blinding of outcome assessors probably increased effect sizes and drop-out rates were high. Also sequence generation was considered unclear in 1 study.

² $I^2 = 0\%$ and $P = 0.52$, indicated no heterogeneity

³ The studies included were all relevant to the review question, particularly given that all studies had to meet the criteria of the ACSM definition of exercise.

DISCUSSION

Summary of main results

This updated review includes seven additional trials (384 additional participants); conclusions are similar to our previous review (Rimer 2012). The pooled standardised mean difference (SMD), for depression (measured by continuous variable), at the end of treatment, represented a moderate clinical effect. The 'Summary of findings' table suggests that the quality of the evidence is moderate.

There was some variation between studies with respect to attendance rates for exercise as an intervention, suggesting that there may be factors that influence acceptability of exercise among participants.

There was no difference between exercise and psychological therapy or pharmacological treatment on the primary outcome. There are too few data to draw conclusions about the effect of exercise on our secondary outcomes, including risk of harm.

Uncertainties

Uncertainties remain regarding how effective exercise is for improving mood in people with depression, primarily due to methodological shortcomings (please see below). Furthermore, if exercise does improve mood in people with depression, we cannot determine the optimum type, frequency and duration of exercise, whether it should be performed supervised or unsupervised, indoors or outdoors, or in a group or alone. There was, however, a suggestion that more sessions have a larger effect on mood than a smaller number of sessions, and that resistance and mixed training were more effective than aerobic training. Adverse events in those allocated to exercise were uncommon, but only a small number of trials reported this outcome. Ideally both the risks and benefits of exercise for depression should be evaluated in future trials. There were no data on costs, so we cannot comment on the cost-effectiveness of exercise for depression. The type of control intervention may influence effect sizes. There was a paucity of data comparing exercise with psychological and pharmacological treatments; the available evidence suggests that exercise is no more effective than either psychological or pharmacological treatments.

Overall completeness and applicability of evidence

For this current update, we searched the CCDAN Group's trial register in September 2012, which is an up-to-date and comprehensive source of trials. We also searched the WHO trials portal in March 2013 in order to identify new ongoing trials. We scrutinised reference lists of the new trials identified. Ideally, we would have performed citation reference searches of all included

studies, but with the large number of trials now in this review, this was no longer practical. Thus, it is possible that we may have missed some relevant trials. We updated our search of the CCDAN trials register up to 1st March 2013 and identified several studies that may need to be included in our next update. It is notable that in a seven-month period (September 2012 to March 2013), several more potentially eligible completed trials have been published ([Characteristics of studies awaiting classification](#)). This demonstrates that exercise for depression is a topic of considerable interest to researchers, and that further updates of this review will be needed, ideally once a year, to ensure that the review is kept as up-to-date as possible.

The results of this review are applicable to adults classified by the trialists as having depression (either by a cut-off score on a depression scale or by having a clinical diagnosis of depression) who were willing to participate in a programme of regular physical exercise, fulfilling the American College of Sports Medicine (ACSM) definition of exercise, within the context of a randomised controlled clinical trial. The trials we included are relevant to the review question. It is possible that only the most motivated of individuals were included in this type of research.

The data we extracted on aspects of feasibility (see [Table 1](#)) suggest that a large number of people need to be screened to identify suitable participants, unless recruiting from a clinical population, e.g. inpatients with depression. Note, though, that there was a wide range in the proportion of those screened who were subsequently randomised; this may be a function of the sampling frame (which may include a range of specifically screened or non-screened potential participants), and interest in being a research participant at a time of low mood, as much as whether potential participants are interested in exercise as a therapy. A substantial number of people dropped out from both the exercise and control programmes, and even those who remained in the trial until the outcome assessments were not able to attend all exercise sessions. We did not include trials in which advice was given to increase activity. Thus, we excluded a large, high-quality trial ($n = 361$) in which people with depression in primary care were randomised to usual care or to usual care plus advice from a physical activity facilitator to increase activity ([Chalder 2012](#)), which showed no effect of the intervention on mood.

We had previously decided to exclude trials which included people both with and without depression, even if they reported data from a subgroup with depression. Thus, for this update, we excluded a large, high-quality, cluster-randomised trial recruiting 891 residents from 78 nursing homes ([Underwood 2013](#)), of whom 375 had baseline Geriatric Depression Scores suggesting depression. At the end of the treatment, there was no difference between the intervention and control group, for people both with and without depression at baseline. For future updates, we will include data from trials that reported subgroups with depression.

If this review had had broader inclusion criteria in relation to the type of intervention, we would have included additional studies,

e.g. trials which provide advice to increase activity (e.g. Chalder 2012) and trials of other types of physical activity interventions that do not fulfil the ACSM definition for exercise (e.g. Tai Chi or Qigong, where mental processes are practiced alongside physical activity and may exert an additional or synergistic effect). Arguably, the review could be broader, but we have elected to keep it more focused, partly to ensure that it remains feasible to update the review on a regular basis, with the resources we have available. The original review questions were conceived more than 10 years ago (Lawlor 2001), and although they are still relevant today, it would be of value to broaden the research questions to include evidence for other modes of physical activity. This could be through a series of related Cochrane reviews. There are already separate reviews of Tai Chi for depression, and we suggest that a review of advice to increase physical activity would be of value.

This review did not attempt to take into account the effects of exercise when the experience is pleasurable and self-determined, though this would have been difficult as such data were not reported in the trials.

There were more women than men in the studies that we included, and there was a wide range in mean ages. We cannot currently make any new recommendations for the effectiveness of exercise referral schemes for depression (DOH 2001; Pavey 2011; Sorensen 2006). One study of the Welsh exercise referral scheme is 'awaiting assessment'. Nor can we be certain about the effect of exercise on other relevant outcomes e.g. quality of life, adverse events or its cost-effectiveness because the majority of trials did not systematically report this information, although our meta-analysis of quality of life suggested that exercise did not significantly improve quality of life compared to control.

We cannot comment about the effect of exercise in people with dysthymia (or sub-clinical depression) and in those without mood disorders, as we explicitly excluded these trials from the review. Future systematic reviews and meta-analyses might include these people, although new reviews would need to ensure that the search strategy was sufficiently comprehensive to identify all relevant trials. We excluded trials of exercise for postnatal depression (as we had done for our previous update).

Quality of the evidence

The majority of the trials we included were small and many had methodological weaknesses. We explicitly aimed to determine the influence of study quality, in particular allocation concealment, blinding and intention-to-treat analyses on effect sizes, as we had done in previous review versions (Lawlor 2001; Mead 2009, Rimer 2012). When only those trials with adequate allocation concealment and intention-to-treat analysis and blinded outcome assessors were included, the effect size was clinically small and not statistically significant (Analysis 6.6).

There was substantial heterogeneity; this might be explained by a number of factors including variation in the control intervention.

However, when only high-quality trials were included, the effect size was small and not statistically significant. Of the eight trials (377 participants) that provided long-term follow-up data, there was only a small effect in favour of exercise (SMD -0.33, 95% CI -0.63 to -0.03) at the end of long-term follow-up. This suggests that any benefits of exercise at the end of treatment may be lost over time. Thus, exercise may need to be continued in the longer term to maintain any early benefits. Our summary of findings tables indicate that the quality of evidence is low ('Summary of findings' table 5).

Our subgroup analyses showed that effect sizes were higher for mixed exercise and resistance exercise than for aerobic exercise alone, but confidence intervals were wide (Analysis 5.1). There were no apparent differences in effect sizes according to intensity of exercise (Analysis 5.2). Effect sizes were smaller in trials which provided fewer than 12 sessions of exercise (Analysis 5.3). Effect sizes were not statistically significant when compared with stretching, meditation or relaxation (Analysis 5.5). Our sensitivity analysis for 'dose' of exercise suggested that a lower dose of exercise was less effective than a higher dose (Analysis 6.7). Although our subgroup analyses, are simply observational in nature, they are not inconsistent with the current recommendations by NICE (NICE 2009).

We extracted information from the trials about other potential sources of biases, in line with the Cochrane Collaboration 'Risk of bias' tool. In exercise trials, it is generally not possible to blind participants or those delivering the intervention to the treatment allocation. Thus, if the primary outcome is measured by self report, this is an important potential source of bias. When we performed sensitivity analysis by including only those trials with blinded outcome assessors, the effect size was smaller than when these trials were included. This suggests that self report may lead to an overestimate of treatment effect sizes. It is important to note, however, that clinician-rated outcomes (e.g. Hamilton Rating Scale for Depression) may also be subject to clinical interpretation and therefore are not free from bias. For random sequence generation, the risk of bias was unclear for most of the trials. For selective reporting, we categorised risk of bias as unclear for most of the trials, although we did not have the study protocols. Furthermore, the funnel plot was asymmetrical suggesting small study bias, heterogeneity or outcome reporting bias.

Potential biases in the review process

We attempted to avoid bias by ensuring that we had identified all relevant studies through comprehensive systematic searching of the literature and contact with authors of the trials to identify other trials, both published and unpublished. However, we accept that some publication bias is inevitable and this is indicated by the asymmetrical funnel plot. This is likely to lead to an overestimate of effect sizes, because positive trials are more likely to be published than negative trials. The searches for this current update were less

extensive than for the initial review in 2001 (Lawlor 2001), but because the CCDAN register of trials is updated regularly from many different sources, we think it is unlikely that we have missed relevant trials.

As noted above, there is considerable interest in the continued development of a robust and accurate evidence base in this field to guide practice and healthcare investment. We are already aware of three recent additional studies that were identified through extensive searches of CCDANCTR. Initial scrutiny of these studies suggests that they would not overturn our conclusions, but they highlight the need to maintain regular updates of this review.

For a previous version of this review (Mead 2009), we made post hoc decisions to exclude trials defined as a 'combination' intervention, a trial in which the exercise intervention lasted only four days (Berlin 2003), and trials of postnatal depression (Armstrong 2003; Armstrong 2004). For the update in 2012, (Rimer 2012), we specified in advance that we would exclude trials that did not fulfil the ACSM criteria (ACSM 2001) for exercise; this meant that we excluded two studies (Chou 2004; Tsang 2006) that had previously been included.

In previous versions of the review, we used data from the arm with the largest clinical effect; this approach could have biased the results in favour of exercise. For this update, we used the largest 'dose' of exercise and performed a sensitivity analyses to determine the effect of using the smaller 'dose' (Analysis 6.7). This showed that the effect size was slightly smaller for the lower dose than the higher dose (-0.44 for the lower dose and -0.62 for the higher dose). This is consistent with one of the subgroup analyses which showed that fewer than 12 sessions was less effective than a larger number of sessions.

We performed several subgroup analyses, which, by their nature, are simply observational. A variety of control interventions were used. We explored the influence of the type of control intervention (Analysis 5.5); this suggests that exercise may be no more effective than stretching/meditation or relaxation on mood. When we performed subgroup analysis of high-quality trials only, we categorised the comparator (relaxation) in one of the trials as a control intervention (Krogh 2009), rather than as an active treatment. Had we categorised relaxation as an active treatment, (e.g. Analysis 6.6), exercise would have had a larger clinical effect in the meta-analysis.

Agreements and disagreements with other studies or reviews

Previous systematic reviews which found that exercise improved depression included uncontrolled trials (Blake 2009; Carlson 1991; Craft 2013; North 1990; Pinquart 2007), so the results of these reviews are probably biased in favour of exercise. Another systematic review (Stathopoulou 2006) which identified trials in peer-reviewed journals only included only eight of the trials which we identified for our review (Doyle 1987; Dunn 2005; Klein

1985; McNeil 1991; Pinchasov 2000; Singh 1997; Singh 2005; Veale 1992), and also included two trials which we had excluded (Bosscher 1993; Sexton 1989). This review (Stathopoulou 2006) found a larger effect size than we did. A further two reviews included mainly older people (Blake 2009; Sjosten 2006), whereas we included participants of all ages (aged 18 and over). Another meta-analysis (Rethorst 2009) concluded that exercise is effective as a treatment for depression, and also found a larger effect size than we did. A narrative review of existing systematic reviews suggested that it would seem appropriate that exercise is recommended in addition to other treatments pending further high-quality trial data (Daley 2008). However, a systematic review that included only studies where participants had a clinical diagnosis of depression according to a healthcare professional found no benefit of exercise (Krogh 2011). Another review of walking for depression suggested that walking might be a useful adjunct for depression treatment, and recommended further trials (Robertson 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Our review suggested that exercise might have a moderate-sized effect on depression, but because of the risks of bias in many of the trials, the effect of exercise may only be small. We cannot be certain what type and intensity of exercise may be effective, and the optimum duration and frequency of a programme of exercise. There are few data on whether any benefits persist after exercise has stopped.

The evidence also suggests that exercise may be as effective as psychological or pharmacological treatments, but the number of trials reporting these comparisons and the number of participants randomised, were both small.

Implications for research

A future update of the current review, including results from ongoing trials and those 'awaiting classification', may increase the precision of estimates of effect sizes. Future systematic reviews and meta-analyses could be performed to investigate the effect of exercise on people with dysthymia.

This review would be strengthened by additional large-scale high-quality studies where all participants at the time of recruitment were diagnosed through clinical interview as having depression, adhered closely to an exercise regimen as a sole intervention and were further assessed through diagnostic clinical interview post-intervention.

It would also be worth considering whether any long-lasting effects of exercise correlated with sustained increases in physical activity over time. Now that we can measure physical activity directly

using accelerometers, this would be a feasible piece of research to perform.

There is a paucity of data comparing exercise with psychological treatments and pharmacological treatments. Further trials are needed in this area.

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Disclaimer:

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blumenthal 1999

Methods	RCT, parallel groups
Participants	Community volunteers recruited via media. Eligible if had DSM-IV major depressive disorder Mean age 70 (range 61 to 88) 63% women N = 156
Interventions	1. Group walking or jogging 3 times per week (n = 53 randomised) 2. Sertraline (SSRI) at standard dose (n = 48 randomised) 3. Combined walking or jogging and sertraline (n = 55 randomised) Duration of interventions: 16 weeks Exercise intensity was 70% to 85% of target heart rate
Outcomes	1. Clinical diagnosis of depression using DSM-IV 2. Hamilton Rating Scale for Depression 3. Beck Depression Inventory
Notes	Analysis intention-to-treat, using last observation carried forward for missing data. Review authors used group 2 and group 3 in the meta-analysis Outcome assessor blind

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation is not described in the paper
Allocation concealment (selection bias)	Low risk	This was categorised as inadequate in the first version of this review, published in the <i>BMJ</i> , after Debbie Lawlor had contacted authors to obtain data on allocation concealment. Further information from the author has enabled us to change this to low risk
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were aware of the treatment group to which they were allocated
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the interventions were aware of treatment group. It is not clear whether this would have introduced bias

Blumenthal 1999 (Continued)

Blinding (performance bias and detection bias) outcome assessors	Low risk	Used HAM-D as an outcome measure. This is rated by clinicians. Every effort was made to ensure that clinical raters were unaware of participants' treatments groups after allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although not all participants completed the interventions, the authors used last observation carried forward to impute missing values
Selective reporting (reporting bias)	Low risk	From the study report, it appears that all the prespecified outcome measures have been reported,
Other bias	Unclear risk	Unclear

Blumenthal 2007

Methods	RCT
Participants	People with major depression recruited through television, radio and newspaper. Mean age 52 (SD 8), 76% women, N = 202
Interventions	1. Home-based aerobic exercise (same 'exercise prescription' as the supervised aerobic group, but performed it on their own (n = 53) 2. Supervised group aerobic exercise (walking and jogging) (n = 51) 3. Sertraline (n = 49) 4. Placebo (n = 49) Intervention 16 weeks
Outcomes	Primary endpoint was remission (no MDD) and a HAM score of < 8, and also a continuous severity score on the HAM-D
Notes	Analysis intention-to-treat using last observation carried forward Blinded outcome assessment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Conditional randomisation, stratified by age, gender and depression severity
Allocation concealment (selection bias)	Low risk	Central allocation by a computer
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were aware of whether they received exercise or not. It is unclear whether this introduced bias

Blumenthal 2007 (Continued)

Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those personnel delivering exercise were aware of group allocation. It is unclear whether this introduced bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	The outcome assessors were unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Imputed missing outcome assessment results by last observation carried forward
Selective reporting (reporting bias)	Low risk	From the study report, it appears that all the prespecified outcome measures have been reported. Authors report protocol on clinicaltrials.gov
Other bias	Unclear risk	Unclear

Blumenthal 2012a

Methods	RCT
Participants	35 years or older with documented coronary artery disease and depressive symptoms (n=101)
Interventions	1. Exercise (group walking, running or jogging on treadmill (n = 37; 65% men) 2. Sertraline (n = 40; 63% men) 3. Placebo (n = 24; 83% men)
Outcomes	Depression as diagnosed by DSM-IV and severity of depression as rated on HAM-D; heart disease biomarkers
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation
Allocation concealment (selection bias)	Low risk	Allocation through distribution of sealed envelopes
Blinding (performance bias and detection bias) participants	Unclear risk	Not possible to blind participants receiving exercise; unclear effect on bias

Blumenthal 2012a (Continued)

Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	No detail given
Blinding (performance bias and detection bias) outcome assessors	Low risk	Telephone surveys (HAMD) by psychologists blinded to arm of trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	95 out of 101 completed protocol and outcome assessment
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported in results. There is a study protocol
Other bias	Unclear risk	Unclear

Bonnet 2005

Methods	RCT
Participants	University counselling service Mean age 23.3 years 82% women N = 11
Interventions	1. CBT plus exercise (n = 5) 2. CBT alone (n = 6) Exercise was walking on a treadmill for 20 minutes, twice a week for 6 weeks Cognitive therapy: met counsellors once a week for 9 weeks
Outcomes	1. DSM-IV MDD, dysthymia or depressive disorder 2. Above cut-off depression on BDI and CES-D
Notes	Self report Randomisation method not stated 7/11 randomised participants completed the interventions Data provided for each participant. Mean and SD calculated by us carrying forward baseline data for those who dropped out

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of randomisation not described

Bonnet 2005 (Continued)

Blinding (performance bias and detection bias) participants	Unclear risk	Participants were not blind to treatment allocation, but it is unclear whether this introduced bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blinded; the effect of this on bias is unclear
Blinding (performance bias and detection bias) outcome assessors	High risk	The primary outcome was the BDI, which is a self report measure
Incomplete outcome data (attrition bias) All outcomes	High risk	4/11 dropped out (2/5 in the exercise and CBT; 2/6 in the CBT only group)
Selective reporting (reporting bias)	Unclear risk	On the basis of the report, all the prespecified outcomes have been reported. No protocol
Other bias	Unclear risk	Unclear

Brenes 2007

Methods	RCT	
Participants	Community-dwelling and nursing home people over 65 with mild depression, recruited through newsletters, newspaper advertisements, distributing flyers at local nursing homes and public presentations Mean age 73.5 (SD 7.8) in exercise, 76.4 (6.4) in medication and 73.9 (5.8) in control group 62% women N = 37	
Interventions	1. Faculty-based group aerobic and resistance training for 60 minutes 3 days a week for 16 weeks (n = 14) 2. Once daily sertraline titrated to response (evaluated at weeks 2, 6, 10 and 14) (n = 11) 3. Control group: contacted at weeks 2, 6, 10, 14 to discuss general health status (n = 12)	
Outcomes	HAM-D	
Notes	Method of randomisation not stated, states intention-to-treat analysis, however data unclear on how many participants dropped out of each group	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Brenes 2007 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated random allocation list
Allocation concealment (selection bias)	Unclear risk	Method not described in the paper
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were not blinded to treatment allocation
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind, but it is not clear what influence this had on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	Used HDRS as an outcome, assessors were blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors of the trial state that it is intention-to-treat, but no data are provided on the number who dropped out of the trial
Selective reporting (reporting bias)	Unclear risk	It appears that all the prespecified outcomes are reported, but no protocol
Other bias	Unclear risk	unclear

Chu 2008

Methods	RCT
Participants	Volunteers aged 18 to 45 recruited via flyers and word of mouth from University and local physician referral. Depression severity mild to moderate, if severe required written permission from physician Mean age 26.4 (18 to 43). 100% women.
Interventions	For 10 weeks: 1. Up to 5 high-intensity aerobic exercise sessions per week (1 supervised) to expend 1000 Kcal per week (n = 15) 2. Up to 5 low-intensity aerobic exercise sessions per week (1 supervised) to expend 1000 Kcal per week (n = 11) 3. Met with investigator once per week for 30 minutes of group stretching exercises (n = 12)
Outcomes	Beck Depression Inventory-II
Notes	Analysis not intention-to-treat BDI-II self-rated depression score

Chu 2008 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Unclear; not described
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind to treatment allocation
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI-II self report was used as the primary outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	16/54 dropped out (3/18 in high dose, 7/18 in low dose and 6/18 in control)
Selective reporting (reporting bias)	Unclear risk	It appears that all prespecified outcomes are reported, but no protocol
Other bias	Unclear risk	Unclear

Doyne 1987

Methods	RCT
Participants	Community volunteers recruited via media Mean age 28.5 (SD 4.36) 100% women N = 40. The number randomised into each group not stated.
Interventions	1. Supervised running or walking 4 times a week for 8 weeks 2. Supervised strength training 4 times a week 3. Waiting list control
Outcomes	1. Beck Depression Inventory 2. Lubin's Depression Adjective List 3. Hamilton Rating Scale for Depression

Doyne 1987 (Continued)

Notes	Outcome assessment not blind Analysis not intention-to-treat	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Report states random assignment after matching participants on baseline BDI scores of intervals of < 19, 20 - 29 and > 30
Allocation concealment (selection bias)	High risk	Inadequate (as assessed by Lawlor and Hopker in <i>BMJ</i> review in 2001)
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind to treatment allocation, but unclear risk of bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI was the primary outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 57 women who met criteria for inclusion, 40 completed treatment, and 32 completed follow-up. Drop-out rates were 40% in 'track', 29% in 'universal' and 13% in waiting list control
Selective reporting (reporting bias)	Unclear risk	It appears that all the prespecified outcome measures are reported, but no protocol
Other bias	Unclear risk	Unclear

Dunn 2005

Methods	RCT
Participants	Community volunteers recruited via media. Men or women aged 20 to 45 with mild to moderate depression Mean age 35.9 75% women N = 80
Interventions	4 different aerobic exercise programmes, that varied in total energy expenditure (7.0 kcal/kg/week or 17.5 kcal/kg/week) and frequency (3 days per week or 5 days per week) . The 17.5 kcal/kg/week is consistent with public health recommendations for physical activity and is termed 'public health dose'.

