

Treating depression with physical activity in adolescents and young adults: a systematic review and meta-analysis of randomised controlled trials

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We aimed to establish the treatment effect of physical activity for depression in young people through meta-analysis. Four databases were searched to September 2016 for randomised controlled trials of physical activity interventions for adolescents and young adults, 12–25 years, experiencing a diagnosis or threshold symptoms of depression. Random-effects meta-analysis was used to estimate the standardised mean difference (SMD) between physical activity and control conditions. Subgroup analysis and meta-regression investigated potential treatment effect modifiers. Acceptability was estimated using dropout. Trials were assessed against risk of bias domains and overall quality of evidence was assessed using GRADE criteria. Seventeen trials were eligible and 16 provided data from 771 participants showing a large effect of physical activity on depression symptoms compared to controls (SMD = −0.82, 95% CI = −1.02 to −0.61, $p < 0.05$, $I^2 = 38\%$). The effect remained robust in trials with clinical samples ($k = 5$, SMD = −0.72, 95% CI = −1.15 to −0.30), and in trials