Dunn 2005 (Continued)

	1. Public health dose 3/week (n = 17) 2. Public health dose 5/week (n = 16) 3. Low dose 3/week.(n = 16) 4. Low dose 5/week (n = 18) 5. Control, (flexibility exercise) 3 sessions per week (n = 13) Exercise was on a treadmill or stationary bike, individually and monitored by laboratory staff. Duration 12 weeks.	
Outcomes	Change in HRSD from baseline to 12 weeks.	
Notes	Intention-to-treat (though data from the last available exercise session rather than data collected at 12 weeks were used in the analysis) Outcome assessors blind	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not stated
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind to treatment allocation, but unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those supervising delivery of the intervention were not blind, but it is unclear what effect this had on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	Trained research assistants applied the HRSD blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses
Selective reporting (reporting bias)	Low risk	There is a published protocol (Dunn 2002)
Other bias	Unclear risk	Unclear

Epstein 1986

Methods	RCT
Participants	Community volunteers recruited via media Mean age 39.4 (range 24 to 60) 92% women
Interventions	1. Group walking or jogging for 30 minutes 3 to 5 times a week for 8 weeks (n = 7) 2. Cognitive therapy 1 session of 1.5 hours per week (n = 9) 3. Waiting list control (n = 10)
Outcomes	1. Beck Depression Inventory 2. Zung Self Rating Depression Scale
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	High risk	Assessed by Lawlor and Hopker for <i>BMJ</i> review
Blinding (performance bias and detection bias) participants	Unclear risk	Information not available
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Information not available
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI: self report
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	From the information available, it appears that all prespecified outcomes were reported
Other bias	Unclear risk	Unclear

Fetsch 1979

Methods	RCT. n = 21
Participants	Depressed people (reactive depression) referred from a University counselling service and recruited via advertisements
Interventions	1. Running 4 sessions over 4 weeks (n = 10). Age range 18 - 51 2. Stroking therapy (a type of 'talking' therapy), 4 sessions over 4 weeks (n = 11) (age range 20 - 35)
Outcomes	Beck Depression inventory
Notes	Outcome assessment not blind (self report) Analysis not intention-to-treat (only 16/21 randomised participants completed trial and were included in the analysis)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) participants	Unclear risk	Not blind to treatment allocation, but unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Not blind, but unclear risk on bias
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI; self report
Incomplete outcome data (attrition bias) All outcomes	High risk	Only included the scores for the 16 people who completed 2 or more sessions
Selective reporting (reporting bias)	Unclear risk	It appears from the information available that all prespecified outcomes were reported, but no protocol
Other bias	Unclear risk	Unclear

Foley 2008

Methods	RCT (parallel group)
Participants	Recruited from media advertisements, pamphlet and poster displays and psychiatric referrals with major depressive episode Age range 18 - 55, mean age and gender data not stated N = 23
Interventions	1. Moderate-intensity aerobic exercise. Each session lasted 30 - 40 minutes (n = 10) 2. Mild-intensity stretching (n = 13) 12-week programme of 3 supervised sessions per week
Outcomes	Beck Depression Inventory Montgomery-Asberg Depression Rating scale
Notes	Intention-to-treat analysis Small sample size with insufficient power to detect small differences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were not blind to treatment allocation, but it is unclear what effect this has had on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention were not blind, but it is unclear what effect this had on bias
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	High risk	10/23 dropped out (2/10 in exercise arm and 8/13 in stretching)
Selective reporting (reporting bias)	Unclear risk	From the study report, it appears that all prespecified outcome measures have been reported; no protocol
Other bias	Unclear risk	Unclear

Fremont 1987

Methods	RCT
Participants	Community volunteers recruited via media Data on age and gender not available N = 61
Interventions	1. Group running (3 times a week, for 10 weeks, with a running coach in small groups of 6 - 8 subjects) (n = 15) 2. Cognitive therapy (10 individual 1 hour sessions with a therapist) (n = 16) 3. Combined running and cognitive therapy (n = 18) 10 weeks
Outcomes	Beck Depression Inventory
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information available
Allocation concealment (selection bias)	High risk	Inadequate (as assessed by Lawlor and Hopker in the 2001 <i>BMJ</i> review)
Blinding (performance bias and detection bias) participants	Unclear risk	Not stated
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Not stated
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	High risk	Categorised as not intention-to-treat for the <i>BMJ</i> review (Lawlor and Hopkins). Data on drop-outs not available to lead author
Selective reporting (reporting bias)	Unclear risk	Protocol not available for scrutiny. From the study report, it appears that all prespecified outcome measures have been reported
Other bias	Unclear risk	Unclear

Gary 2010

Methods	RCT	
Participants	Depressed people with heart failure (NYHA Class II to III) 42% men Age 30 - 70	
Interventions	<p>1. Home exercise programme: 12 weekly face-to-face home visits to monitor walking and to tailor the exercise prescription. Participants were advised to walk for 3 days per week for 12 weeks, and to increase duration to a maximum of 1 hour for 3 days per week at moderate intensity (n = 20)</p> <p>2. Home exercise programme plus CBT (n = 18)</p> <p>3. CBT alone, based on Beck's CBT model. Each session lasted 1 hour. Total number of sessions not stated, but we assume this was 12 because in the combined group they were delivered at the same time as the home exercise programme visits (n = 18)</p> <p>4. Usual care (n = 17)</p>	
Outcomes	HAM-D, 6-minute walk	
Notes	Small sample size	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised, but no details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were not blinded to treatment allocation; unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering treatment were not blinded; unclear effect on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	"Data collectors were blind to group assessment"
Incomplete outcome data (attrition bias) All outcomes	High risk	68/74 provided outcome data post-intervention. Classified as high risk, as more than 5% did not provide outcome data
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No other source of bias identified

Greist 1979

Methods	RCT
Participants	Community volunteers Age range 18 - 30 53.4% women N = 28
Interventions	1. Supervised running (n = 10). running leader met individually with his participants 3 - 4 times per week for 1 hour, then in the 5th week, only 2 sessions were scheduled with the leader, and in the 7th and 8th weeks, only 1 was scheduled. 2. Time-limited psychotherapy (n = 6) 3. Time-unlimited psychotherapy (n = 12)
Outcomes	Symptom checklist score
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information in report
Allocation concealment (selection bias)	High risk	Categorised in <i>BMJ</i> review (Lawlor and Hopker) as inadequate
Blinding (performance bias and detection bias) participants	Unclear risk	Not blinded to treatment allocation
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering exercise not blinded, effect on bias unclear
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report symptom checklist score
Incomplete outcome data (attrition bias) All outcomes	High risk	6/28 dropped out (2/10 in the running group and 4/18 in the psychological groups)
Selective reporting (reporting bias)	High risk	Outcome measures were not prespecified. There was no methods section in the paper; after an introduction, the entry criteria were stated and the interventions were described. The first time the outcome measures were described was in the results section

Greist 1979 (Continued)

Other bias	High risk	The authors conclude the paper by saying that “our bias (and we purposely label it as bias that requires additional evaluation) is that running may prove to have antidepressant properties for many individuals with moderate depression”. It is possible that this author bias was present before the trial was completed, and so may have influenced results
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Hemat-Far 2012

Methods	RCT
Participants	University students aged 18 - 25 with depression 100% women
Interventions	1. 40 - 60 minutes of running, 3 times a week, supervised. (n = 10) 2. Control group with no active intervention (n = 10)
Outcomes	Beck Depression Inventory score
Notes	Small sample size (10 participants in each arm); specific population under study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Clinician judgement used at recruitment. After reviewing questionnaires psychiatrists “selected” 20 women
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blinded to intervention; unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	No information given
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No discussion on attrition rate
Selective reporting (reporting bias)	Low risk	BDI specified at outset and completed in results

Other bias	High risk	The control group were told not to do so much exercise.
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Hess-Homeier 1981

Methods	RCT
Participants	Community volunteers recruited via media Data on age and gender distribution not available N = 17
Interventions	1. Running or walking with the instructor for 30 minutes 4 times a week for 8 weeks (n = 5) 2. Cognitive therapy: 1 session of 1 hour and 2 of ½ hour per week (n = 6) 3. Waiting list control (n = 6)
Outcomes	Beck Depression Inventory
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that "random assignment" was performed
Allocation concealment (selection bias)	High risk	Categorised as inadequate in <i>BMJ</i> review (Lawlor and Hopker)
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blinded to treatment allocation
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	High risk	Previously categorised by Lawlor and Hopker as not intention-to-treat, but data on drop-outs are not reported
Selective reporting (reporting bias)	Unclear risk	The BDI was listed as the first outcome measure and data on BDI were reported. The authors also mentioned the Zung Self rating Depression Scale, but data were not reported in the abstract. No

Hess-Homeier 1981 (Continued)

		protocol was available
Other bias	Unclear risk	Unclear

Hoffman 2010

Methods	RCT
Participants	People with a history of traumatic brain injury occurring between 6 months and 5 years prior to trial with at least mild depression (n = 80)
Interventions	1. Aerobic exercise of participant's choosing, 60 minutes of gym-based supervised exercise per week and 4 x 30-minute home exercise sessions per week (n = 40; 38% men) 2. No intervention in control group (n = 40; 50% men)
Outcomes	Beck Depression Inventory Score
Notes	The control group were informed they could participate in exercise programme post-trial intervention period. Authors report that both intervention and control groups showed a substantial increase in exercise SDs received from author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participation open to anyone who met inclusion criteria. Random distribution of sealed envelopes
Allocation concealment (selection bias)	Low risk	Use of sealed envelopes
Blinding (performance bias and detection bias) participants	Unclear risk	All participants informed of nature of the study and both groups increased total amount of exercise over study period
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	No detail provided
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI self report
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of missing data
Selective reporting (reporting bias)	Low risk	All findings reported

Hoffman 2010 (Continued)

Other bias	Unclear risk	Unclear
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Klein 1985

Methods	RCT (parallel group)
Participants	Community volunteers recruited via media Mean age 30.1 (SD 6.72) 72% women N = 74
Interventions	1. Supervised running twice a week for 12 weeks (n = 27) 2. Group cognitive therapy for 2 hours once a week (n = 24) 3. Control group: meditation for 1 hour twice weekly (n = 23)
Outcomes	1. Symptom checklist 2. Target symptoms 3. Structural Analysis of Social Behaviour 4. Social Adjustment Self reported Questionnaire 5. Cornell Medical Index 6. Role Rating Questionnaire 7. Hamilton Rating Scale 8. Global Assessment Scale
Notes	Main outcome assessment not blind. Hamilton Rating Scale administered by interviewer blind to allocation. Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	High risk	Inadequate. Categorised by Lawlor and Hopker for <i>BMJ</i> review
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind but unclear whether this had an effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report for main outcome

Klein 1985 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 74 randomised, 32 dropped out or never started treatment (12/27 in the running group; 12/23 in the meditation group and 8/24 in the group therapy group)
Selective reporting (reporting bias)	Unclear risk	It appears that all outcomes specified in methods are reported. No protocol
Other bias	Unclear risk	Unclear

Knubben 2007

Methods	RCT (parallel group)
Participants	Inpatients with major depression Mean age 49 55% women N = 38
Interventions	1. Walking training on a treadmill for 10 days (n = 10) 2. Placebo (low-intensity stretching and relaxation) light stretching exercises for the calves, thighs, back, shoulders and pectoral muscles, as well as relaxation exercises, daily for 30 minutes (n = 18)
Outcomes	1. Bech-Rafaelsen Scale (BRMS) 2. Center for Epidemiologic Studies Depression Scale (CES-D)
Notes	Authors state intention-to-treat, but of the 39 recruited only 38 were used in the analysis. Outcome assessor for BRMS blinded to treatment allocation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block list
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding (performance bias and detection bias) participants	Unclear risk	Participants aware of treatment allocation, unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention aware of allocation, unclear effect on bias

Knubben 2007 (Continued)

Blinding (performance bias and detection bias) outcome assessors	Low risk	A single psychologist (blinded to treatment allocation) assessed outcome using the BRMS
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report states 39 were randomised, but the outcome data relate to only 38. Three participants dropped out. Missing data were imputed, but authors have not accounted for the 1 participant who seems to have been randomised but was not reported in the tables of results
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes seem to have been reported, but no protocol
Other bias	Unclear risk	Unclear

Krogh 2009

Methods	RCT (parallel group)	
Participants	Referred from general practitioners, private psychiatrists, psychologists and psychiatric wards institutions. Included if met criteria for major depression Mean age 38.9 73.9% women N = 165	
Interventions	1. Strength circuit training (n = 55) 2. Aerobic (machine-based) training (n = 55) 3. Relaxation control (n = 55) Twice-weekly intervention for 32 sessions delivered over a 4-month period	
Outcomes	Hamilton Rating Scale for Depression	
Notes	Intention-to-treat analysis Significant drop-outs in each group Changed sample size calculation after first 50 participants on basis of observed standard deviation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised restricted randomisation with a block size of 8
Allocation concealment (selection bias)	Low risk	The block size and allocation sequence were unknown to the DEMO trial staff

Krogh 2009 (Continued)

Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, but unclear what influence this had on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Physiotherapists delivering the intervention were not blind. Unclear how this influenced risk of bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	The assessor was blind to intervention group. The investigators asked the outcome assessors to guess intervention group. The kappa values for agreement between the right allocation and the guessed allocation were 0.15 and 0.05 for the assessments at 4 and 12 months respectively
Incomplete outcome data (attrition bias) All outcomes	Low risk	137/165 were available for follow-up at the end of the intervention. Eighteen were lost to follow-up and 10 refused to participate (8/55 in strength group, 7/55 in aerobic group and 13/55 in the relaxation group). The authors used a likelihood-based mixed-effect model with an unstructured variance matrix available in SPSS, which is able to handle missing data with higher precision and power than last observation carried forward. The authors reported no significant difference between missing participants and participants included in the analyses at either 4 or 12 months, and concluded that it was reasonable to assume that the missing data were 'missing at random'
Selective reporting (reporting bias)	Low risk	All prespecified outcomes seem to have been reported. Protocol was published in advance of the trial
Other bias	Unclear risk	The authors repeated power calculations part-way through the trial, and reduced the sample size as the standard deviation was lower than anticipated

Martinsen 1985

Methods	RCT (parallel group)
Participants	Psychiatric hospital inpatients Mean age 40 (range 17 - 60) Data on sex distribution not available N = 49
Interventions	1. Aerobic exercise with instructor for 1 hour 3 times a week for 9 weeks at 50 - 70% of maximum aerobic capacity (n = 28 randomised) 2. Control group attended occupational therapy whilst intervention group exercised (n = 21 randomised)

Martinsen 1985 (Continued)

Outcomes	Beck Depression Inventory	
Notes	Outcome assessment not blind Analysis not intention-to-treat	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation with respect to age
Allocation concealment (selection bias)	Low risk	Categorised by Lawlor and Hopker as low risk
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants dropped out, leaving 43 who completed the study
Selective reporting (reporting bias)	Unclear risk	Prespecified outcome measures were reported, but no protocol
Other bias	Unclear risk	unclear

Mather 2002

Methods	RCT (parallel group)
Participants	Primary care, psychiatric services, advertisement in paper and radio. N = 86 (59 women and 27 men). Mean age 63.7 (range 53 - 78) in exercise and 66.2 (56 - 91) in control group
Interventions	1. Endurance, muscle strengthening and stretching, in a group exercise class, lasting 45 minutes. An instructress ran the class from a podium in the centre of a hall (n = 43). Twice weekly for 10 weeks 2. Health education classes (n = 43), twice weekly for 10 weeks

Mather 2002 (Continued)

Outcomes	1. Hamilton Rating Scale for Depression 2. Geriatric Depression Scale 3. Clinical Global Impression 4. Patient Global Impression
Notes	Outcome assessor blind Intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number list
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention aware of allocation, unclear effect on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	Primary outcome was HRSD delivered by one of 2 psychiatrists who were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Unclear risk	All prespecified outcome measures reported, but no protocol
Other bias	Unclear risk	Unclear

McCann 1984

Methods	RCT (parallel group)
Participants	Undergraduate psychology students with a requirement to participate in a research project No details of age 100% women N = 47
Interventions	1. Aerobic exercise: group running, jogging or dancing for 1 hour twice weekly for 10 weeks (n = 16 randomised) 2. Placebo control group - muscle relaxation for 15 - 20 minutes 4 times a week (n = 15)

McCann 1984 (Continued)

	randomised) 3. Waiting list control (n = 16 randomised)	
Outcomes	Beck Depression Inventory	
Notes	Outcome assessment not blind Analysis not intention-to-treat	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	High risk	Classified as inadequate by Lawlor and Hopker
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report depression scores
Incomplete outcome data (attrition bias) All outcomes	High risk	4/47 withdrew (1 from the aerobic exercise, 1 from the placebo condition and 2 from the 'no treatment' condition). 43 remained
Selective reporting (reporting bias)	Unclear risk	No prespecified outcomes. Reported depression scores before and after the intervention. No protocol
Other bias	Unclear risk	Unclear

McNeil 1991

Methods	RCT
Participants	Community volunteers from religious and community organisations Mean age 72.5 Details of gender distribution not provided N = 30. number randomised into each group not stated, we assume this is 10 in each group)

McNeil 1991 (Continued)

Interventions	1. Walking accompanied by investigator for 20 minutes 3 times a week for 6 weeks 2. Social contact control group (visit by investigator for a “chat” avoiding any discussion of depression or health, twice a week) 3. Waiting list control group	
Outcomes	Beck Depression Inventory	
Notes	Outcome assessment not blind All completed intervention so classified as intention-to-treat	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	High risk	Inadequate (as assessed by Lawlor and Hopker for <i>BMJ</i> review)
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, but this on its own does not necessary imply bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Investigator delivering intervention was not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report BDI
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Unclear risk	All prespecified outcome measures were reported, but no protocol
Other bias	Unclear risk	Note Lawlor and Hopker categorised this study as “not intention-to-treat”

Mota-Pereira 2011

Methods	RCT
Participants	18 - 60 year-olds with treatment resistant major depressive disorder selected from out-patient setting (n = 33)

Mota-Pereira 2011 (Continued)

Interventions	1. Five sessions a week of 30 - 45 minutes moderate intensity walking. Four of these were unsupervised and one was supervised on a hospital gym treadmill (n = 22, 57.9% women) 2. Control group, receiving no exercise (n = 11 : 80% women)
Outcomes	Hamilton Depression Scale Global Assessment of Functioning Scale Clinical Global Impression Scale.

Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) participants	Unclear risk	Participants were not blinded to intervention, but were not provided with information on how the intervention might benefit them
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention not blinded to treatment group
Blinding (performance bias and detection bias) outcome assessors	Low risk	Investigators carrying out rating tests post-intervention were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Prespecified outcomes all reported
Other bias	Low risk	Appears to be free of other bias

Mutrie 1988

Methods	RCT
Participants	Depressed people referred to study by general practitioner (primary care physician) Mean age 42.1 83% women N = 36

Mutrie 1988 (Continued)

Interventions	1. Aerobic exercise - conducted on an individual basis and without group contact, 29 minutes 3 times a week for 4 weeks (n = 9) 2. Strength and stretching exercise completed on an individual basis and without group contact, 20 minutes 3 times a week (n = 8) 3. Waiting list control (n = 7) i.e. delayed treatment
Outcomes	1. Beck Depression Inventory 2. Profile of Mood States
Notes	Outcome assessment not blind All completed intervention so analysis intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data in report
Allocation concealment (selection bias)	High risk	Inadequate (classified by Lawlor and Hopker in <i>BMJ</i> review)
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	BDI self report
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the intervention
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes are reported, but no protocol
Other bias	Unclear risk	Unclear

Nabkasorn 2005

Methods	RCT
Participants	Student nurses with mild to moderate depressive symptoms Aged 18 to 20 All women N = 59

Nabkasorn 2005 (Continued)

Interventions	1. Group jogging 50 minutes a day 5 days a week for 8 weeks (n = 28) 2. Usual care (n = 31)
Outcomes	1. CES-D scores (data from means and SD at end of treatment not available so obtained from published graph)
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information in the paper; wrote to authors but no response
Allocation concealment (selection bias)	Unclear risk	No information in the paper
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention not blind, unclear effect on bias
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report using CES-D score, so not blind
Incomplete outcome data (attrition bias) All outcomes	High risk	59 randomised, 7/28 in jogging group not available at follow-up, 3/31 in control group not available for follow-up; leaving data from 49 to be analysed
Selective reporting (reporting bias)	Unclear risk	All prespecified outcome measures seem to have been reported, but no protocol
Other bias	Unclear risk	Unclear

Orth 1979

Methods	RCT
Participants	College students with dysphoria or depression Mean age 22 27% women N = 11

Orth 1979 (Continued)

Interventions	1. Jogging 5 times a week for 30 minutes over 4 weeks (n = 3) 2. Meditation (n = 3) 3. Self-chosen activity (n = 3) 4. Self monitoring (control) (n = 2)
Outcomes	1. Depression Adjective Checklist 2. Minnesota Multiphasic Personality Inventory
Notes	Not stated whether intention-to-treat though all participants allocated control and running provided data at baseline and post-intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear, not specified. Too old a study to contact authors
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) participants	Unclear risk	Unclear
Blinding (performance bias and detection bias) those delivering intervention	Low risk	Not relevant as activities done on own
Blinding (performance bias and detection bias) outcome assessors	High risk	Self-report outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, data from all reported
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes reported, but no protocol
Other bias	Unclear risk	Unclear

Pilu 2007

Methods	RCT
Participants	Recruited from clinical activity registries of the University psychiatric unit if diagnosed with major depression Data on age not stated (inclusion criteria range 40 - 60) 100% women N = 30

Interventions	1. Physiological strengthening exercises plus pharmacological treatment (n=10). The physical activity programme included 2 60-minute lessons per week, held by skilled an instructor, with ISEF (Physical Education) diploma, Psychology degree and post-degree diploma in sport Psychopathology (MS). Each session was set in three steps: Step I: welcome and warming up (about 5 minutes) Step II: physiological strengthening (about 50 minutes) Step III: stretching, cooling down, goodbye (about 5 minutes) 2. Pharmacological treatment only (n = 20) Intervention delivered twice per week for 8 months	
Outcomes	Hamilton Rating Scale for Depression	
Notes	Not stated if intention-to-treat analysis No information given regarding drop-out rates	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear risk of bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention were not blind, unclear risk of bias
Blinding (performance bias and detection bias) outcome assessors	Unclear risk	Unclear. Two different trained psychiatrists rated outcomes, including the HAM-D, but authors did not report whether these psychiatrists were blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All those starting the intervention had outcome data reported
Selective reporting (reporting bias)	High risk	The authors stated that a structured diagnostic interview was performed to make a diagnosis of depression at 8 months (follow-up), but these data were not reported
Other bias	Unclear risk	Unclear

Pinchasov 2000

Methods	RCT
Participants	Several groups including one with depression in the absence of seasonal affective disorder. Also 1 group of depressed people fulfilling criteria for seasonal affective disorder mean age 35.2. 100% women N = 63
Interventions	1. 54 minutes per day of cycling on stationary bicycle for 1 week 2. Bright light therapy 7 groups, 9 participants in each We are using data from the cycling and bright light therapy
Outcomes	1. HDRS score 2. Body weight 3. Oxygen consumption
Notes	Randomisation method unclear Unclear if outcome assessment was blind

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	The authors did not state how the intervention was delivered
Blinding (performance bias and detection bias) outcome assessors	Unclear risk	HDRS, but not stated whether outcome assessor blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	63 participants were recruited, and were included in 7 groups, 9 per group. Data not provided on number still in the trial at the end of the interventions
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided to make this judgement
Other bias	Unclear risk	Unclear

Reuter 1984

Methods	RCT
Participants	University students presenting to mental health clinic with depression Details of age and gender distribution not provided N = 18
Interventions	1. Supervised running for at least 20 minutes 3 times a week for 10 weeks plus counselling 2. Counselling only
Outcomes	Beck Depression Inventory
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information to make this judgement
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) participants	Unclear risk	No information
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind, but the effect on bias is uncertain
Blinding (performance bias and detection bias) outcome assessors	High risk	Judged by Lawlor and Hopker in <i>BMJ</i> review as not blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Judged by Lawlor and Hopker as not intention-to-treat
Selective reporting (reporting bias)	Unclear risk	Insufficient information; no protocol
Other bias	Unclear risk	Unclear

Schuch 2011

Methods	RCT
Participants	Hospital inpatients being treated for severe depression with conventional therapy (n = 26) Gender not specified
Interventions	1. 3 sessions per week of participant-selected aerobic exercise (n = 15) 2. Control group receiving conventional therapy (i.e. pharmacotherapy/ECT only) (n = 11)
Outcomes	Depressive symptom rating by psychiatrist using HAM-D scoring
Notes	Intervention continued 'until discharge' but no further information on length of intervention. No detail on exercise compliance rates. Of 40 originally invited to take part, 14 declined at outset

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but details not given
Allocation concealment (selection bias)	Unclear risk	No details on how participants were allocated
Blinding (performance bias and detection bias) participants	Unclear risk	No details given on to what extent participants were aware of the theoretical effects of exercise on depression. Participants not blinded to intervention but unclear of the effect of this on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering exercise not blinded to group; effect of this on bias is unclear
Blinding (performance bias and detection bias) outcome assessors	Unclear risk	No detail given on whether those assessing outcome measures were blinded to group
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants remained in trial throughout intervention
Selective reporting (reporting bias)	Unclear risk	Reported on all measures outlined at start of trial
Other bias	Unclear risk	Unclear

Setaro 1985

Methods	RCT (parallel group)	
Participants	Community volunteers recruited via the media Age range 18 - 35 (mean age not stated) 26% women N = 150	
Interventions	1. Cognitive therapy and aerobic dance classes (n = 30) 2. Aerobic dance classes only (n = 30) 3. Cognitive therapy only using the principles of A Beck (n = 30) 4. Cognitive therapy and non-aerobic exercise classes (n = 30) 5. Non-aerobic exercise only (arts and crafts) (n = 30) 6. No intervention (n = 30) Duration of interventions was 10 weeks	
Outcomes	Minnesota Multiphasic Personality Inventory	
Notes	Outcome assessment not blind Analysis not intention-to-treat	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants blocked by gender; male-female ratios kept constant
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear risk on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Group intervention, unclear if those delivering the intervention were blind
Blinding (performance bias and detection bias) outcome assessors	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	180 randomised, 150 completed trial
Selective reporting (reporting bias)	Unclear risk	Reported prespecified outcomes; no protocol
Other bias	Unclear risk	Unclear

Shahidi 2011

Methods	RCT
Participants	Older members of a local cultural community Age 60 - 80 100% women all with geriatric depression score greater than 10 (n = 70)
Interventions	1. 10 sessions of aerobic group exercise, each 30 minutes in duration, including jogging and stretching (n = 23) 2 “Laughter yoga” - 10 sessions of structured group activity which includes laughing, clapping, chanting and positive discussion (n = 23) 3. Control (n = 24)
Outcomes	Depression scoring on Geriatric Depression Scale, Life Satisfaction scale
Notes	Overall drop-out of 10 participants

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detail given
Allocation concealment (selection bias)	Unclear risk	No detail given
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blinded to intervention; unclear what effect this may have on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Not blinded; unclear effect on bias
Blinding (performance bias and detection bias) outcome assessors	High risk	Geriatric depression scale; self-reported
Incomplete outcome data (attrition bias) All outcomes	High risk	14% attrition rate
Selective reporting (reporting bias)	Low risk	All measures listed at outset reported in results
Other bias	Unclear risk	Unclear

Sims 2009

Methods	RCT	
Participants	Recruited from hospital databases of stroke patients discharged in last year, general practitioners and newspaper articles. Had to be over 6 months post-stroke and have depression confirmed by a psychiatrist Mean age 67.13 (range 21 to 93) 40% women N = 45	
Interventions	1. Group-based moderate-intensity strengthening exercises twice a week for 10 weeks. The PRT programme included 2 high-intensity sessions/week for 10 weeks at a community-based gymnasium. (n = 23) 2. Usual care (n = 22)	
Outcomes	Centre for Epidemiologic Studies for Depression scale	
Notes	Intention-to-treat analysis Outcome was self-rated symptoms of depression by CES-D scale	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomised list
Allocation concealment (selection bias)	Low risk	Randomisation was conducted centrally by an independent person
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear risk of bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention were not blind, unclear risk of bias
Blinding (performance bias and detection bias) outcome assessors	High risk	Self report outcome (depressive symptoms by CES-D scale)
Incomplete outcome data (attrition bias) All outcomes	High risk	Baseline assessment was performed in 45 people; complete data were available for 43 people at 6 months (23/23 in intervention group and 20/22 in the control)
Selective reporting (reporting bias)	Unclear risk	Reported all prespecified outcome (though we do not have access to the protocol)
Other bias	Unclear risk	Unclear

Singh 1997

Methods	RCT
Participants	Community volunteers from 2 registers of individuals interested in participation in research Mean age 70 (range 61 - 88) 63% women N = 32
Interventions	1. Supervised non-aerobic progressive resistance training 3 times a week for 10 weeks (n = 17) 2. Control group received health seminars twice a week in which depression and mental health were not discussed (n = 15)
Outcomes	1. Beck Depression Inventory 2. Hamilton Rating Scale of Depression
Notes	Outcome assessment not blind Intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of blocks of 5
Allocation concealment (selection bias)	Low risk	Assessed by Lawlor and Hopker as adequate
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention were not blind
Blinding (performance bias and detection bias) outcome assessors	High risk	Self-rated BDI
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed the study
Selective reporting (reporting bias)	Unclear risk	All prespecified outcomes reported, though no protocol
Other bias	Unclear risk	Unclear

Singh 2005

Methods	RCT
Participants	People responding to a postal questionnaire who had DSM-IV depression or dysthymia Mean age 69 55% women N = 60
Interventions	1. Progressive resistance training at 80% of 1 repetition max (n = 20) 2. Resistance training at 20% of 1 repetition max (n = 20) 3. Usual care (n = 20) Each intervention group held 3 times a week for 8 weeks
Outcomes	1. Hamilton Rating Scale for depression 2. Geriatric Depression score
Notes	Not intention-to-treat (50/60 completed the study and were available for assessment) Outcome assessment blind

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Adequate. Sealed opaque envelopes open after baseline assessment
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear effect on bias
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind to treatment allocation, unclear effect on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	HRSD performed by blinded outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	6/60 dropped out (2 from the high-dose, 3 from the low-dose and 1 from the usual care group)
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes in paper were reported, but no protocol
Other bias	Unclear risk	Unclear

Veale 1992

Methods	RCT
Participants	Psychiatric hospital outpatients and hospital day-patients Mean age 35.5 (range 19 - 58) 64% women N = 83
Interventions	1. Group running 3 times a week for 12 weeks, plus routine care (n = 48) 2. Control group: routine care only (n = 35)
Outcomes	1. Beck Depression Inventory 2. State-Trait Anxiety Inventory
Notes	Outcome assessment not blind Analysis not intention-to-treat

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Adequate (categorised by Lawlor and Hopker)
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, unclear risk
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering the intervention were not blind, but the influence on bias is unclear
Blinding (performance bias and detection bias) outcome assessors	High risk	Self-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 18 dropped out, leaving 65 for analyses
Selective reporting (reporting bias)	Unclear risk	All the prespecified outcomes stated in the paper were reported, but no protocol
Other bias	Unclear risk	unclear

Williams 2008

Methods	RCT
Participants	Residents recruited from 8 long-term care facilities if clinical evidence of Alzheimer's Disease dementia and depression Mean age 87.9 (range 71 to 101) 89% women N = 45
Interventions	1. Comprehensive exercise - strength, balance, flexibility and walking (n = 16) 2. Supervised walking at pace of individual (n = 17) 3. Control group of casual conversation (n = 12) Intervention delivered individually 5 days per week for 16 weeks
Outcomes	Cornell Scale for Depression in Dementia
Notes	Analysis intention-to-treat Substantial drop-out rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not stated
Allocation concealment (selection bias)	Low risk	Adequate. Participants were assigned a code number, which was drawn by a research assistant who had no access to pretest results
Blinding (performance bias and detection bias) participants	Unclear risk	Participants not blind, though effect on bias unclear
Blinding (performance bias and detection bias) those delivering intervention	Unclear risk	Those delivering intervention were not blind, unclear risk on bias
Blinding (performance bias and detection bias) outcome assessors	Low risk	Observational assessment by raters blind to treatment group allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	9/45 dropped out (1/16 in comprehensive exercise group, 6/17 in walking group, 2/12 in conversation)
Selective reporting (reporting bias)	Unclear risk	All prespecified outcome seem to be reported (although we do not have the trial protocol)
Other bias	Unclear risk	Unclear

BDI: Beck Depression Inventory; BRMS: Bech-Rafaelsen Scale; CBT: cognitive behavioural therapy; CES-D: Center for Epidemiologic Studies Depression Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HRSD/HAM-D: Hamilton Rating Scale for Depression; RCT: randomised controlled trial; SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abascal 2008	Did not have to have depression to enter trial
Akandere 2011	Did not have to have depression to enter trial
Annesi 2010	subgroup analysis from a trial in people with obesity
Arcos-Carmona 2011	Did not have to have depression to enter trial
Armstrong 2003	Postnatal depression
Armstrong 2004	Postnatal depression
Asbury 2009	Did not have to have depression to enter trial
Attia 2012	Not RCT for exercise in depression
Aylin 2009	Did not have to have depression to enter trial
Badger 2007	Did not have to have depression to enter trial
Baker 2006	Did not have to have depression to enter trial
Bartholomew 2005	Single bout of exercise
Beffert 1993	Trial involving adolescents
Berke 2007	Did not have to have depression to enter trial
Berlin 2003	Duration of exercise was only 4 days
Biddle 1989	Non-systematic review
Blumenthal 2012b	Did not have to have depression to enter trial
Bodin 2004	Single bout of either martial arts or stationary bike
Bosch 2009	Did not have to have depression to enter trial
Bosscher 1993	Comparing different types of exercise with no non-exercising control group

(Continued)

Bowden 2012	Not exercise according to ACSM; all arms received an intervention
Boyll 1986	College students, did not have to have depression
Brittle 2009	Did not have to have depression to enter trial
Bromby 2010	Non-randomised study
Broocks 1997	Non-systematic review
Brown 1992	Trial involving adolescents with diagnoses of dysthymia and conduct disorder
Burbach 1997	Non-systematic review
Burton 2009	Did not have to have depression to enter trial and multimodal intervention
Carney 1987	Participants were those undergoing haemodialysis and did not have to have depression to be included
Chalder 2012	Intervention not exercise; multimodal intervention including motivational interviewing, life coaching, support
Chan 2011	Intervention is Dejian mind-body intervention, not exercise.
Chen 2009	Did not have to have depression to enter trial and intervention was yoga
Chou 2004	Exercise intervention was Tai Chi
Chow 2012	Exercise intervention was Qigong
Christensen 2012	Did not have to have a depression to enter trial
Ciocon 2003	Published in abstract form only, intervention appeared not to be exercise according to ACSM definition, and no further information available from the authors
Clegg 2011	Did not have to have depression to enter trial
Courneya 2007	Did not have to have depression to enter trial
Dalton 1980	Trial in a "wheelchair bound population" with diverse aetiologies
Demiralp 2011	Did not have to have depression to enter trial
Deslandes 2010	Not randomized; participants chose their intervention
DeVaney 1991	A trial of reducing exercise in those exercising more than 6 hours per week
DiLorenzo 1999	People with depression were excluded

(Continued)

Eby 1985	Trial of exercise in students who did not have to have depression to enter trial
Elavsky 2007	Did not have to have depression to enter trial
Emery 1990a	Participants did not have to have depression
Emery 1990b	Participants did not have to have depression
Ersek 2008	Did not have to have depression to enter trial
Fitzsimmons 2001	Not exercise (the participant was placed in wheelchair adapted for connection to the front of a bicycle, the carer pedaled and steered the bicycle)
Fox 2007	Did not have to have depression to enter trial
Gary 2007	Did not have to have depression to enter trial
Ghroubi 2009	Did not have to have depression to enter trial
Gottlieb 2009	Did not have to have depression to enter trial
Gusi 2008	Did not all have to have depression to enter trial
Gustafsson 2009	Single bout of exercise with no non-exercising control group
Gutierrez 2012	Did not have to have depression to enter trial
Haffmans 2006	Did not have to have depression to enter trial (mixed population of people with affective disorders)
Hannaford 1988	General mental health patients with no separation of those with depression
Haugen 2007	Did not have to have depression to enter trial
Hedayati 2012	Not a trial
Hembree 2000	Participants were ageing female population residing in a retirement home environment who did not have diagnosis of depression to enter the trial
Herrera 1994	Participants did not have to have depression to enter the trial
Hughes 1986	Effect of exercise on mood in people free from psychopathology
Hughes 2009	Outline trial involving adolescents
Immink 2011	Yoga as intervention

(Continued)

Jacobsen 2012	Participants did not have to have depression to enter the trial
Johansson 2011	Did not have to have depression to enter trial; intervention Qigong
Karlsson 2007	Did not have to have depression to enter trial
Kerr 2008	Did not have to have depression to enter trial
Kerse 2010	Did not all have diagnosis of depression to enter trial
Kim 2004	Effect of exercise on mental distress in healthy participants
Knapen 2003	Non-psychotic psychiatric patients with no separation of those with depression
Knapen 2006	Did not have to have depression to enter trial (mixed depression and/or anxiety and/or personality disorders)
Kubesh 2003	Outcome was executive function; Mood was measured using a subjective mental state scale. People with depression and some controls underwent neuropsychological testing prior to, or after exercise. Participants were randomly allocated to 2 doses of exercise. Thus, people with depression were not randomly allocated to exercise or control
Kulcu 2007	Did not have to have depression to enter trial
Kupecz 2001	Participants were veterans and did not have diagnosis of depression to enter the trial
Labbe 1988	Comparison of exercise with exercise and instructions about how to improve compliance to exercise
Lacombe 1988	Three types of exercise, no non-exercising control
Lai 2006	Trial in stroke patients. Did not have to have depression to be eligible
Latimer 2004	Did not have to have depression to enter trial
Lautenschlager 2008	Did not have to have depression to enter trial
Lavretsky 2011	Control is health education, an active intervention
Legrand 2009	Comparing 2 exercise regimens (of walking intensity) with no non-exercising control group
Leibold 2010	Qualitative analysis
Leppämäki 2002	Effects of exercise on symptoms of mental distress in healthy participants
Levendoglu 2004	Did not have to have depression to enter trial
Lever-van Milligen 2012	Did not have to have depression to be included in trial

(Continued)

Levinger 2011	Did not have to have depression to enter trial
Lin 2007	Did not have to have depression to enter trial
Littbrand 2011	Did not have to have depression; control group undertake activity as intervention
Lolak 2008	Did not have to have depression to enter the trial
Machado 2007	Did not have to have depression to enter trial
MacMahon 1988	Trial involving adolescents
Mailey 2010	Participants were having mental health counselling, but there is no statement that they had to have depression to enter the study
Martin 2009	Did not have to have depression to enter trial
Martinsen 1988a	Non-systematic review
Martinsen 1988b	RCT (block randomisation with respect to sex) but compared different types of exercise without including a non-exercising control group
Martinsen 1989c	Non-systematic review
Martinsen 1993	Non-systematic review
Matthews 2011	Educational intervention and stretching exercises in control; did not have to be depressed to enter trial
McClure 2008	intervention included a combination of interventions including a pedometer, Step Up program workbook, and a series of counselling calls from a study counsellor
Midtgaard 2011	Did not have to have depression to enter trial
Milani 2007	Retrospective evaluation of patients with depressive symptoms who participated in cardiac rehabilitation programme post major cardiac event
Morey 2003	Older sedentary adults who did not have a diagnosis of depression to enter the trial
Motl 2004	Older adults who did not have to be depressed to be included in the trial
Mudge 2008	Did not have to have depression to enter trial
Munro 1997	Cost-effectiveness analysis of the likely public health benefits of purchasing exercise for over 65s
Mutrie 2007	Did not have to have depression to enter trial
NCT00416221	Study not randomised

(Continued)

NCT00546221	Comparing 2 different exercise interventions with no non-exercising control arm
NCT00964054	Trial in adolescents
NCT01152086	Comparing 2 exercise regimens (of hiking programme) with no non-exercising control group, in participants with chronic suicidality, not depression
Neidig 1998	Participants had HIV infection and did not have diagnosis of depression to enter trial
Netz 1994	General mental health patients with no separation of those with depression
Neuberger 2007	Did not have to have depression to enter trial
Nguyen 2001	Trial in people with chronic obstructive pulmonary disease who did not have to have depression to enter trial
O'Neil 2011	Multimodal intervention - telephone based lifestyle advice as well as exercise
Oeland 2010	Combination of people with depression and/or anxiety disorders
Oretzky 2006	Exercise intervention was yoga
Ouzouni 2009	Did not have to have depression to enter trial
Pakkala 2008	Did not have to have depression to enter trial
Palmer 2005	Participants were recovering from substance abuse
Passmore 2006	Aerobic exercise versus aerobic and resistance exercise; no non-exercising control
Peacock 2006	The methodology fulfilled criteria but the study was not completed due to staff sickness
Pelham 1993	General mental health patients with no separation of those with depression
Penninx 2002	Retrospective subgroup analysis of patients who participated in a randomised trial of exercise for knee osteoarthritis who also had depression
Penttinen 2011	A study in survivors of breast cancer, not depression
Perna 2010	A study in breast cancer, not depression
Perri 1984	No outcome measure of depression. This must have been excluded by Debbie Lawlor
Piette 2011	Does not fulfill ACSM criteria for exercise; intervention largely psychological
Raglin 1990	Non-systematic review

(Continued)

Rhodes 1980	Not randomised, participants not depressed
Robledo Colonia 2012	Did not have to have depression to enter trial
Rofey 2008	Trial involving adolescents
Roshan 2011	Trial in adolescents
Roth 1987	No outcome measure of depression. This must have been excluded by Debbie Lawlor
Ruunsunen 2012	Did not have to have depression to enter trial; intervention multimodal
Salminen 2005	Coronary heart disease patients with no separation of those with depressive symptoms Intervention described by authors as health advocacy, counselling and activation programme
Salmon 2001	Non-systematic review
Sarsan 2006	Did not have to have depression to enter trial
Schwarz 2012	Unable to get access to full text of study; attempts made to contact authors were unsuccessful
Sexton 1989	Comparing different types of exercise with no non-exercising group
Silveira 2010	Unable to assess if randomized; attempts made to contact authors unsuccessful, assumed to be non-random
Sims 2006	Did not all have diagnosis of depression to enter trial
Skrinar 2005	DSM-IV or psychotic disorders; no separation of those with depression
Smith 2008	Did not have to have depression to enter trial
Sneider 2008	intervention was combined diet and exercise
Songoygard 2012	Did not have to have depression to be included in trial
Stein 1992	Not described as randomised. Did not have to be depressed to participate
Stern 1983	Trial in patients with myocardial infarction who did not have to be depressed to enter trial
Strömbeck 2007	Did not have to have depression to enter trial
Sung 2009	Did not have to have depression to enter trial
Tapps 2009	Did not have to have depression to enter trial
Taylor 1986	Trial in patients with myocardial infarction (no diagnosis of depression to enter trial)

(Continued)

Tenorio 1986	Trial in subclinical depression
Thomson 2010	Did not have to have depression to enter the trial
Tomas-Carus 2008	Did not have to have depression to enter trial
TREAD 2003	Ongoing trial comparing 2 intensities of exercise
Trivedi 2011	No true control group; both arms of trial receive exercise
Tsang 2003	Participants had chronic physical disease not depression
Tsang 2006	Exercise intervention was Qigong
Underwood 2013	Did not have to have depression to enter trial
Van de Vliet 2003	Single study design
Van der Merwe 2004	Intervention was a manual-based therapy programme not exercise
Vickers 2009	Intervention was not exercise (exercise counselling)
Weinstein 2007	Did not have to have depression to enter trial
Weiss 1989	Not randomised controlled trial
White 2007	Did not have to have depression to enter trial
Whitham 2011	Trial in bipolar affective disorder
Wieman 1980	Jogging versus racket ball so no non-exercising control
Wilbur 2009	Did not have to have depression to enter trial
Williams 1992	Aerobic versus low-intensity exercise. No control group
Wipfli 2008	Did not have to have depression to enter trial
Wipfli 2011	Participants did not have to be depressed to enter trial; control arm had intervention of yoga and stretching

Characteristics of studies awaiting assessment *[ordered by study ID]*

Aghakhani 2011

Methods	Randomised trial
Participants	People with MI in selected hospitals in Iran
Interventions	Education programme, including 'exercises'
Outcomes	Hospital anxiety and depression score
Notes	Unlikely to fulfil inclusion criteria, as participants did not have to have depression and the intervention was multimodal

DEMO II 2012

Methods	Randomised Controlled Trial
Participants	Outpatients with major depressive disorder (DSM-IV)
Interventions	Supervised stretching or supervised aerobic fitness programme
Outcomes	Hamilton depression rating Scale
Notes	Unlikely to fulfil inclusion criteria, as the control arm also received exercise

Gotta 2012

Methods	Clinical trial
Participants	People > 65 years with a recent decline in memory or thinking
Interventions	Aerobic or stretching exercise group, 60 minutes 3 times a week for 12 weeks
Outcomes	Depression included as an outcome measure
Notes	unlikely to be eligible for inclusion as it appears that people did not have to have depression to enter the trial

Martiny 2012

Methods	Randomised trial, 75 adults
Participants	Major depression
Interventions	9-week 'chronotherapeutic intervention' or 9 weeks of daily exercise. Both groups received duloxetine
Outcomes	17-item Hamilton depression rating scale

Martiny 2012 (Continued)

Notes	Likely to be eligible for inclusion N=75 Study unlikely to contribute to current review comparisons. Further scrutiny required
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Murphy 2012

Methods	Randomised clinical trial
Participants	People with 1 of several conditions (e.g. mental health problems, coronary heart disease)
Interventions	Welsh exercise referral scheme or usual care, Euroquol 5D, Hospital anxiety and depression score, Client Service Receipt Inventory questionnaire,
Outcomes	Total minutes of physical activity per week
Notes	Unlikely to be eligible for inclusion as the 'mental health' subgroup included people with depression, anxiety and stress, and because we have previously excluded trials that reported subgroups with depression

Pinniger 2012

Methods	Randomised trial; three groups. (n = 97)
Participants	people with "self-declared" depression
Interventions	6-week programme of Argentine tango dance, mindfulness meditation, waiting list control
Outcomes	Depression, anxiety and stress scale, self esteem scale, satisfaction with life scale, and mindful attention awareness scale
Notes	Likely to be eligible for inclusion N=66 Study could contribute data to two comparisons, although three-arm trial with small sample size. Results positive for intervention involving exercise. Unlikely to affect review conclusions

Sturm 2012

Methods	Randomised trial (n = 20)
Participants	People with previous suicidal attempts and clinically diagnosed with "hopelessness"
Interventions	9-week hiking, 9-week control
Outcomes	Hopelessness, depression, physical endurance, suicidal ideation

Sturm 2012 (Continued)

Notes	Likely to be eligible for inclusion N=20 Study could contribute data for one comparison, although very small sample size. Results positive for intervention involving exercise. Unlikely to affect review conclusions
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CBT: cognitive behavioural therapy; HAM-D: Hamilton Rating Scale for Depression

Characteristics of ongoing studies [ordered by study ID]**ACTRN12605000475640**

Trial name or title	Does a home-based physical activity programme improve function and depressive symptomatology in older primary care patients: a randomised controlled trial
Methods	Randomised controlled trial
Participants	Those aged 75 or older with depression
Interventions	Home-based physical activity programme
Outcomes	Change in geriatric depression score
Starting date	2006
Contact information	Karen Hayman k.hayman@auckland.ac.nz
Notes	

ACTRN12609000150246

Trial name or title	Promoting physical activity to improve the outcome of depression in later life (ACTIVEDEP)
Methods	Randomised controlled trial - parallel
Participants	Age 50 or over with DSM-IV diagnosis of depression
Interventions	Mixed aerobic and strength training programme
Outcomes	Montgomery-Asperg Depression Rating Scale; remission of symptoms
Starting date	2009

ACTRN12609000150246 (Continued)

Contact information	Oswaldo Ameida osvaldo.almeida@uwa.edu.au
Notes	

ACTRN12612000094875

Trial name or title	A randomised controlled trial to improve depression in family carers through a physical activity intervention IMPACCT Study
Methods	Randomised controlled trial
Participants	Depressed carers over 60 and their care recipients
Interventions	6-month physical activity programme
Outcomes	Rating on Geriatric Depression Scale
Starting date	2012
Contact information	Ms Kirsten Moore k.moore@nari.unimelb.edu.au
Notes	Completed, unreported study

CTR/2012/09/002985

Trial name or title	Effect of sprint interval training on depression: a randomised controlled trial
Methods	Randomisation, blinding
Participants	Age 20 35, male, diagnosis of depression
Interventions	Sprint training exercise or aerobic exercise
Outcomes	Depression scale
Starting date	September 2012
Contact information	Dr Khaled Badaam khalid.badaam@yahoo.com
Notes	Completed, unreported study

EFFORT D

Trial name or title	Effect of running therapy on depression (EFFORT-D). Design of a randomised controlled trial in adult patients [ISRCTN 1894]
Methods	Randomised controlled trial
Participants	People with a depressive disorder
Interventions	Group-based 1-hour exercise sessions of increased intensity over 6 months
Outcomes	Reduction in depressive symptoms as measured by HAM-D
Starting date	2012
Contact information	Frank Kruisdijk f.kruisdijk@ggzcentraal.nl
Notes	

IRCT201205159763

Trial name or title	The effect of regular exercise on the depression of haemodialysis patients
Methods	
Participants	Age 15 - 65, chronic kidney disease receiving haemodialysis
Interventions	Exercise
Outcomes	Beck Depression Inventory Score
Starting date	June 2012
Contact information	Alireza Abdi alireza_abdi61@yahoo.com
Notes	Depression not specified in inclusion criteria Completed, unreported study

IRCT2012061910003N1

Trial name or title	A comparative study of the efficiency of group cognitive-behavioural therapy with aerobic exercise in treating major depression
Methods	Randomised
Participants	18 - 25 with depressive symptoms
Interventions	Either exercise or CBT or no intervention as control

IRCT2012061910003N1 (Continued)

Outcomes	Beck Depression Inventory score
Starting date	July 2012
Contact information	Kheirollah Sadeghi khsadeghi@kums.ac.ir
Notes	Completed, unreported study

ISRCTN05673017

Trial name or title	Psycho-education physical exercise effects: does treating subsyndromal depression improve depression- and diabetes-related outcomes? PEPEE
Methods	Randomised controlled three-arm study
Participants	18 - 60 years with depression and Type II diabetes
Interventions	Psycho-education or exercise intervention or control
Outcomes	Depressive symptoms
Starting date	2010
Contact information	Mirjana Pibernik-Okanovic mirjana.pibernik@idb.hr
Notes	

NCT00103415

Trial name or title	Randomized clinical trial Investigating the effect of different exercise forms on depression
Methods	Randomised interventional model
Participants	18 - 55 with depression
Interventions	Strength endurance training
Outcomes	Hamilton Depression Scoring Scale
Starting date	2006
Contact information	Merete Nordentoft Bispebjerg Hospital

NCT00103415 (Continued)

Notes	
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NCT00643695

Trial name or title	Efficacy of an exercise intervention to decrease depressive symptoms in veterans with hepatitis C
Methods	Randomised interventional model
Participants	Adults positive for hepatitis C with depression
Interventions	Home-based walking programme
Outcomes	Reduction in Beck Depression Scale
Starting date	2008
Contact information	Patricia Taylor-Young Portland VA Medical Centre
Notes	

NCT00931814

Trial name or title	Effects of exercise on depression symptoms, physical function, and quality of life in community-dwelling elderly
Methods	Randomised interventional model
Participants	Community-dwelling participants age 65 or older
Interventions	Group exercise 3 times per week
Outcomes	Taiwanese Geriatric Depression Scale
Starting date	2009
Contact information	Ying-Tai Wu National Taiwan University
Notes	

NCT01024790

Trial name or title	Exercise study to help patients who have type 2 diabetes and depression
Methods	Randomised interventional model
Participants	Eomen 21 - 65, with depression and diabetes
Interventions	Exercise group
Outcomes	Depression symptoms
Starting date	2009
Contact information	Kristin Schneider University of Massachusetts, Worcester
Notes	

NCT01383811

Trial name or title	Clinical and neuroendocrine/metabolic benefits of exercise in treatment resistant depression (TRD): a feasibility study
Methods	Randomised controlled trial
Participants	Sedentary adults with depression
Interventions	Moderate intensity aerobic exercise
Outcomes	Change from baseline depression score on Hamilton Scale
Starting date	2011
Contact information	Ravi Singareddy Penn State University College of Medicine
Notes	

NCT01401569

Trial name or title	Efficacy of exercise and counselling Intervention on relapse in smokers with depressive disorders STOB-ACTIV
Methods	Randomised, intervention model
Participants	18-65 with depression
Interventions	Exercise

NCT01401569 (Continued)

Outcomes	Evaluation of depression
Starting date	2010
Contact information	Xavier Quantin x-quantin@chu-montpellier.fr
Notes	May be multimodal with counselling for smoking cessation

NCT01464463

Trial name or title	The impact of psychological interventions (with and without exercise) on psychometric and immunological measures in patients with major depression
Methods	Randomised controlled trial
Participants	18 - 65 year-olds with depression diagnosed according to DSM-IV
Interventions	Exercise and psychological input
Outcomes	Change in depression symptomology
Starting date	2011
Contact information	Frank Euteneuer frank.euteneuer@staff.uni-marburg.de
Notes	Intervention may be multimodal

NCT01573130

Trial name or title	An internet-administered, therapist-supported physical exercise program for the treatment of depression
Methods	Randomised intervention model
Participants	Adults with DSM-IV diagnosis of depression
Interventions	Physical exercise programme
Outcomes	Change in MADRS rating scale for depression
Starting date	March 2012
Contact information	Prof Per Carlbring per.carlbring@psy.umu.se

NCT01573130 (Continued)

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NCT01573728

Trial name or title	Role of exercise in depression in middle aged and older adults
Methods	Randomised, double-blind
Participants	Age 46 or older; diagnosis of depression
Interventions	Low-dose exercise
Outcomes	PHQ 9 depression score
Starting date	May 2012
Contact information	Daniel O Clark Indiana University School of Medicine
Notes	

NCT01619930

Trial name or title	The effects of behavioral activation and physical exercise on depression
Methods	Randomised, Intervention Model
Participants	Participants with depression
Interventions	Behavioural activation, motivational interviewing, physical activity
Outcomes	Change from baseline in Patient Health Questionnaire
Starting date	August 2012
Contact information	Professor Per Carlbring per.carlbring@psy.umu.se
Notes	

NCT01696201

Trial name or title	Effect of a supervised exercise program during whole pregnancy on outcomes and level of depression. A randomized controlled trial
Methods	Randomised, intervention
Participants	Pregnant women
Interventions	Exercise group
Outcomes	Change in level of depression
Starting date	2009
Contact information	Maria Perales m.perales.santaella@gmail.com
Notes	

NCT01763983

Trial name or title	Effects of Cognitive Behavioural Therapy and exercise on depression and cognitive deficits in Multiple Sclerosis
Methods	Randomised, single-blind, intervention model
Participants	18 - 50 years-old with multiple sclerosis and depression
Interventions	Exercise, CBT
Outcomes	Change in Hamilton Depression rating, cognitive scoring
Starting date	January 2013
Contact information	Bethany Lerman bethany.lerman@sunnybrook.ca
Notes	

NCT01787201

Trial name or title	The effects of exercise in depression symptoms using levels of neurotransmitters and EEG as markers
Methods	Randomised, intervention model
Participants	18 - 65 years old with depression
Interventions	Exercise

NCT01787201 (Continued)

Outcomes	Beck Depression Inventory score, serum levels serotonin and catecholamines
Starting date	March 2013
Contact information	Dr Timothy Barclay thbarclay@liberty.edu
Notes	

NCT01805479

Trial name or title	Exercise training in depressed traumatic brain injury survivors
Methods	Randomised, single-blind intervention model
Participants	Depressed, sedentary survivors of traumatic brain injury
Interventions	Aerobic exercise
Outcomes	Mood assessment, MRI, neuropsychology testing, biochemical assays, suicide severity rating
Starting date	February 2013
Contact information	Justin Alicea joalicea@vcu.edu
Notes	

UMIN000001488

Trial name or title	A randomised controlled trial of exercise class for older persons with mild depression
Methods	Parallel randomised trial
Participants	60 - 86 year-olds with mild depression
Interventions	Low-intensity exercise programme
Outcomes	Hamilton Depression Rating Scale
Starting date	2009
Contact information	Kazushige Ihara ihara1@med.toho-u.ac.jp
Notes	

BDI: Beck Depression Inventory; RCT: randomised controlled trial; MDD: major depressive disorder

DATA AND ANALYSES

Comparison 1. Exercise versus 'control'

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in depression symptoms post-treatment	35	1353	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-0.81, -0.42]
2 Reduction in depression symptoms follow-up	8	377	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.63, -0.03]
3 Completed intervention or control	29	1363	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.97, 1.04]
4 Quality of life	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Mental	2	59	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.76, 0.29]
4.2 Psychological	2	56	Std. Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.29, 0.86]
4.3 Social	2	56	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.35, 0.74]
4.4 Environment	2	56	Std. Mean Difference (IV, Fixed, 95% CI)	0.62 [0.06, 1.18]
4.5 Physical	4	115	Std. Mean Difference (IV, Fixed, 95% CI)	0.45 [0.06, 0.83]

Comparison 2. Exercise versus psychological therapies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in depression symptoms post-treatment	7	189	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.26]
2 Completed exercise or psychological therapies	4	172	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.95, 1.24]
3 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Physical	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Mental	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Exercise versus bright light therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in depression symptoms post-treatment	1	18	Mean Difference (IV, Fixed, 95% CI)	-6.4 [-10.20, -2.60]

Comparison 4. Exercise versus pharmacological treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in depression symptoms post-treatment	4	300	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.34, 0.12]
2 Completed exercise or antidepressants	3	278	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.86, 1.12]
3 Quality of Life	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Mental	1	25	Mean Difference (IV, Fixed, 95% CI)	-11.90 [-24.04, 0.24]
3.2 Physical	1	25	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.67, 3.27]

Comparison 5. Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise vs control subgroup analysis: type of exercise	35		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Aerobic exercise	28	1080	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.77, -0.34]
1.2 Mixed exercise	3	128	Std. Mean Difference (IV, Random, 95% CI)	-0.85 [-1.85, 0.15]
1.3 Resistance exercise	4	144	Std. Mean Difference (IV, Random, 95% CI)	-1.03 [-1.52, -0.53]
2 Exercise vs control subgroup analysis: intensity	35		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 light/moderate	3	76	Std. Mean Difference (IV, Random, 95% CI)	-0.83 [-1.32, -0.34]
2.2 moderate	12	343	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.01, -0.28]
2.3 hard	11	595	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.93, -0.20]
2.4 vigorous	5	230	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.30, -0.24]
2.5 Moderate/hard	2	66	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.13, -0.13]
2.6 Moderate/vigorous	2	42	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-1.61, 0.85]
3 Exercise vs control subgroup analysis: number of sessions	35		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 0 - 12 sessions	5	195	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-1.26, 0.43]
3.2 13 - 24 sessions	9	296	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.09, -0.31]
3.3 25 - 36 sessions	8	264	Std. Mean Difference (IV, Random, 95% CI)	-0.80 [-1.30, -0.29]
3.4 37+ sessions	10	524	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.69, -0.23]
3.5 unclear	3	73	Std. Mean Difference (IV, Random, 95% CI)	-0.89 [-1.39, -0.40]
4 Exercise vs control subgroup analysis: diagnosis of depression	35		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 clinical diagnosis of depression	23	967	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.81, -0.32]
4.2 depression categorised according to cut points on a scale	11	367	Std. Mean Difference (IV, Random, 95% CI)	-0.67 [-0.95, -0.39]
4.3 unclear	1	18	Std. Mean Difference (IV, Random, 95% CI)	-2.00 [-3.19, -0.82]

5 Exercise vs control subgroup analysis: type of control	35	1353	Mean Difference (IV, Fixed, 95% CI)	-1.57 [-1.97, -1.16]
5.1 placebo	2	156	Mean Difference (IV, Fixed, 95% CI)	-2.66 [-4.58, -0.75]
5.2 No treatment, waiting list, usual care, self monitoring	17	563	Mean Difference (IV, Fixed, 95% CI)	-4.75 [-5.72, -3.78]
5.3 exercise plus treatment vs treatment	6	225	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-2.21, -0.23]
5.4 stretching, meditation or relaxation	6	219	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.65, 0.48]
5.5 occupational intervention, health education, casual conversation	4	190	Mean Difference (IV, Fixed, 95% CI)	-3.67 [-4.94, -2.41]

Comparison 6. Exercise versus control: sensitivity analyses

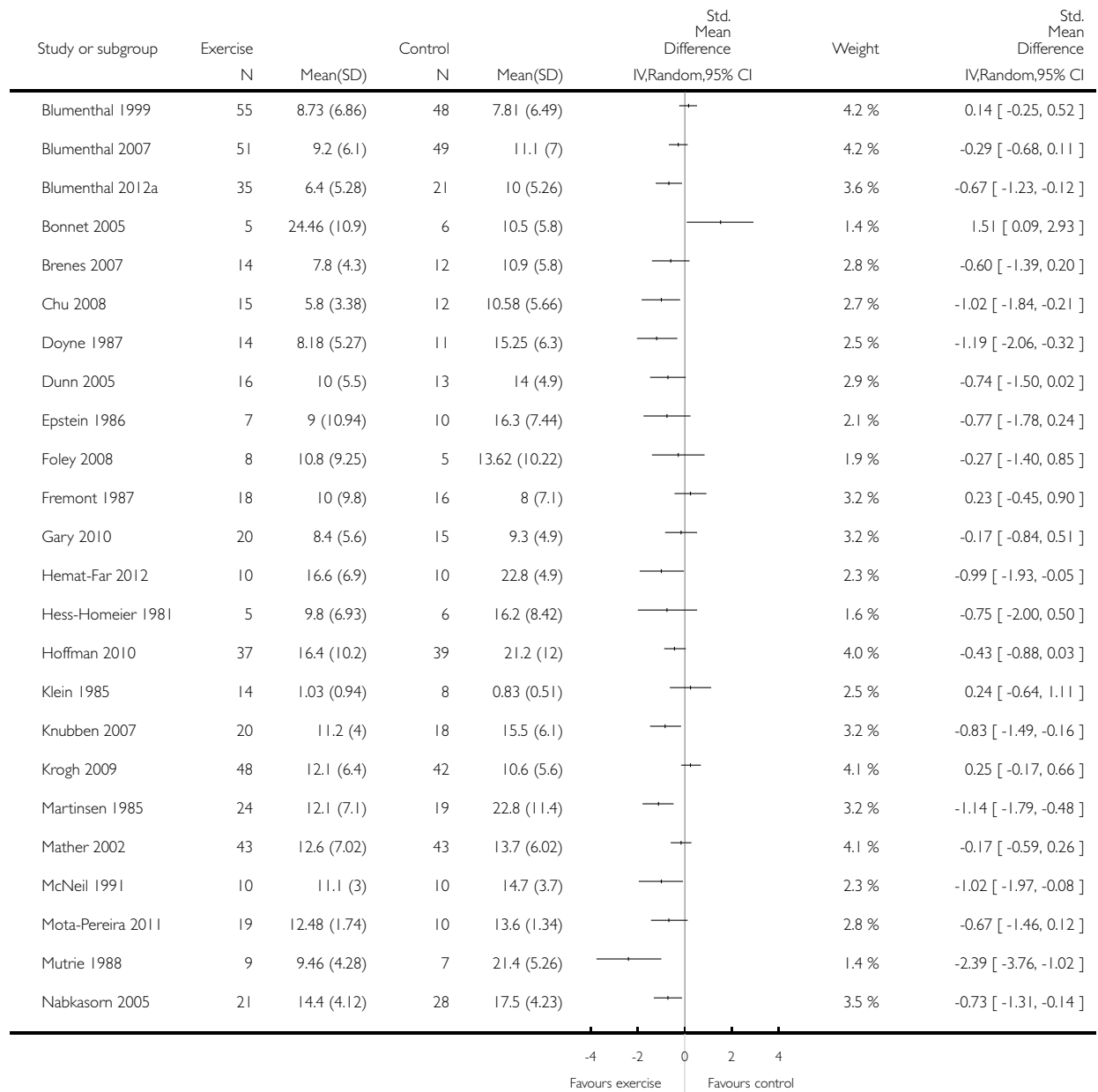
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in depression symptoms post-treatment: peer-reviewed journal publications and doctoral theses only	34	1335	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-0.78, -0.40]
2 Reduction in depression symptoms post-treatment: studies published as abstracts or conference proceedings only	1	18	Std. Mean Difference (IV, Random, 95% CI)	-2.00 [-3.19, -0.82]
3 Reduction in depression symptoms post-treatment: studies with adequate allocation concealment	14	829	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-0.75, -0.24]
4 Reduction in depression symptoms post-treatment: studies using intention-to-treat analysis	11	567	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [1.00, -0.22]
5 Reduction in depression symptoms post-treatment: studies with blinded outcome assessment	12	658	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.60, -0.12]
6 Reduction in depression symptoms post-treatment: allocation concealment, intention-to-treat, blinded outcome	6	464	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.47, 0.11]
7 Reduction in depression symptoms post-treatment: Lowest dose of exercise	35	1347	Std. Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.55, -0.33]

Analysis 1.1. Comparison 1 Exercise versus 'control', Outcome 1 Reduction in depression symptoms post-treatment.

Review: Exercise for depression

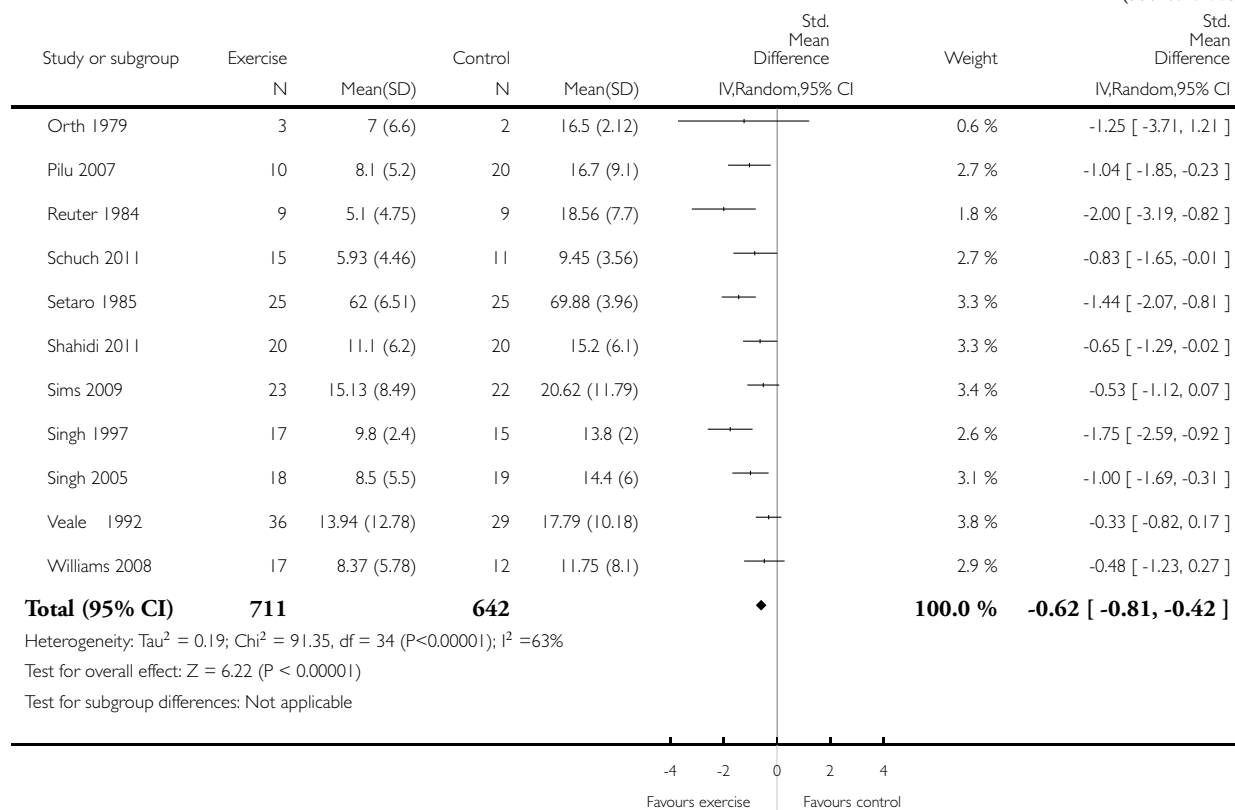
Comparison: 1 Exercise versus 'control'

Outcome: 1 Reduction in depression symptoms post-treatment



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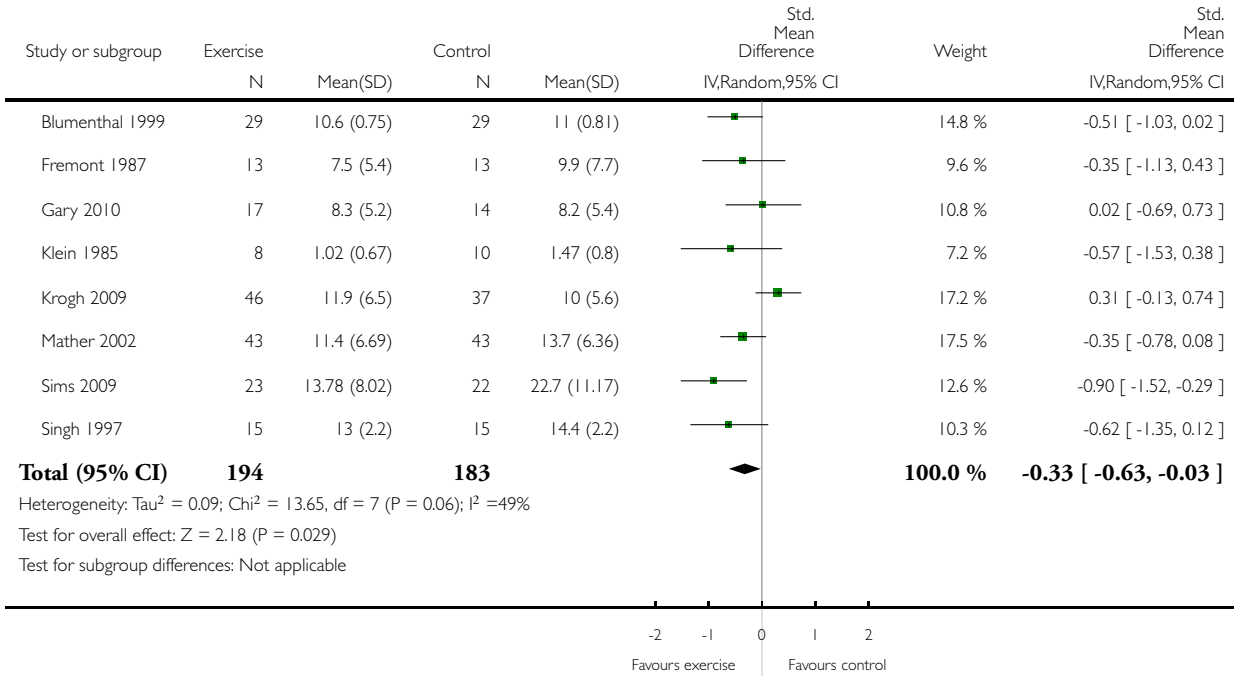


Analysis 1.2. Comparison 1 Exercise versus 'control', Outcome 2 Reduction in depression symptoms follow-up.

Review: Exercise for depression

Comparison: 1 Exercise versus 'control'

Outcome: 2 Reduction in depression symptoms follow-up

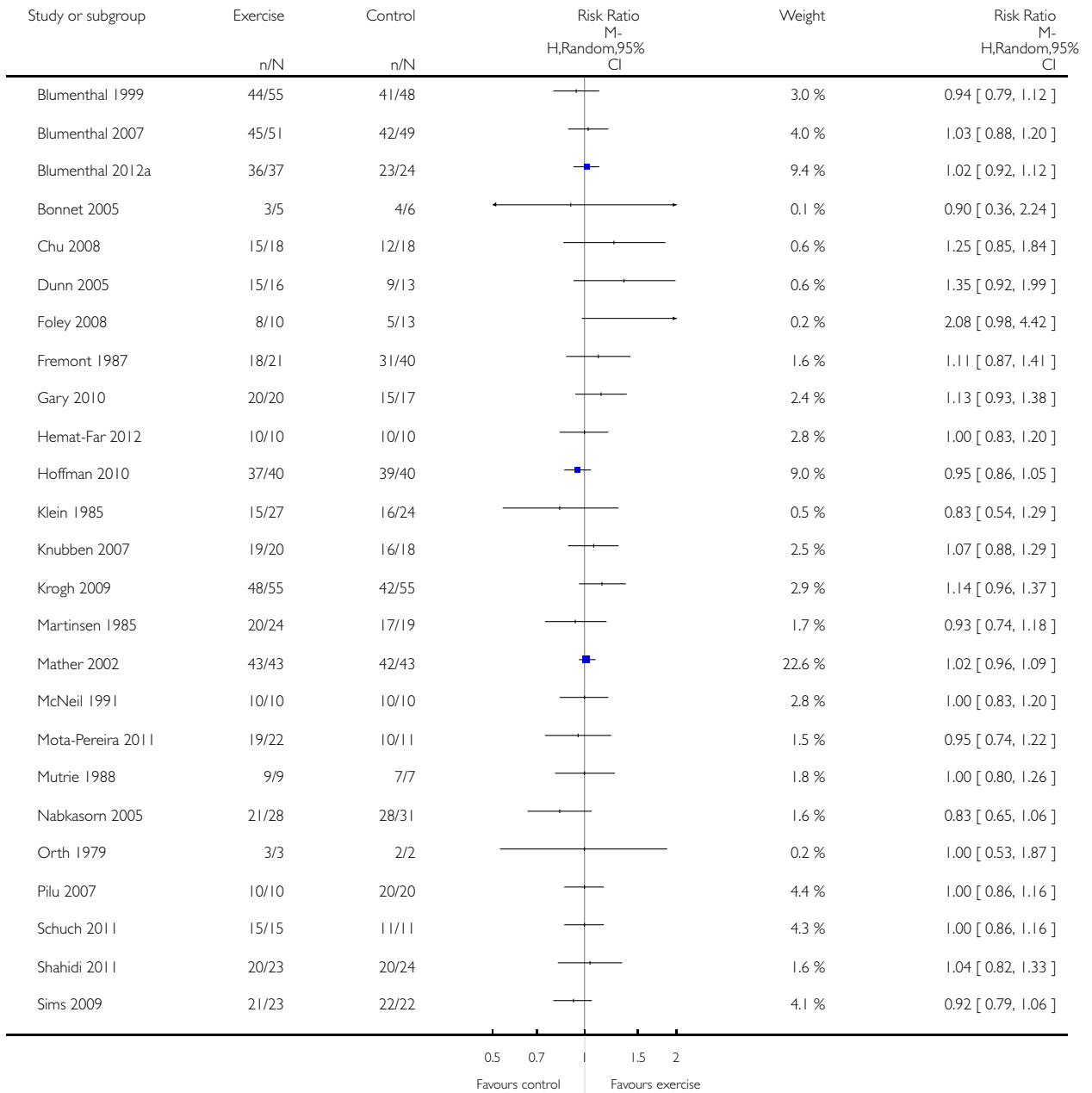


Analysis 1.3. Comparison 1 Exercise versus 'control', Outcome 3 Completed intervention or control.

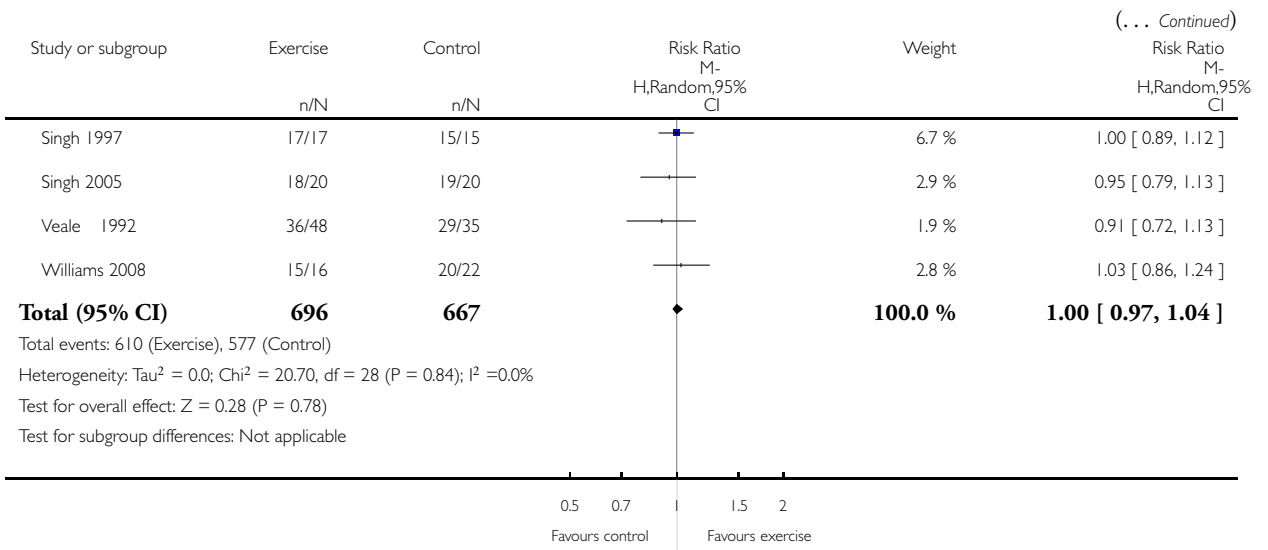
Review: Exercise for depression

Comparison: 1 Exercise versus 'control'

Outcome: 3 Completed intervention or control



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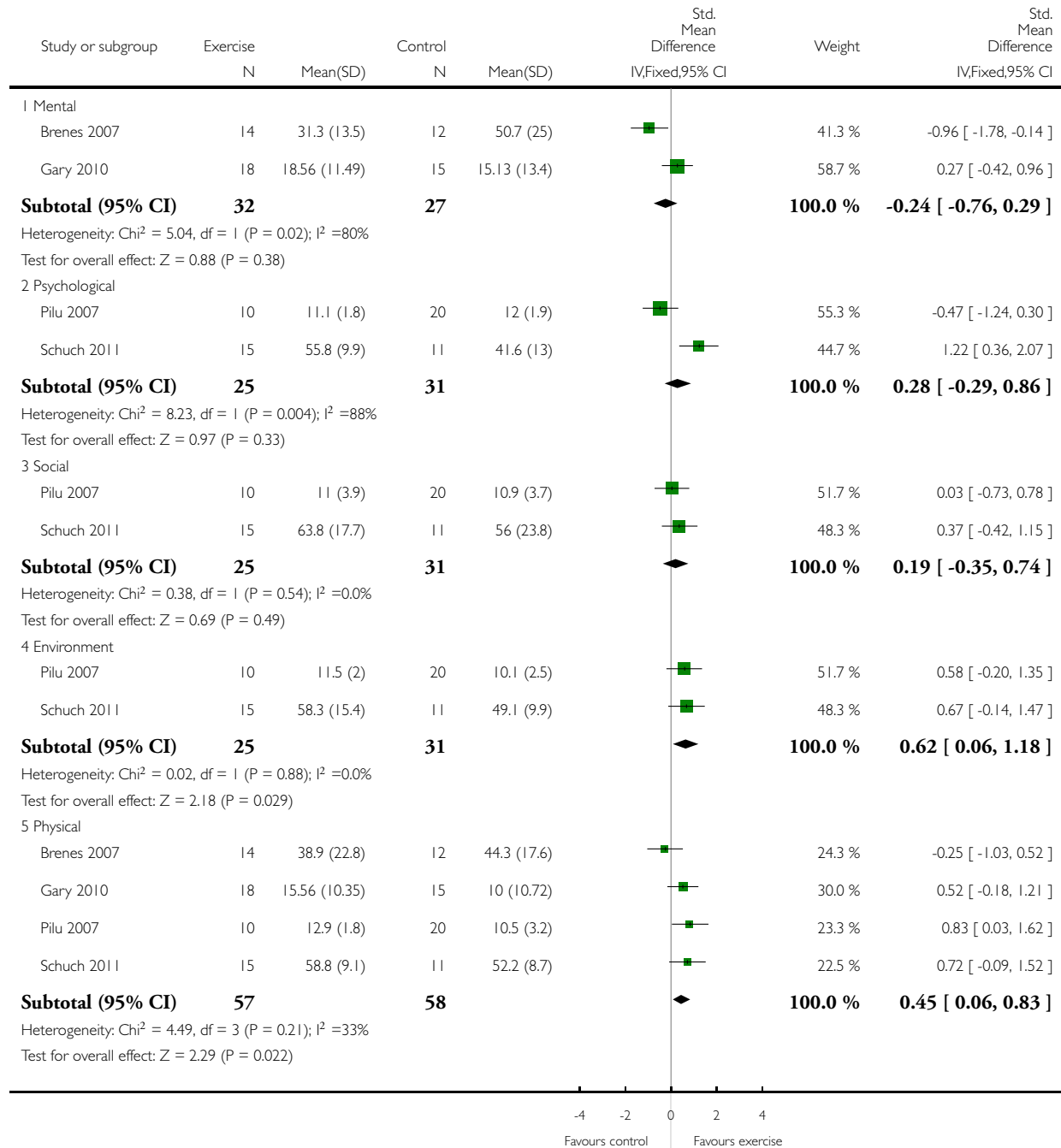


Analysis 1.4. Comparison 1 Exercise versus 'control', Outcome 4 Quality of life.

Review: Exercise for depression

Comparison: 1 Exercise versus 'control'

Outcome: 4 Quality of life

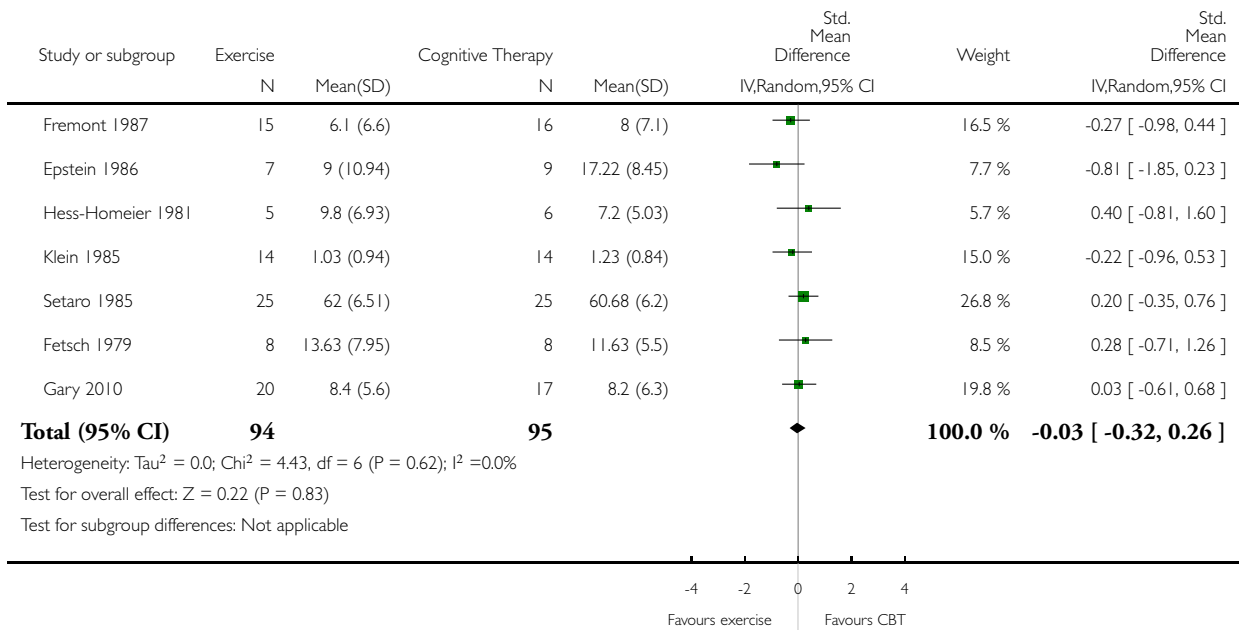


Analysis 2.1. Comparison 2 Exercise versus psychological therapies, Outcome 1 Reduction in depression symptoms post-treatment.

Review: Exercise for depression

Comparison: 2 Exercise versus psychological therapies

Outcome: 1 Reduction in depression symptoms post-treatment

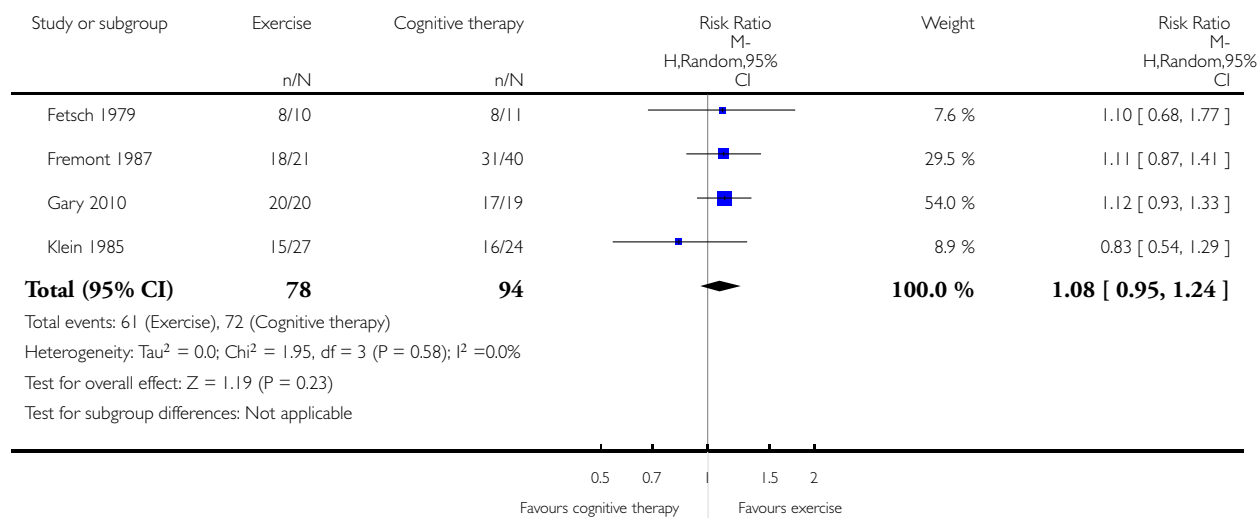


Analysis 2.2. Comparison 2 Exercise versus psychological therapies, Outcome 2 Completed exercise or psychological therapies.

Review: Exercise for depression

Comparison: 2 Exercise versus psychological therapies

Outcome: 2 Completed exercise or psychological therapies

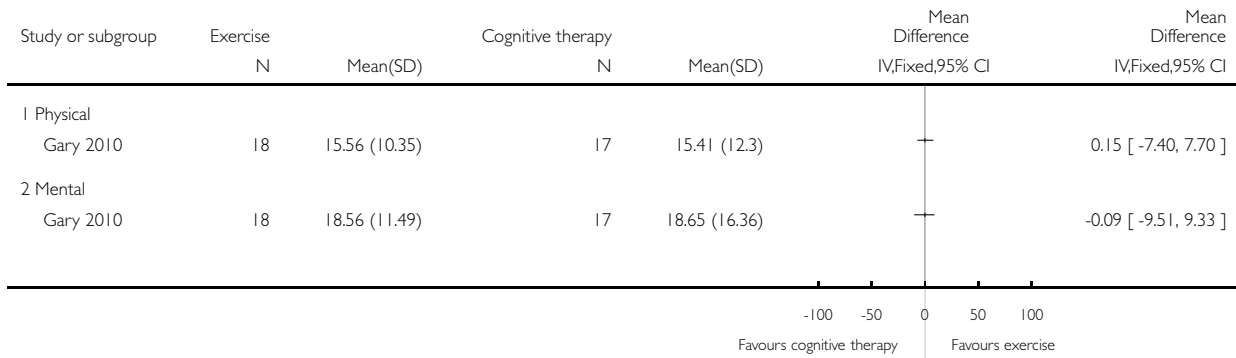


Analysis 2.3. Comparison 2 Exercise versus psychological therapies, Outcome 3 Quality of life.

Review: Exercise for depression

Comparison: 2 Exercise versus psychological therapies

Outcome: 3 Quality of life

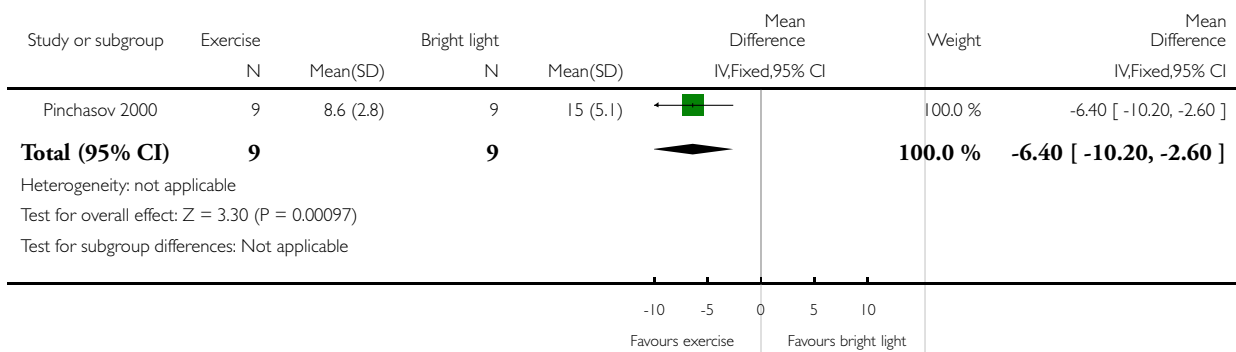


Analysis 3.1. Comparison 3 Exercise versus bright light therapy, Outcome 1 Reduction in depression symptoms post-treatment.

Review: Exercise for depression

Comparison: 3 Exercise versus bright light therapy

Outcome: 1 Reduction in depression symptoms post-treatment

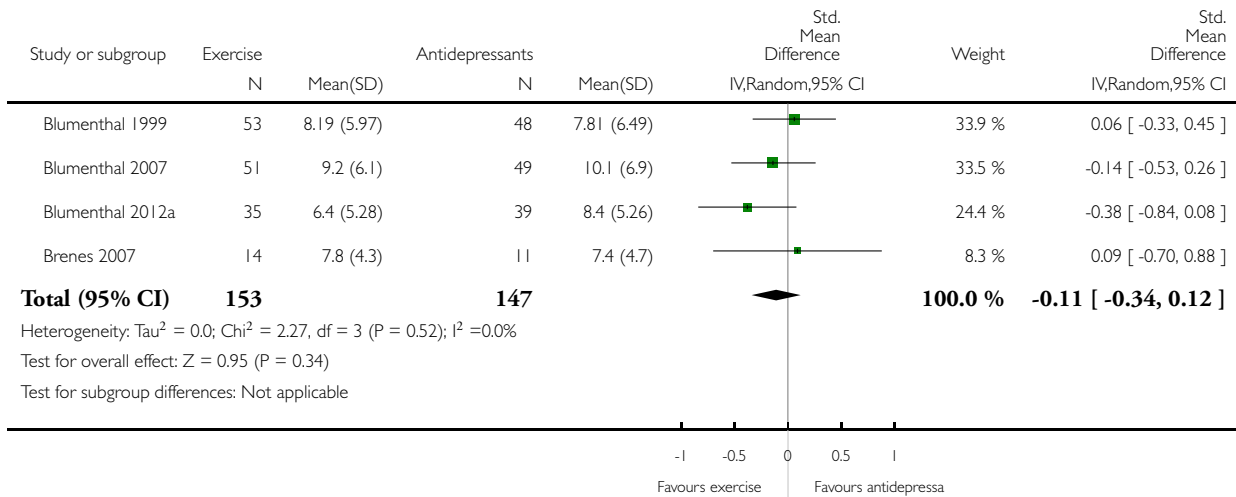


Analysis 4.1. Comparison 4 Exercise versus pharmacological treatments, Outcome 1 Reduction in depression symptoms post-treatment.

Review: Exercise for depression

Comparison: 4 Exercise versus pharmacological treatments

Outcome: 1 Reduction in depression symptoms post-treatment

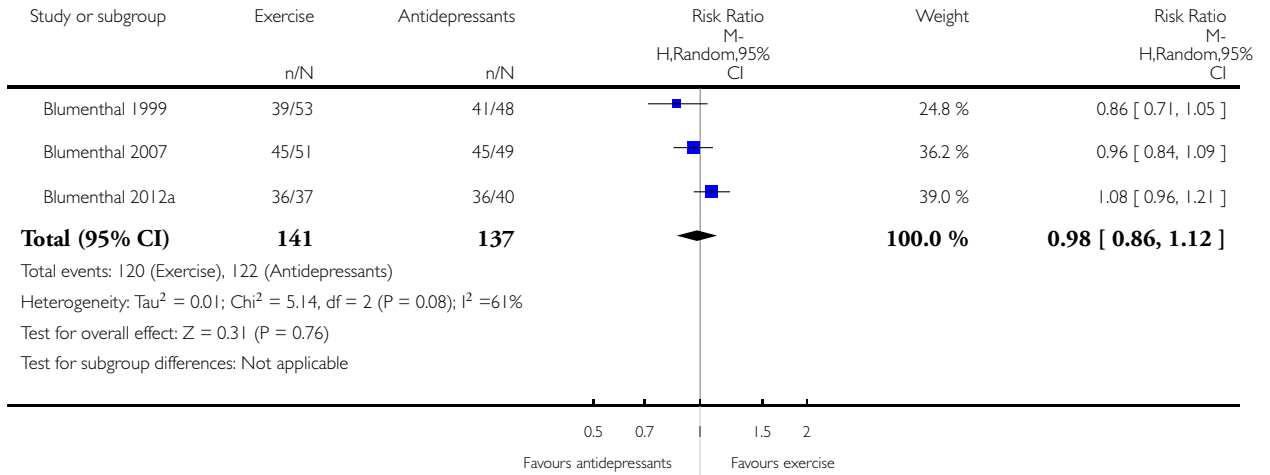


Analysis 4.2. Comparison 4 Exercise versus pharmacological treatments, Outcome 2 Completed exercise or antidepressants.

Review: Exercise for depression

Comparison: 4 Exercise versus pharmacological treatments

Outcome: 2 Completed exercise or antidepressants

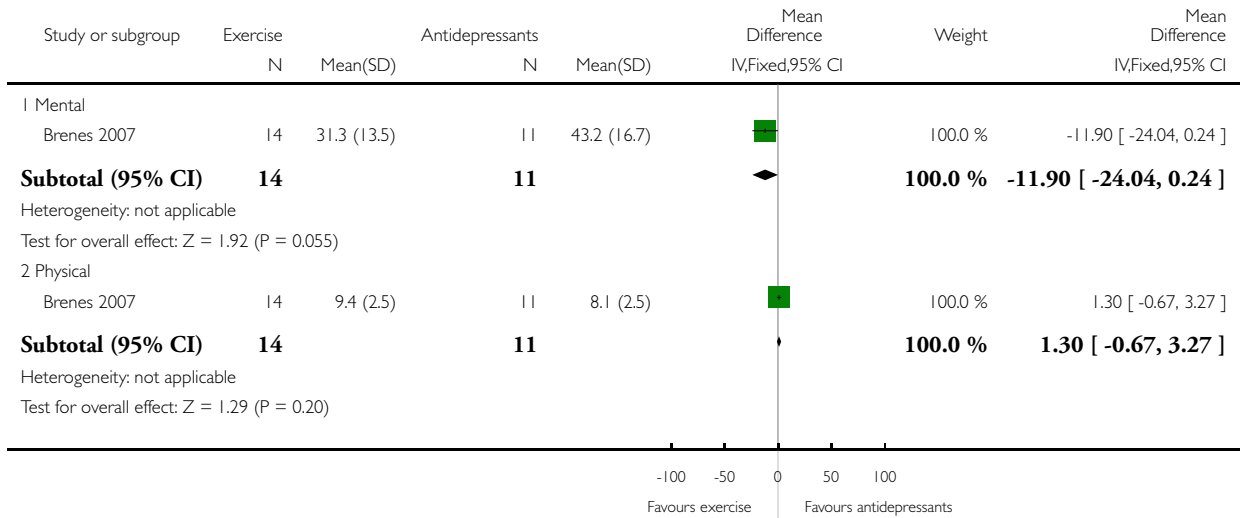


Analysis 4.3. Comparison 4 Exercise versus pharmacological treatments, Outcome 3 Quality of Life.

Review: Exercise for depression

Comparison: 4 Exercise versus pharmacological treatments

Outcome: 3 Quality of Life

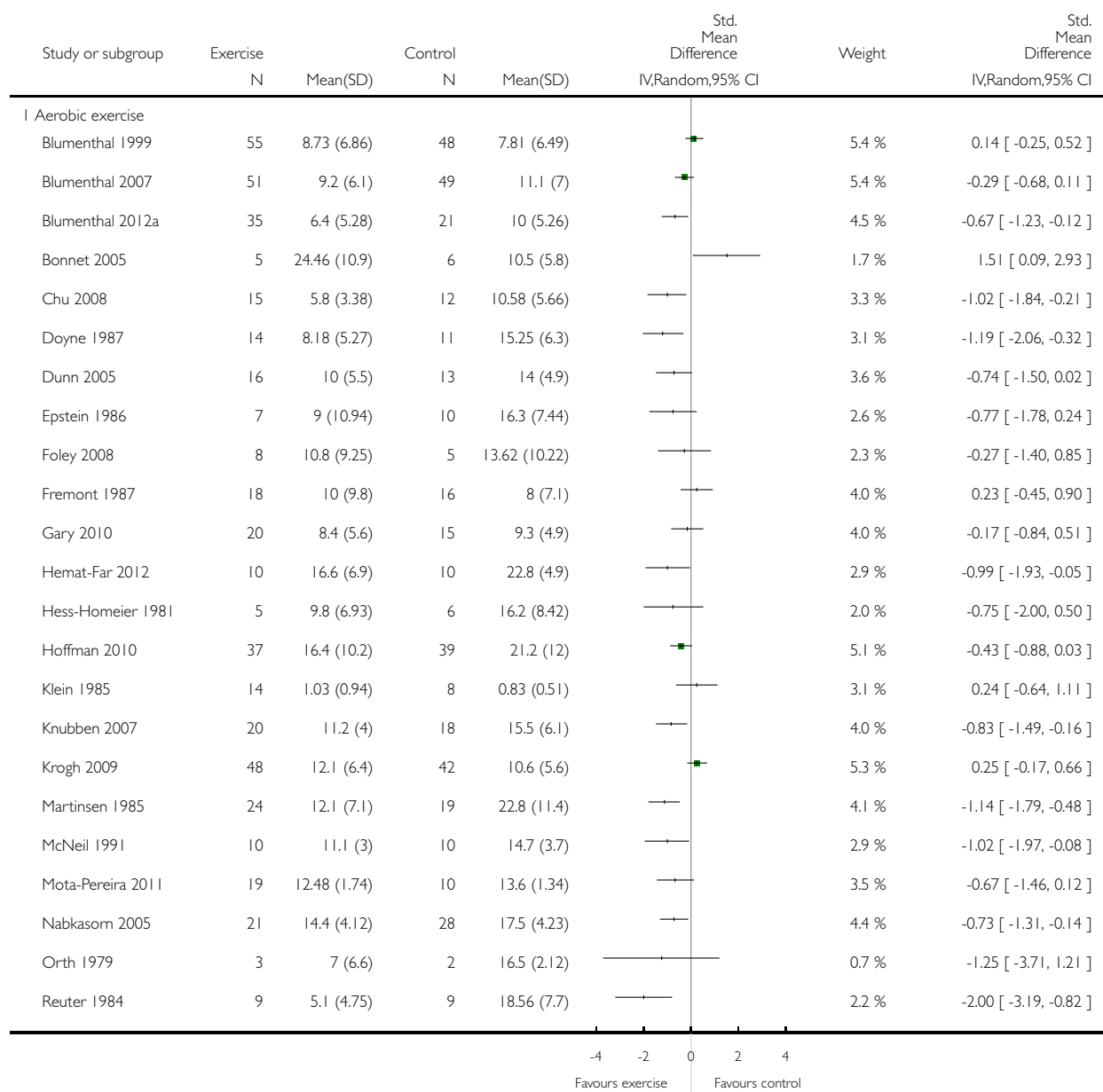


Analysis 5.1. Comparison 5 Reduction in depression symptoms post-treatment: Subgroup analyses, Outcome 1 Exercise vs control subgroup analysis: type of exercise.

Review: Exercise for depression

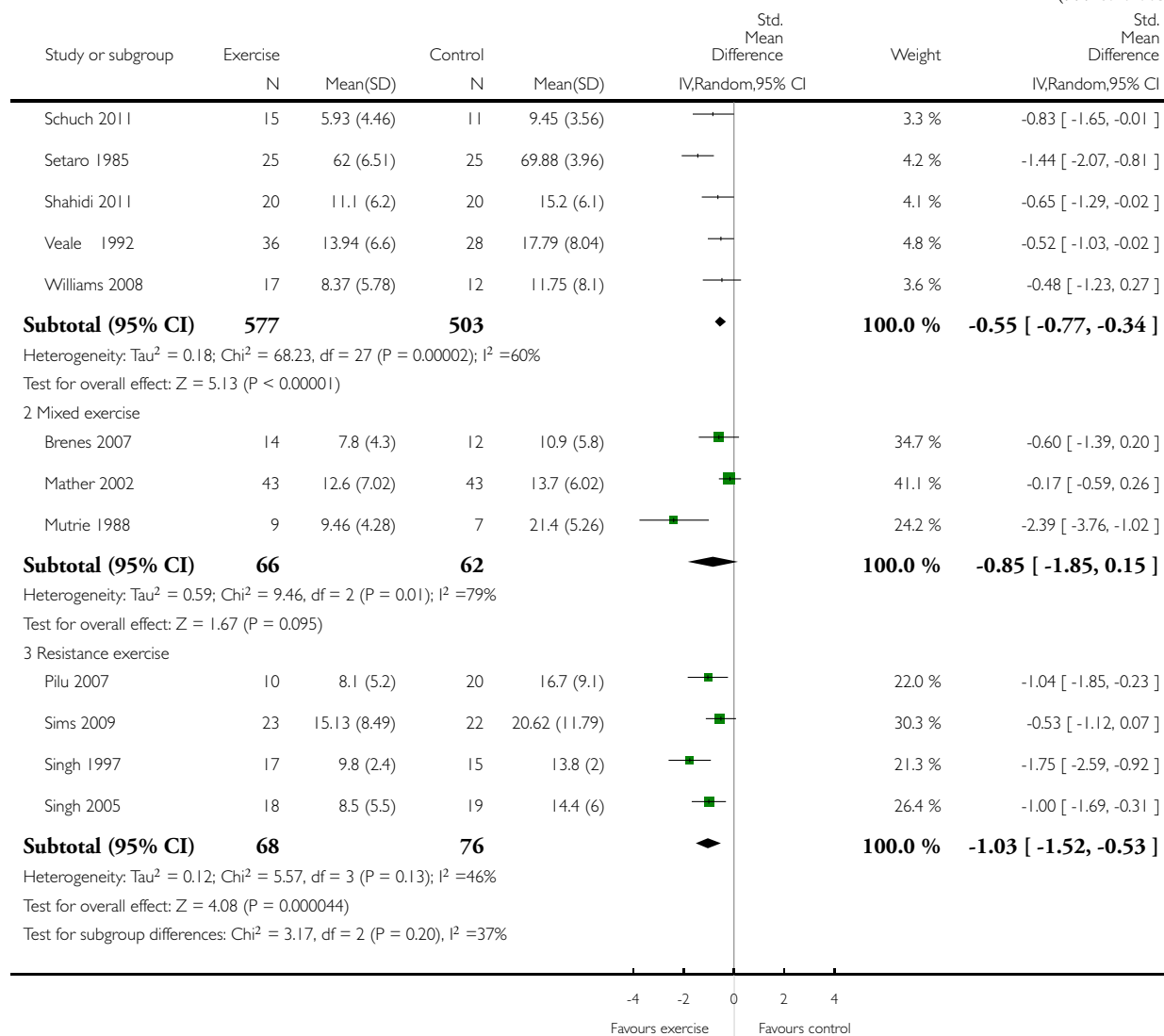
Comparison: 5 Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome: 1 Exercise vs control subgroup analysis: type of exercise



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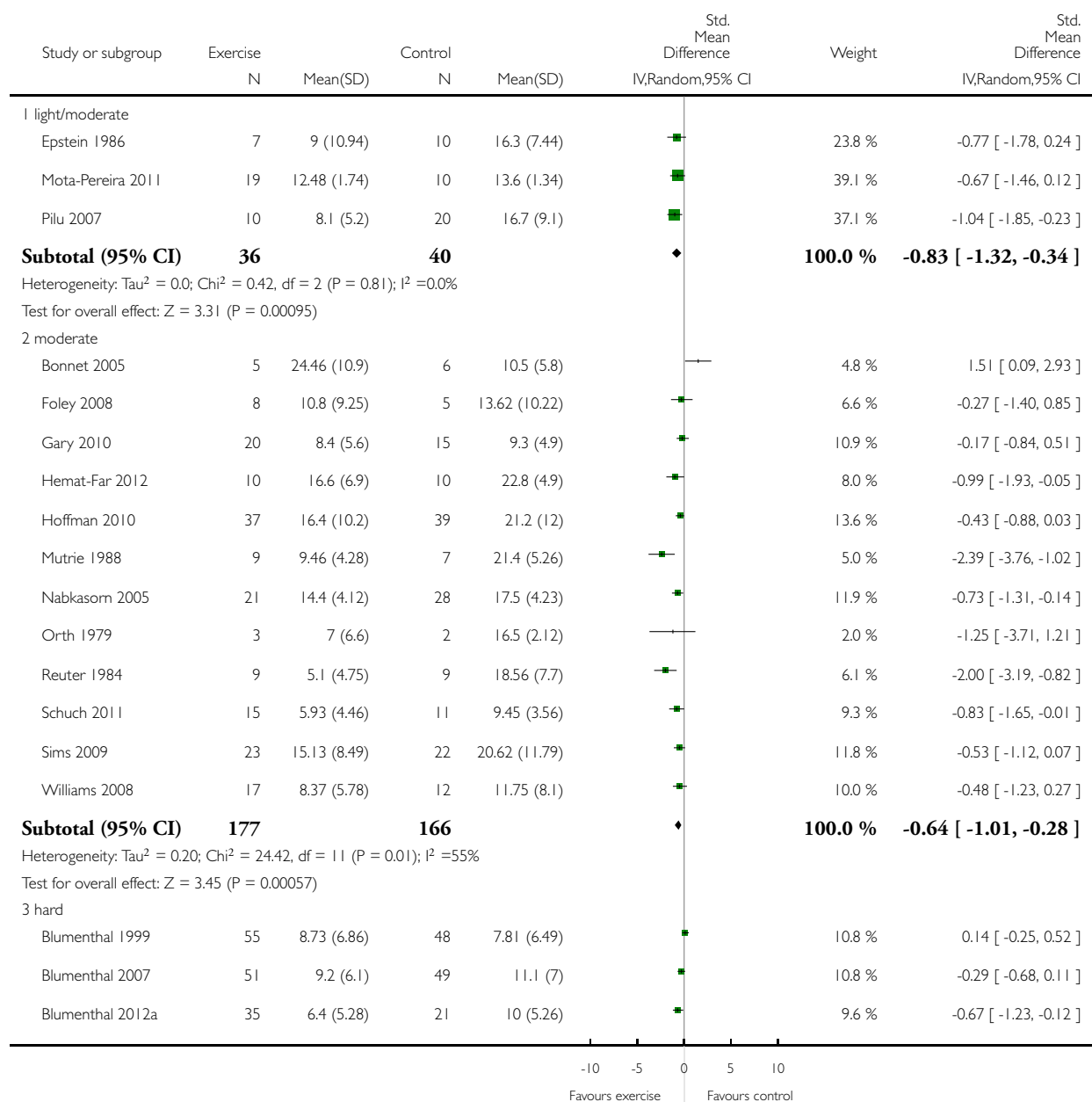


Analysis 5.2. Comparison 5 Reduction in depression symptoms post-treatment: Subgroup analyses, Outcome 2 Exercise vs control subgroup analysis: intensity.

Review: Exercise for depression

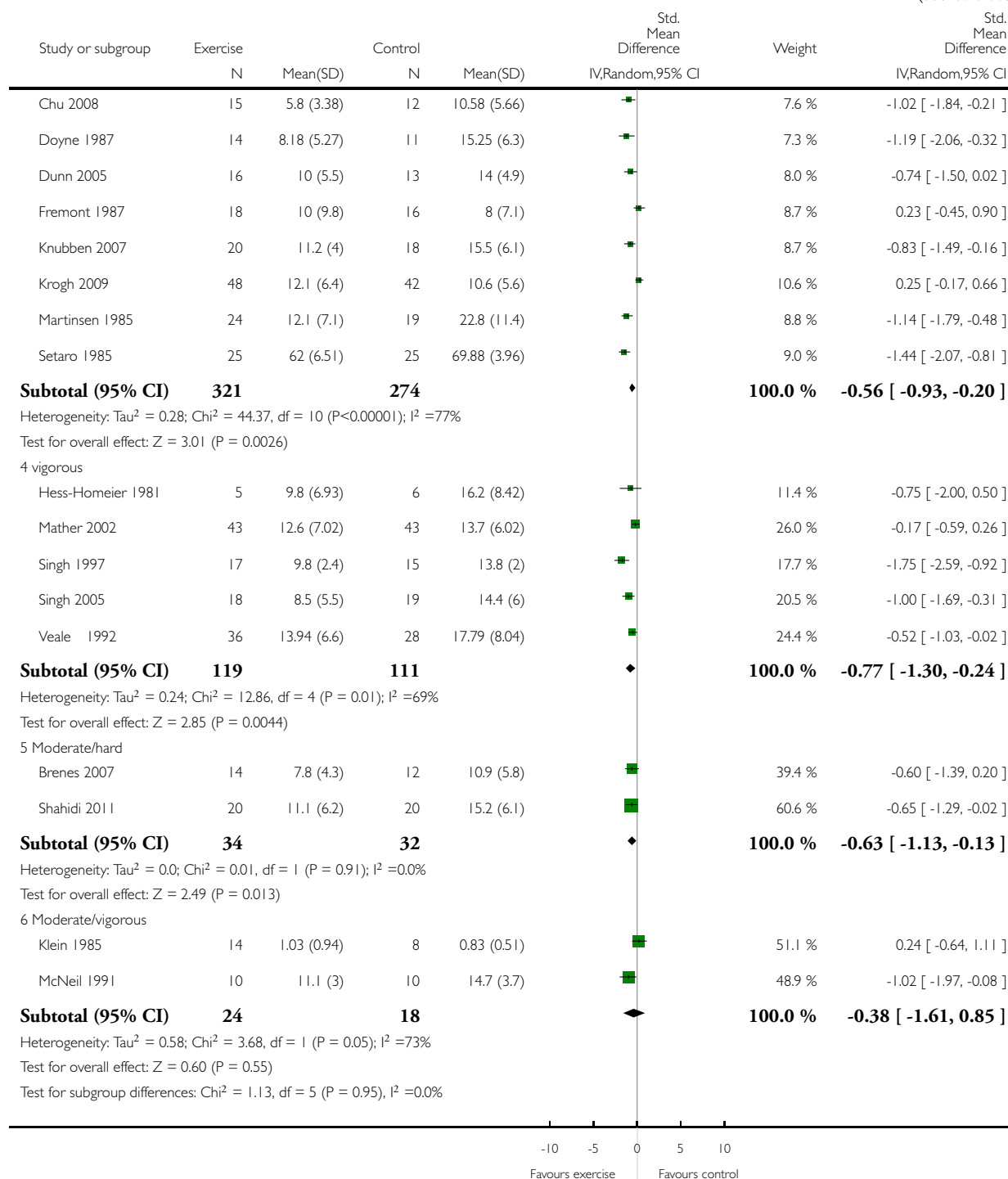
Comparison: 5 Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome: 2 Exercise vs control subgroup analysis: intensity



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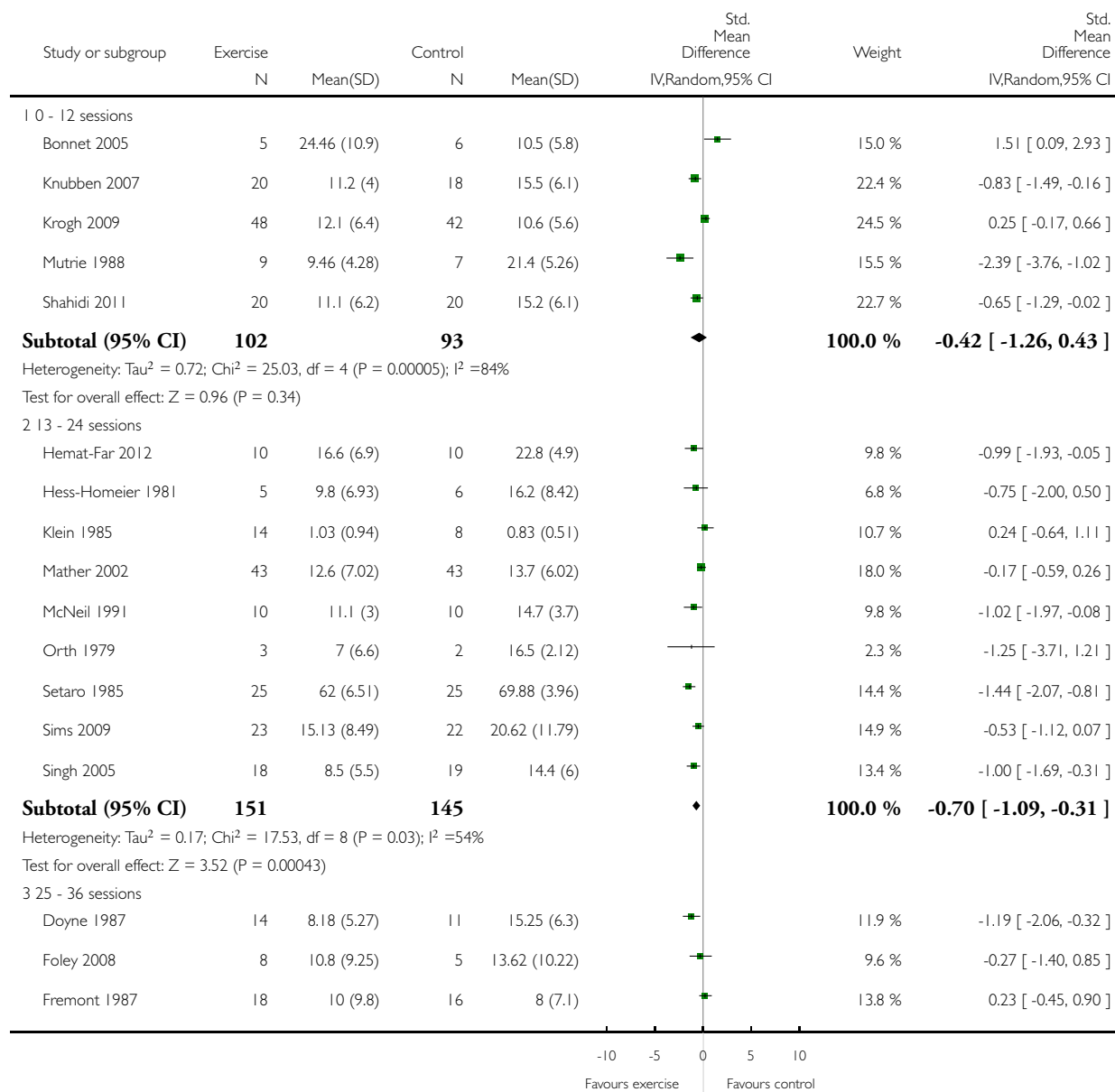


Analysis 5.3. Comparison 5 Reduction in depression symptoms post-treatment: Subgroup analyses, Outcome 3 Exercise vs control subgroup analysis: number of sessions.

Review: Exercise for depression

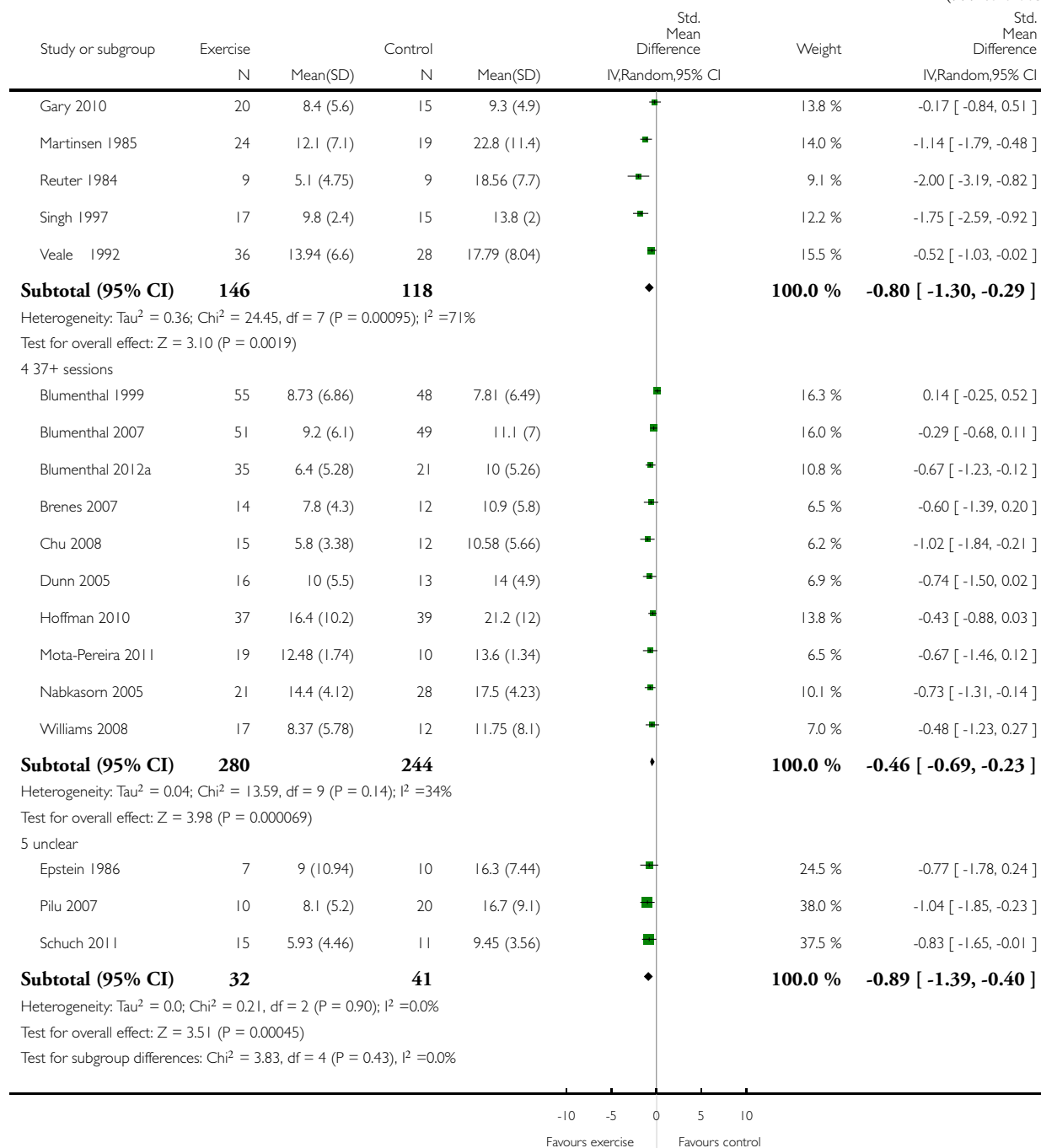
Comparison: 5 Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome: 3 Exercise vs control subgroup analysis: number of sessions



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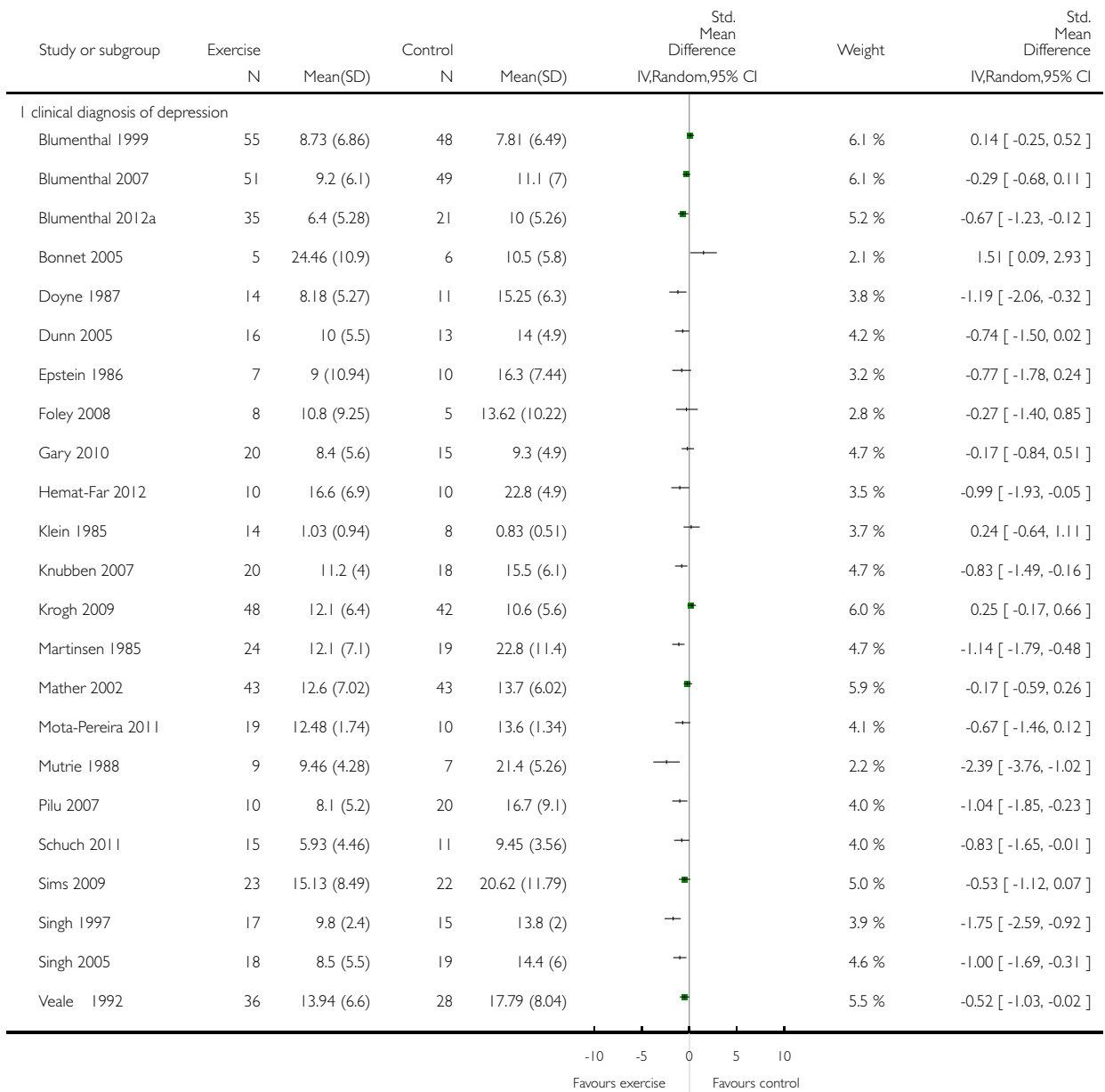


Analysis 5.4. Comparison 5 Reduction in depression symptoms post-treatment: Subgroup analyses, Outcome 4 Exercise vs control subgroup analysis: diagnosis of depression.

Review: Exercise for depression

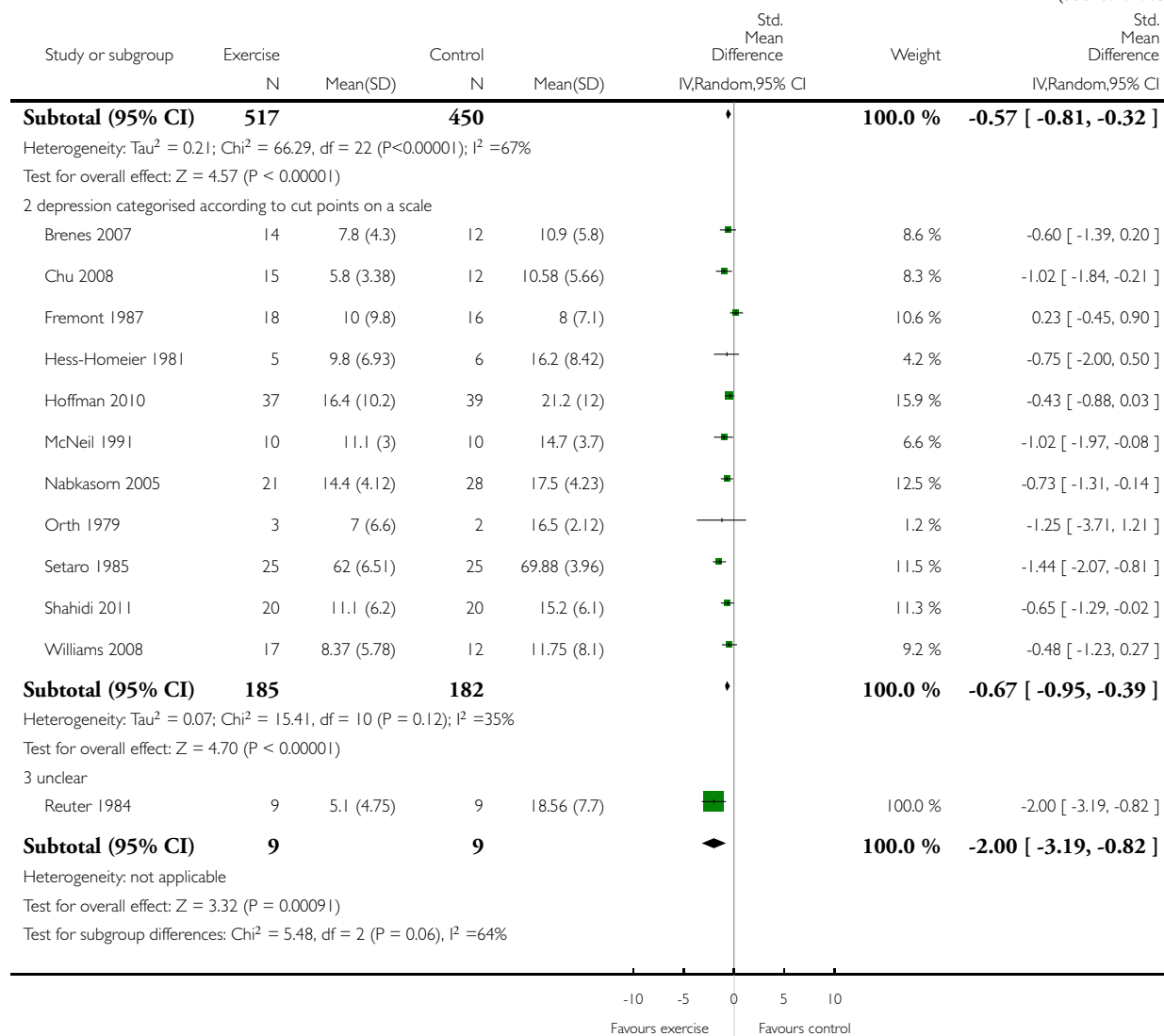
Comparison: 5 Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome: 4 Exercise vs control subgroup analysis: diagnosis of depression



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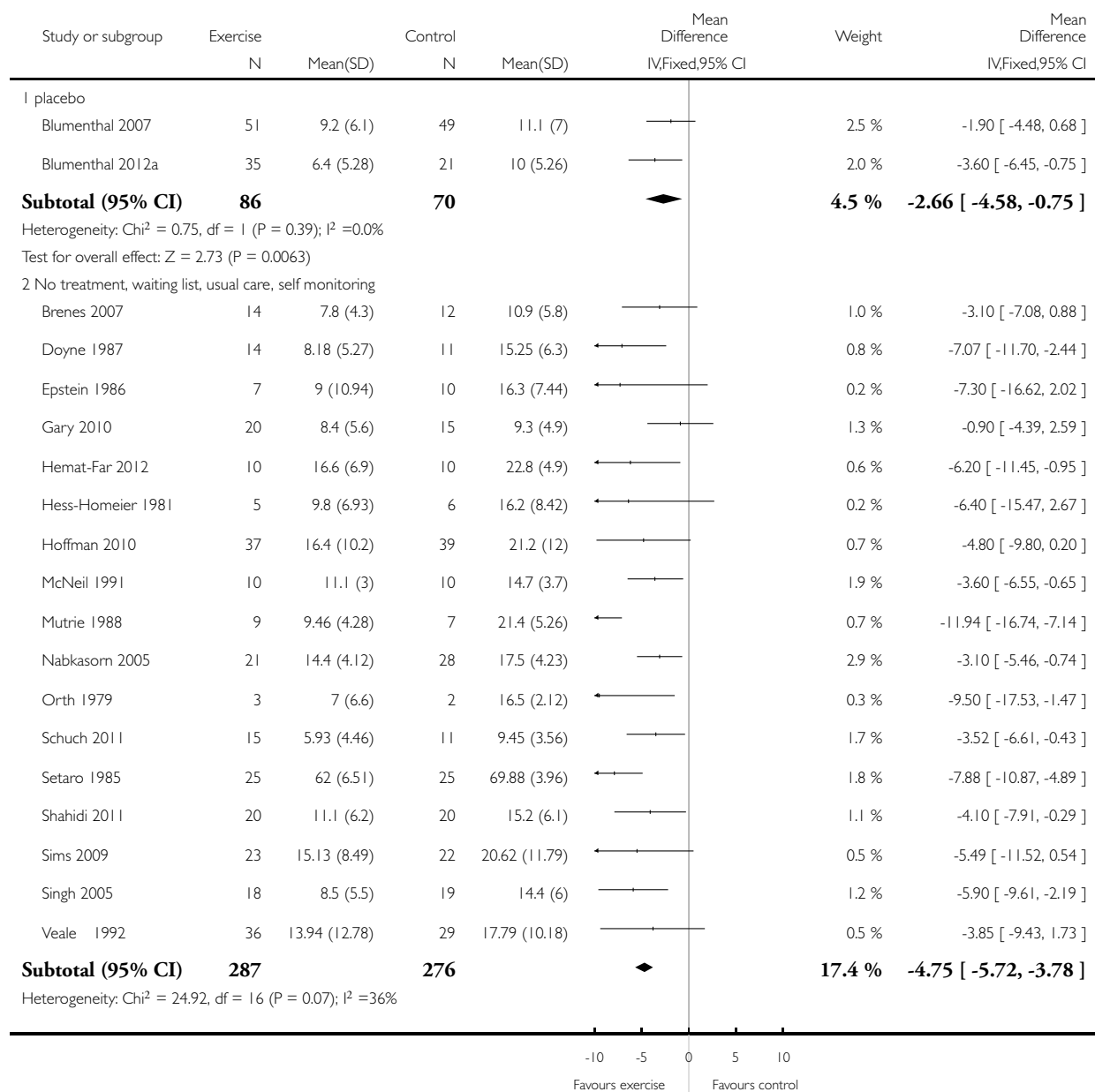


Analysis 5.5. Comparison 5 Reduction in depression symptoms post-treatment: Subgroup analyses, Outcome 5 Exercise vs control subgroup analysis: type of control.

Review: Exercise for depression

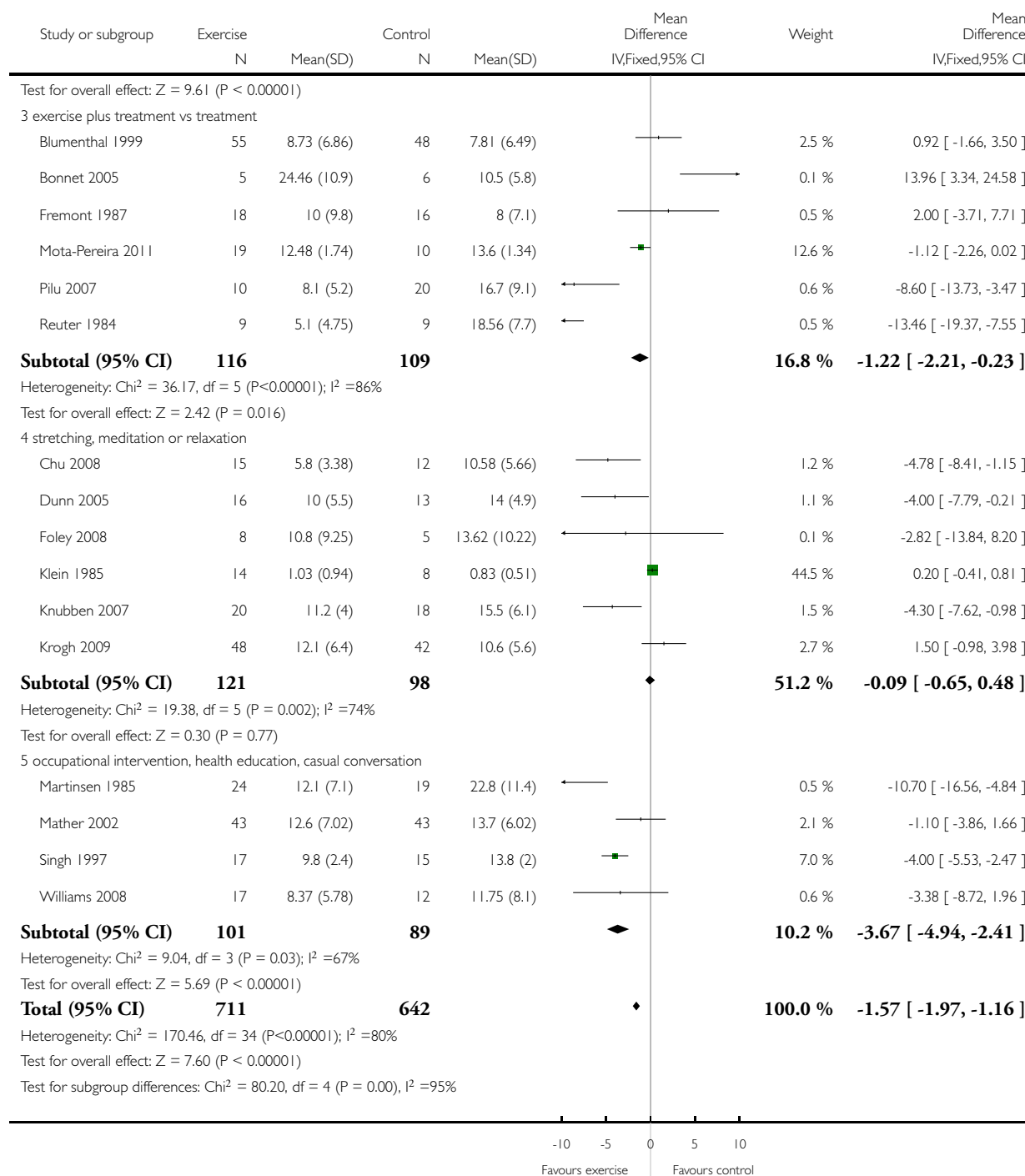
Comparison: 5 Reduction in depression symptoms post-treatment: Subgroup analyses

Outcome: 5 Exercise vs control subgroup analysis: type of control



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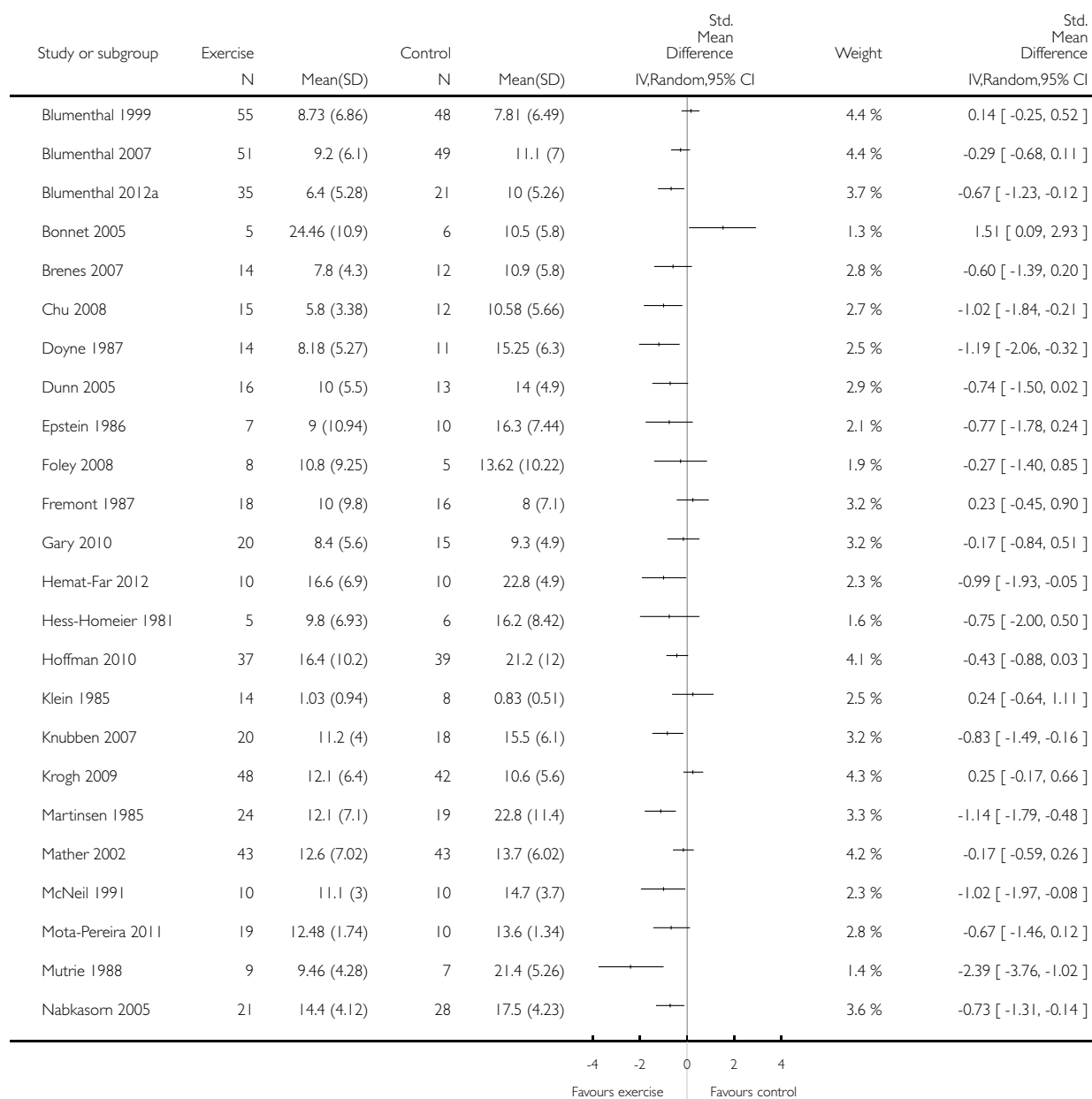


Analysis 6.1. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 1 Reduction in depression symptoms post-treatment: peer-reviewed journal publications and doctoral theses only.

Review: Exercise for depression

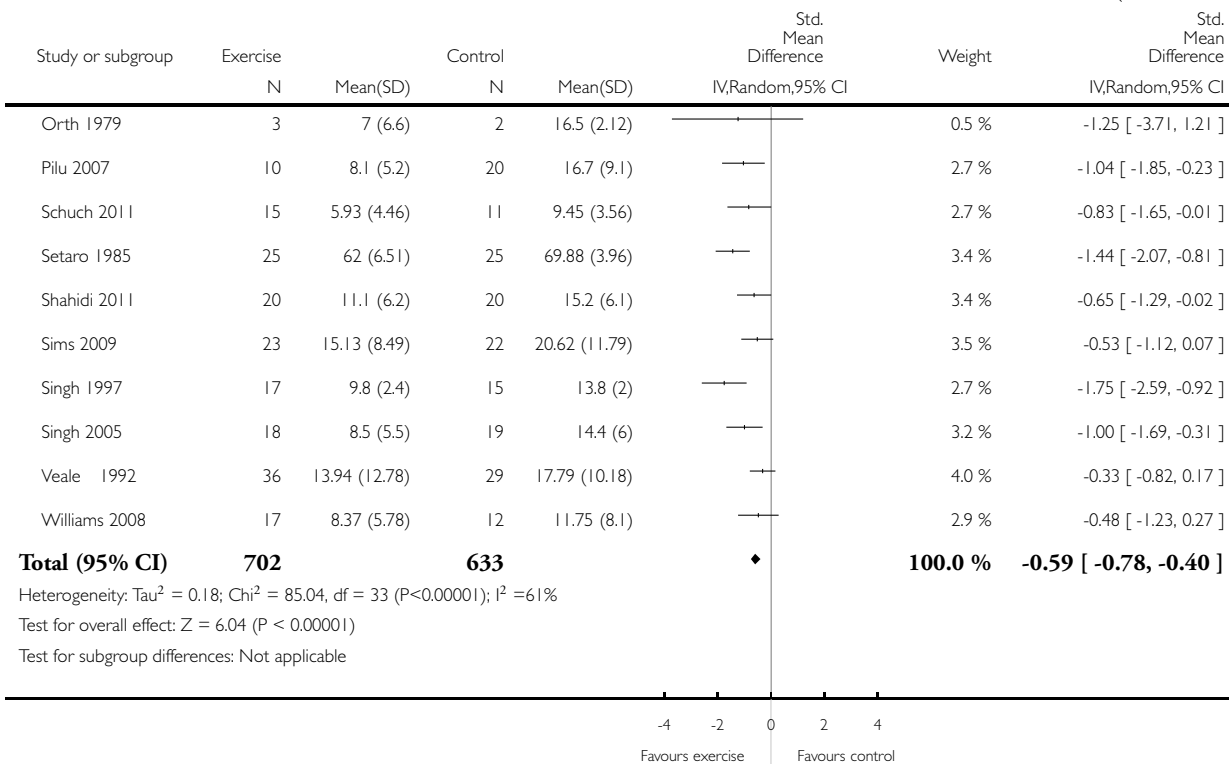
Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 1 Reduction in depression symptoms post-treatment: peer-reviewed journal publications and doctoral theses only



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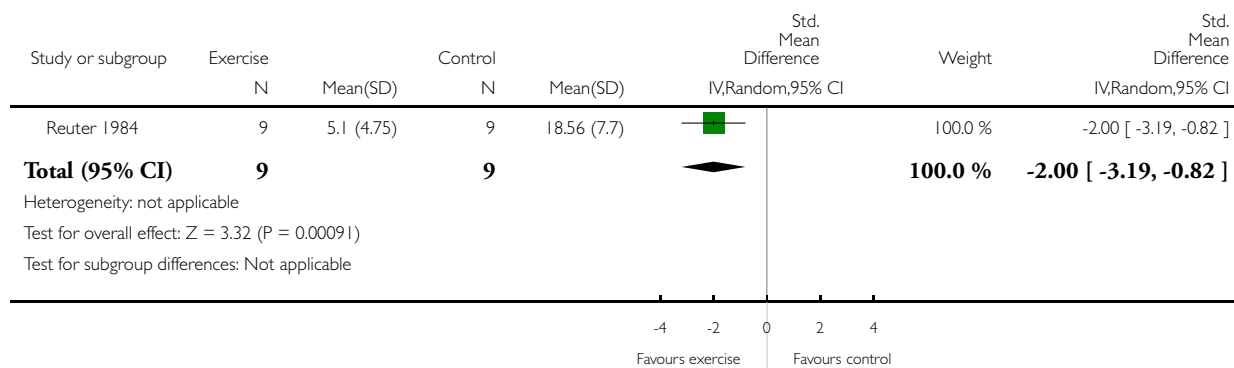


Analysis 6.2. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 2 Reduction in depression symptoms post-treatment: studies published as abstracts or conference proceedings only.

Review: Exercise for depression

Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 2 Reduction in depression symptoms post-treatment: studies published as abstracts or conference proceedings only

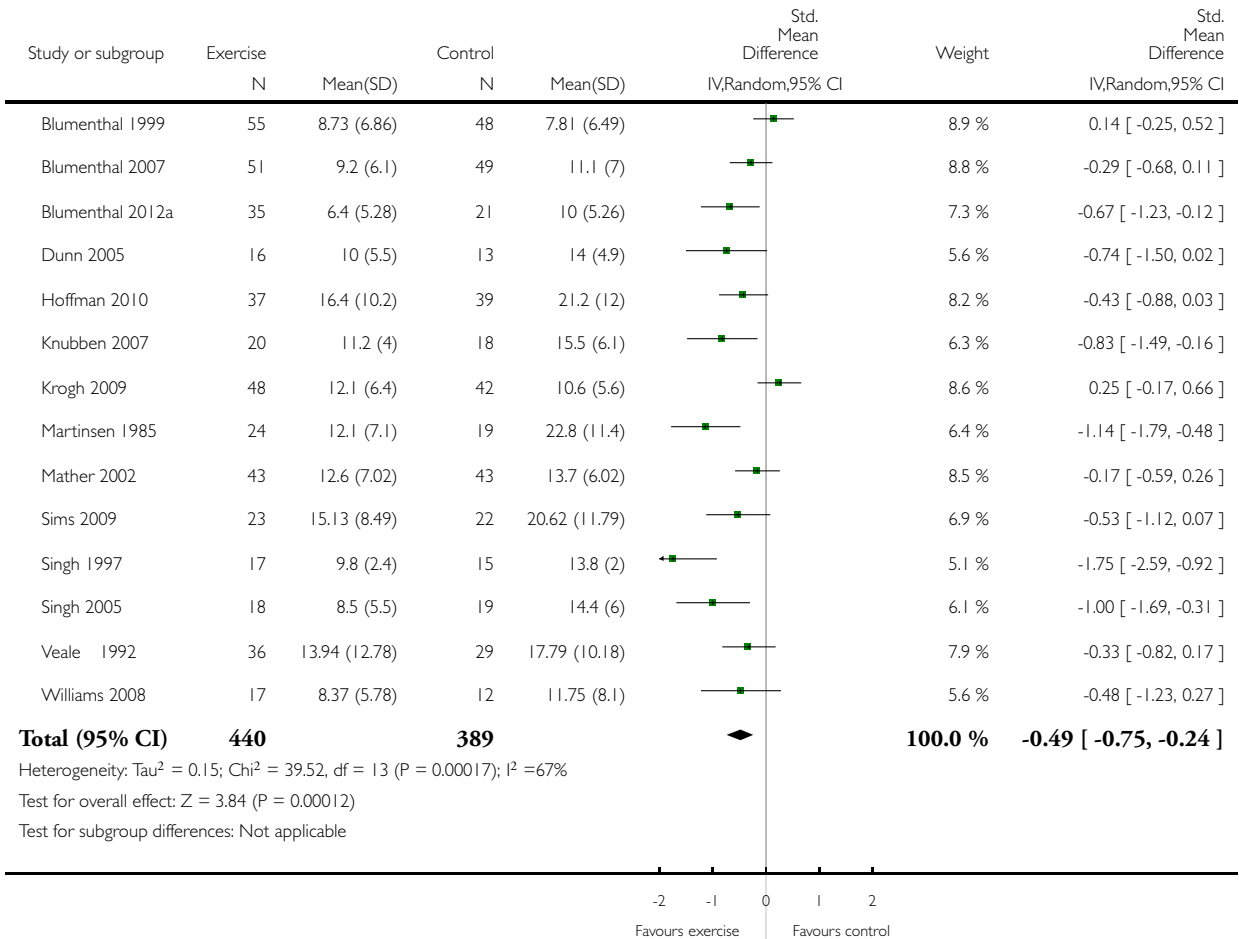


Analysis 6.3. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 3 Reduction in depression symptoms post-treatment: studies with adequate allocation concealment.

Review: Exercise for depression

Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 3 Reduction in depression symptoms post-treatment: studies with adequate allocation concealment

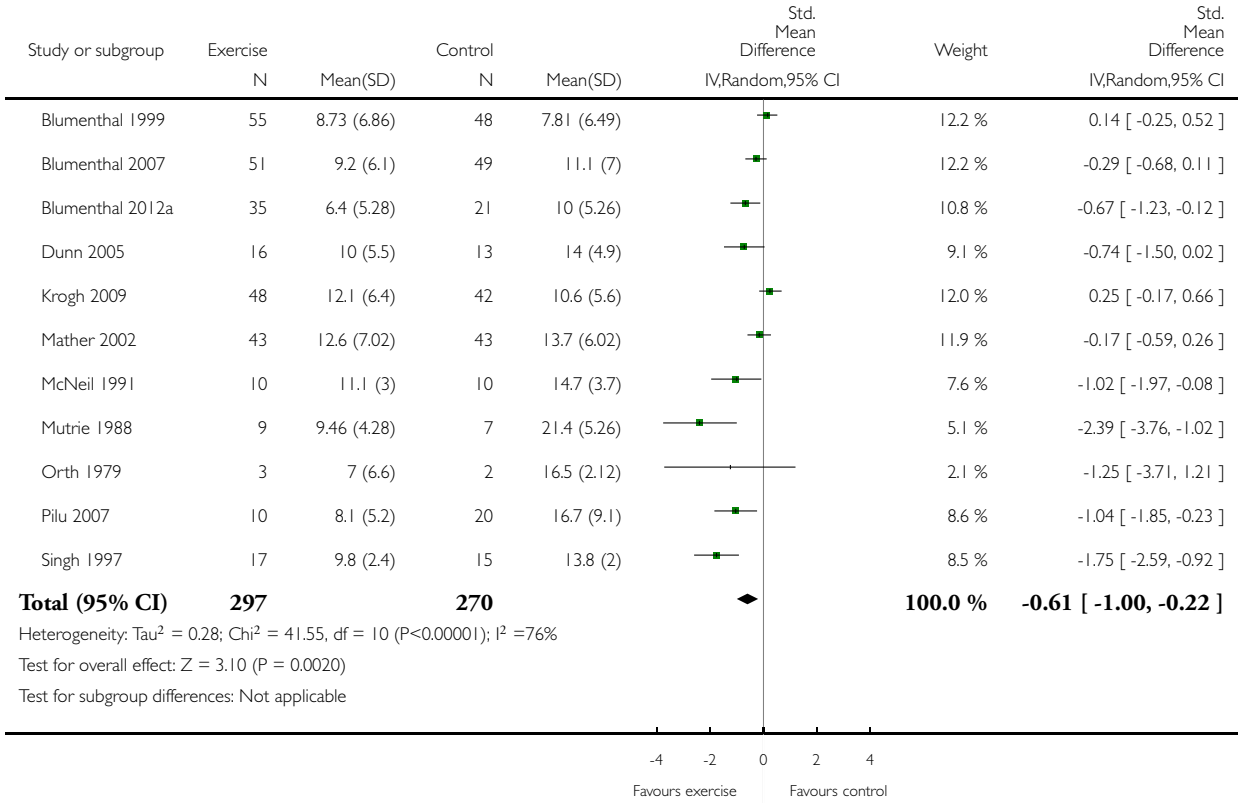


Analysis 6.4. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 4 Reduction in depression symptoms post-treatment: studies using intention-to-treat analysis.

Review: Exercise for depression

Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 4 Reduction in depression symptoms post-treatment: studies using intention-to-treat analysis

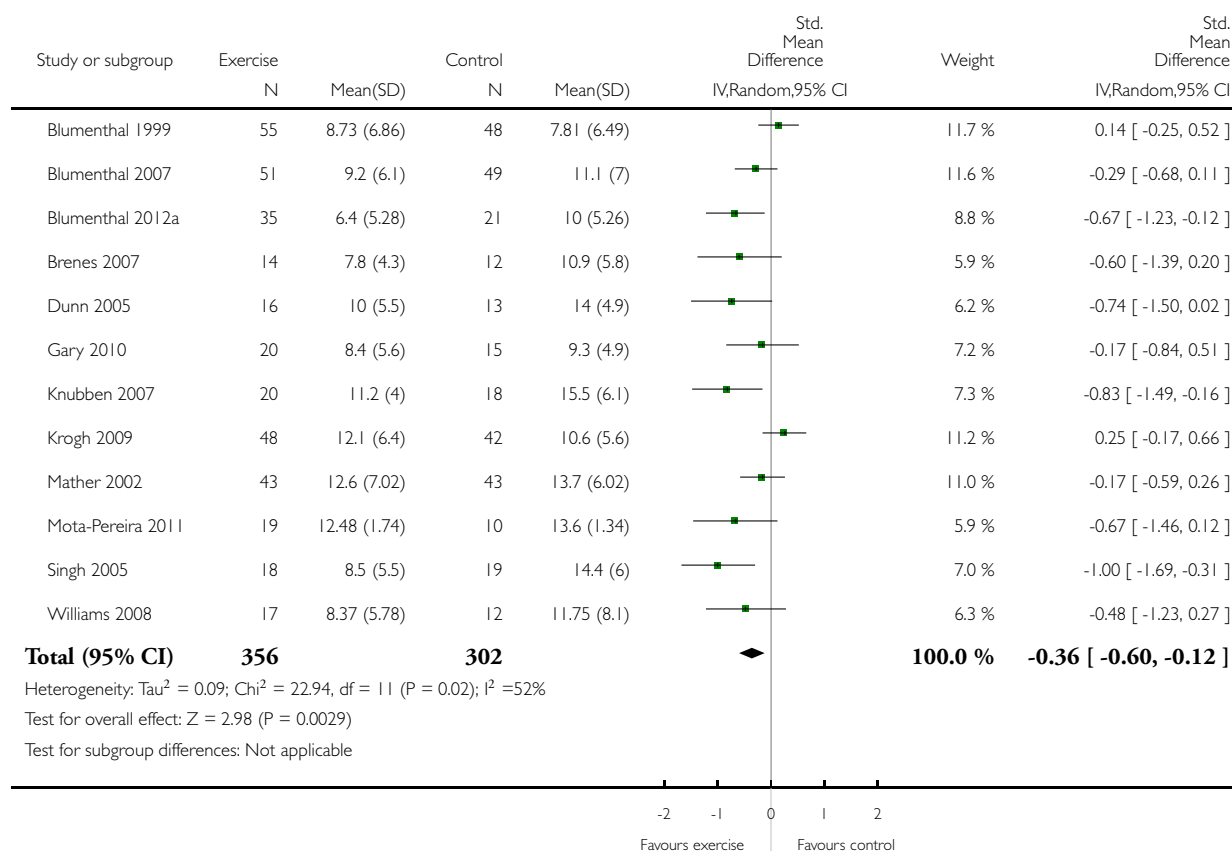


Analysis 6.5. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 5 Reduction in depression symptoms post-treatment: studies with blinded outcome assessment.

Review: Exercise for depression

Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 5 Reduction in depression symptoms post-treatment: studies with blinded outcome assessment

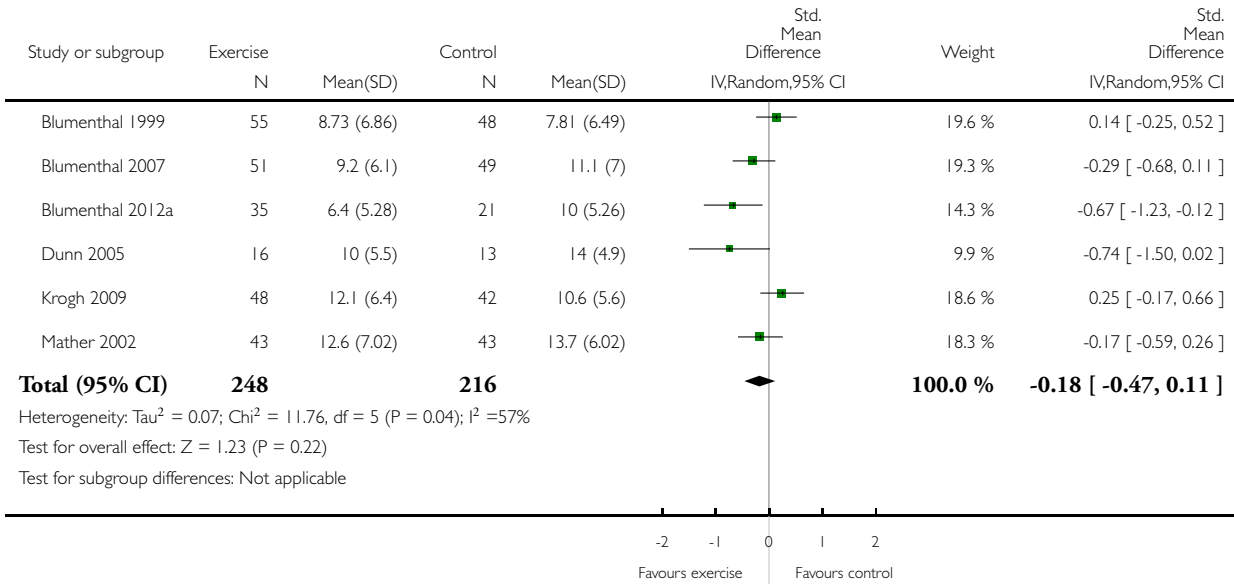


Analysis 6.6. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 6 Reduction in depression symptoms post-treatment: allocation concealment, intention-to-treat, blinded outcome.

Review: Exercise for depression

Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 6 Reduction in depression symptoms post-treatment: allocation concealment, intention-to-treat, blinded outcome

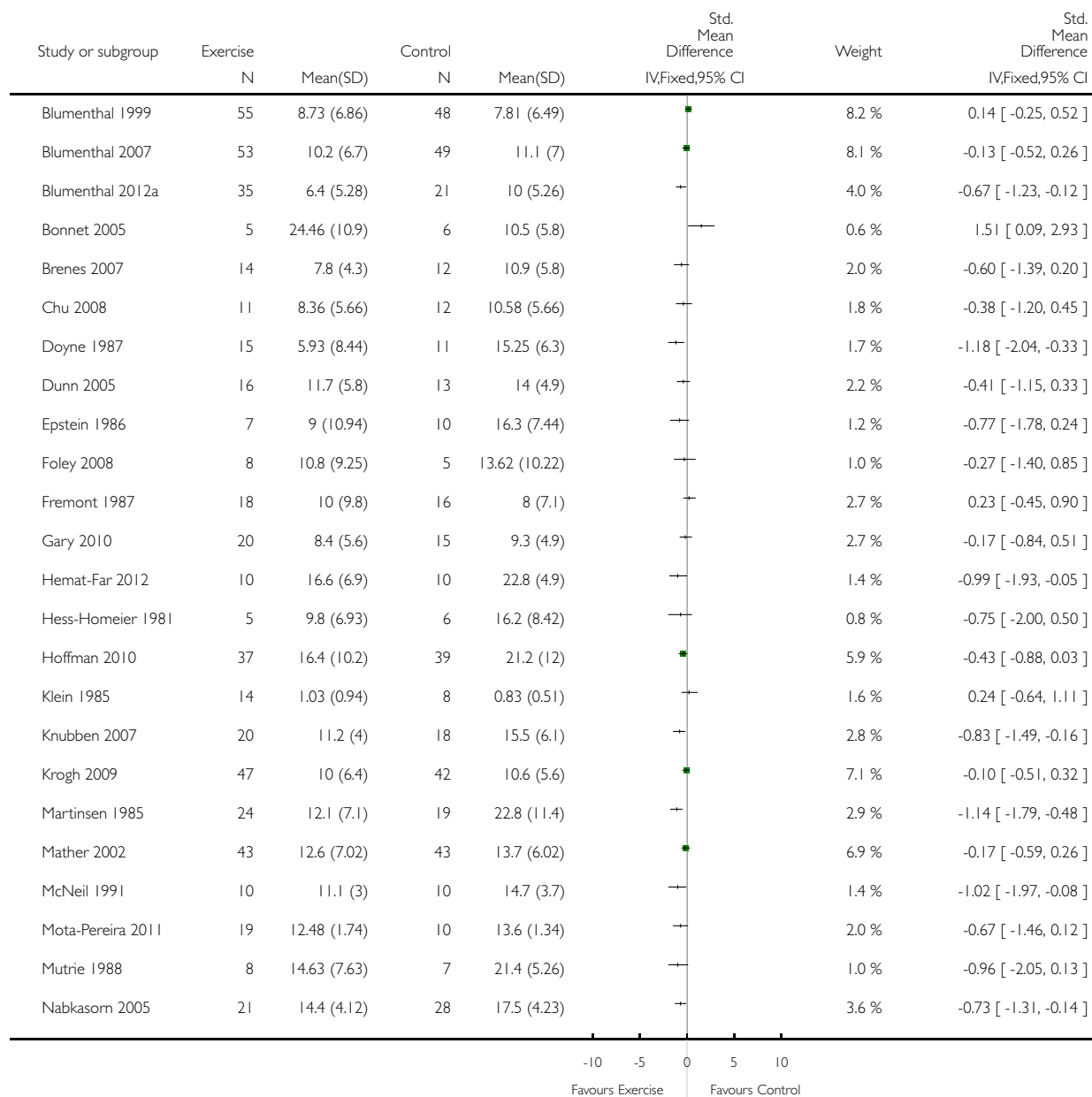


Analysis 6.7. Comparison 6 Exercise versus control: sensitivity analyses, Outcome 7 Reduction in depression symptoms post-treatment: Lowest dose of exercise.

Review: Exercise for depression

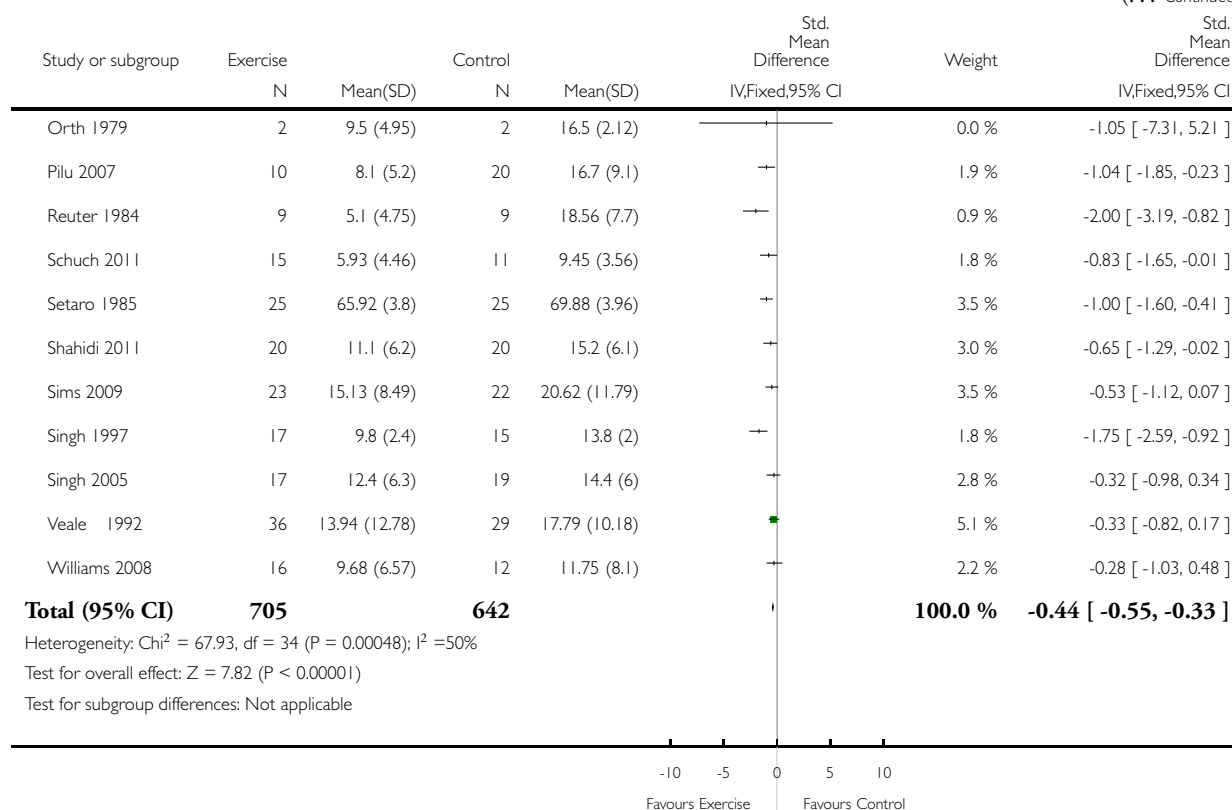
Comparison: 6 Exercise versus control: sensitivity analyses

Outcome: 7 Reduction in depression symptoms post-treatment: Lowest dose of exercise



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ADDITIONAL TABLES

Table 1. Number screened; number still in trial and exercise intervention at end of trial

Trial ID	Screened	Randomised	Allocated exercise	Completed trial	Completed comparator group, e.g. control, other treatment (as a proportion of those allocated)	Completed exercise (as a proportion of those allocated)
Blumenthal 1999	604 underwent telephone screening	156	55	133	41/48 (medication)	44/55 (exercise plus medication) 39/53 (exercise alone)

Table 1. Number screened; number still in trial and exercise intervention at end of trial (Continued)

Blumenthal 2007	457	202	51 (supervised), 53 home-based	183	42/49 (placebo) 45/49 (sertraline)	45/51 (supervised), 51/53 home-based
Blumenthal 2012b	1680 enquired about the study	101	37	95	23/24 completed 'placebo' and 36/40 completed the medication	36/37 completed the exercise
Brenes 2007	Not reported	37	14	Not reported	Not reported	Not reported
Bonnet 2005	Not reported	11	5	7	4/6	3/5
Chu 2008	104 responded to adverts	54	36	38	12/18	26/36 (both exercise arms combined) 15/18 in the high-intensity arm
Dunn 2005	1664 assessed for eligibility	80	17	45	9/13	11/17 (public health dose 3 times per week)
Doyne 1987	285 responded to adverts	57	Not reported	40 completed treatment or control	27 (denominator not known)	13 (denominator not known)
Epstein 1986	250 telephone inquiries received	33	7	Not reported	Not reported	7
Fetsch 1979	Not reported	21	10	16	8/11	8/10
Foley 2008	215 responded to adverts	23	10	13	5/13	8/10
Fremont 1987	72 initially expressed an interest	61	21	49	31/40	18/21
Gary 2010	982 referred, 242 had heart failure, 137 had a BDI > 10 and 74 eligible and consented	74	20	68/74 completed post-intervention assessments and 62 completed follow-up assess-	usual care 15/17	exercise only: 20/20

Table 1. Number screened; number still in trial and exercise intervention at end of trial (Continued)

				ments		
Greist 1979	Not reported	28	10	22	15/18	8/10
Hemat-Far 2012	350 screened	20	10	20	not stated	not stated
Hess-Homeier 1981	Not reported	17	5	Not reported	Not reported	Not reported
Hoffman 2010	253 screened, 58 ineligible	84	42	76	39/42 (2 were excluded by the trialists and 1 did not attend follow-up)	37/42 of exercise group provided data for analysis
Klein 1985	209 responded to an advertisement	74	27	42	11/23 (meditation) 16/24 (group therapy)	15/27
Knubben 2007	Not reported	39 (note data on only 38 reported)	20	35	16/18	19/20
Krogh 2009	390 referred	165	110	137	42/55	95/110 (both exercise arms combined) 47/55 (strength) 48/55 (aerobic)
Martinsen 1985	Not reported	43	24	37	17/19	20/24
Mather 2002	1185 referred or screened	86	43	86	42/43	43/43
McCann 1984	250 completed BDI, 60 contacted	47	16	43	14/15 completed placebo 14/16 completed 'no treatment'	15/16
McNeil 1991	82	30	10	30	10/10 (waiting list) 10/10 (social contact)	10/10
Mota-Pereira 2011	150	33	22	29/33	10/11	19/22

Table 1. Number screened; number still in trial and exercise intervention at end of trial (Continued)

Mutrie 1988	36	24	9	24	7/7	9/9
Nabkasorn 2005	266 volunteers screened	59	28	49	28/31	21/28
Orth 1979	17	11	3	7	2/2	3/3
Pilu 2007	Not reported	30	10	30	20/20	10/10
Pinchasov 2000	Not reported	18	9	Not reported	Not reported	Not reported
Reuter 1984	Not reported	Not reported	9	Not reported	Not reported	9
Schuch 2011	14/40 invited patients were not interested in participating	26	15	“no patient withdrew from intervention”	“no patient withdrew from intervention”	“no patient withdrew from intervention”
Setaro 1985	211 responses to advertisement	180	30	150	Not reported	25/30
Shahidi 2011	70 older depressed women chosen from 500 members of a district using the geriatric depression scale	70	23	60/70	20/24	20/23
Sims 2009	1550 invitations, 233 responded	45	23	43	22/22	21/23
Singh 1997	Letters sent to 2953 people, 884 replied	32	17	32	15/15	17/17
Singh 2005	451	60	20	54	19/20 (GP standard care)	18/20 (high-intensity training)
Veale 1992	Not reported	83	48	57	29/35	36/48
Williams 2008	96 in parent study	43	33	34	8/10	26/33 (both exercise groups combined) 15/16 exercise 11/17 walking

BDI: Beck Depression Inventory

APPENDICES

Appendix I. CCDAN searches all years to 1 March 2013

The Cochrane Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR)

The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK: a references register and a studies based register. The CCDANCTR-References Register contains over 31,500 reports of trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Coordinator for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of [CCDAN's generic search strategies](#) (used to identify RCTs) can be found on the Group's website.

The CCDANCTR was searched all years to 31 March 2013.

The CCDANCTR-Studies Register was searched using the following terms:

Diagnosis =Depressi* or Dysthymi* and Intervention = Exercise

The CCDANCTR-References Register was searched using a more sensitive set of terms to identify additional untagged/uncoded references:

Title/Abstract/Keywords = (depressi* or dysthymi*)

AND

Free-text = (sport* or exercis* or aerobic* or running or jogging or walk* or hiking or swim* or aquatic* or cycling or bicycl* or ((physical or strength*) and (activit* or educat* or fitness or train*)) or "physical medicine" or ((resistance or weight*) and (train* or lift*)))

Additional searches were conducted on MEDLINE, EMBASE, PsycINFO and CENTRAL (2007 to 2010) by CCDAN's Trials Search Co-ordinator (TSC) when the CCDANCTR was out of date due to relocation of the Group's editorial base and a changeover of staff.

MEDLINE

OID MEDLINE (2007 to 2010) was searched using the following terms:

1. exp Exercise/
2. exp Exercise Therapy/
3. exp "Physical Education and Training"/
4. Physical Fitness/
5. Physical Exertion/
6. exp Walking/
7. Running/ or Jogging/
8. Swimming/
9. (cycling or bicycling).tw.
10. (exercise\$ or exercising).tw.
11. (physical adj3 (education or training)).tw.
12. or/1-11
13. Depression/
14. exp Depressive Disorder/
15. or/13-14
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. randomly.ab.
19. trial.ab.

20. groups.ab.
21. (control\$ adj3 (trial\$ or study or studies)).tw.
22. randomi#ed.ab.
23. placebo\$.ab.
24. or/16-23
25. 12 and 15 and 24
26. (2007\$ or 2008\$ or 2009\$ or 2010\$).ed,yr.
27. 25 and 26

EMBASE

OVID EMBASE (2007 to 2010) was searched using the following terms:

1. exp exercise/
2. exp physical activity/
3. exp sport/
4. (exercise\$ or exercising).tw.
5. or/1-4
6. exp depression/
7. randomized controlled trial/
8. controlled clinical trial/
9. major clinical study/
10. randomization/
11. placebo/
12. randomi#ed.ti,ab.
13. placebo\$.tw.
14. trial.ti,ab.
15. randomly.ab.
16. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$ or dummy)).mp.
17. (control\$ adj3 (trial\$ or study or studies\$)).tw.
18. or/6-16
19. (2007\$ or 2008\$ or 2009\$ or 2010\$).em,yr.
20. 5 and 6 and 18 and 19

PsycINFO

OVID PsycINFO (2007 to 2010) was searched using the following terms:

1. exp major depression/
2. atypical depression/
3. seasonal affective disorder/
4. (depress\$ adj3 (patient\$ or symptom\$ or disorder\$)).ti,ab.
5. or/1-4
6. exp physical activity/
7. exp sports/
8. running/ or walking/
9. (cycling or bicycling).tw.
10. (exercise\$ or exercising).tw.
11. (physical adj3 (education or training)).tw.
12. or/6-11
13. treatment effectiveness evaluation/
14. clinical trials/
15. mental health program evaluation/
16. placebo/
17. placebo\$.tw.

18. randomly.ab.
19. randomi#ed.tw.
20. trial\$.tw.
21. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$ or dummy)).tw.
22. (control* adj3 (trial* or study or studies)).tw.
23. "2000".md.
24. or/13-23
25. 5 and 12 and 24
26. (2007\$ or 2008\$ or 2009\$ or 2010\$).an,up,yr.
27. 25 and 26

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL was searched using the following terms:

- #1 MeSH descriptor Exercise explode all trees
- #2 MeSH descriptor Exercise Therapy explode all trees
- #3 MeSH descriptor Physical Education and Training explode all trees
- #4 MeSH descriptor Physical Fitness, this term only
- #5 MeSH descriptor Physical Exertion, this term only
- #6 MeSH descriptor Walking explode all trees
- #7 MeSH descriptor Running explode all trees
- #8 MeSH descriptor Swimming, this term only
- #9 (cycling or bicycling)
- #10 (exercise* or exercising)
- #11 (physical NEAR/5 (education or training))
- #12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
- #13 MeSH descriptor Depressive Disorder explode all trees
- #14 MeSH descriptor Depression, this term only
- #15 (#13 OR #14)
- #16 (#12 AND #15)
- #17 (#16), from 2007 to 2010
- #18 SR-DEPRESSN
- #19 HS-DEPRESSN
- #20 (#17 AND NOT (#18 OR #19))

Appendix 2. Previous search to 2007

The authors searched Ovid MEDLINE and EMBASE, PsycINFO and Sports Discus on the Silver Platter platform, the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews. Details of the search strategy used in MEDLINE are provided below ([Lawlor 2001](#)); this search was modified as appropriate for other databases. Appropriate filters were applied to identify randomised controlled trials.

MEDLINE search strategy:

1. exp EXERCISE/
2. exp Exercise Therapy/
3. exp Exertion/
4. exp Physical Fitness/
5. exp Walking/
6. exp Running/
7. exp Swimming/
8. exp Jogging/
9. exp "Physical Education and Training"/
10. exercise\$ near aerobic\$.tw.

11. train\$ near aerobic\$.tw.
12. exercise\$ near strength\$.tw.
13. train\$ near strength\$.tw.
14. bicycling\$.tw.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp DEPRESSION/
17. exp Depressive Disorder/
18. exp Dysthymic Disorder/
19. 16 or 17 or 18
- 20 15 and 19

F E E D B A C K

Concerning the DOSE 2002 trial, 3 November 2009

Summary

I recently read [the] review entitled "Exercise for Depression" and would like to point out some errors in your review. First, you stated the following in your review,

"We attempted to extract data on intensity of exercise but this was reported for only a few trials, and there was too much variation in other aspects of the trial methodologies to attribute differences in outcomes to differences exercise intensities. One of the included trials compared four different 'doses' of aerobic exercise (DOSE 2002) and found that high intensity exercise was more effective than low intensity exercise."

In actuality, participants were allowed to self-select intensity and the two factors that were manipulated were frequency of exercise and total energy expenditure. It was the total energy expenditure that seemed to have a great effect on reduction of symptoms when the low dose was compared with the higher dose.

Second, the study is not cited correctly throughout the article and finally I am not sure why the main results paper was not included in this review because it was published in 2005. What was included was our baseline design paper that had no results.

I would like to see this error corrected in the review.

Andrea L. Dunn, PhD

Reply

Reply of Dr Gillian Mead, 10 November 2009

The 2005 paper is now cited as well as the 2002 paper.

The purpose of our review was to determine the effectiveness of exercise for depression. Thus we included trials which compared exercise with 'no treatment' and trials which compared exercise to other treatments for depression e.g. CBT. Our conclusions were that 'It is reasonable to recommend exercise to people with depressive symptoms and to those who fulfil diagnostic criteria for depression....'

I agree... that it would be misleading if people with depression and researchers were given the impression that exercise had to be intense to bring about benefits. Based on our subgroup analyses, we have stated that 'we cannot give people accurate information about how effective exercise might be, nor can recommendations be made about the relative benefits of aerobic exercise, resistance exercise or mixed exercise, whether group or individual exercises are better, nor about the optimum duration of exercise'. We then go on to say that further research is required.

[Concerning intensity within the DOSE study] - text has been added for clarification in both the 'Description of studies' and the 'Discussion'.

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WHAT'S NEW

Last assessed as up-to-date: 13 July 2012.

Date	Event	Description
2 May 2013	New citation required but conclusions have not changed	New studies incorporated
2 May 2013	New search has been performed	Review updated

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2008

Date	Event	Description
12 November 2009	Feedback has been incorporated	Feedback received from a trialist received 3 November 2009 concerning the DOSE 2002 study was addressed on 10 November 2009
13 May 2009	New citation required but conclusions have not changed	Incorrect 'date assessed as up to date' changed from February 2000 to March 2007 (date of last electronic searches). Abstract corrected to reflect true history of searches
13 August 2008	New search has been performed	This is an updated version of a previous review published in the <i>BMJ</i> in 2001 and includes several new trials
30 July 2008	Amended	Converted to new review format
21 February 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

This review is based on a previously published *BMJ* review by Debbie Lawlor and Stephen Hopker. For this update, Dr Cooney and Professor Mead scrutinised studies and selected studies for inclusion. Dr Waugh and Dr Cooney performed data extraction, Dr Dwan performed the analysis, Dr Greig categorised intensity of exercise, and assisted with study selection. Professor Mead, Dr Cooney and Dr Dwan wrote the text. The text was read by all authors.

DECLARATIONS OF INTEREST

Marion McMurdo is co-director of D.D. Developments, a University of Dundee not-for-profit organisation which provides exercise classes for older people.

Gillian E Mead developed a course on exercise after stroke which is licensed to Later Life Training. She receives royalty payments from Later Life Training, which are paid into an account at University of Edinburgh to support further research. She personally receives royalties from a book about Exercise and Fitness Training after Stroke. She receives expenses for speaking at conferences on exercise and fatigue after stroke.

Kerry Dwan: none known.

Carolyn A Greig: none known.

Debbie A Lawlor: none known.

Gary Cooney: None known

Jane Rimer: none known.

Fiona Waugh: none known.

SOURCES OF SUPPORT

Internal sources

- NHS Lothian, University of Edinburgh, UK.

External sources

- National Institute for Health Research, Cochrane Review Incentive Scheme 2012, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update, we defined exercise according to the American College of Sports Medicine (ACSM) definition of exercise, rather than the trialist's own definition of exercise. We performed an additional sensitivity analysis to explore the effect of excluding those trials for which we used the arm with the largest clinical effect, rather than the largest 'dose' of exercise.

Changes for this update: we added subgroups, performed a sensitivity analysis for low/high 'dose' of exercise, included more detail in 'included study' table; we decided to include cluster-RCTs, we produced a PRISMA diagram for the results of the searches for update; and we produced a 'Summary of findings' tables.

INDEX TERMS

Medical Subject Headings (MeSH)

Depression [*therapy]; Exercise [*psychology]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adult; Humans; Middle Aged; Young Adult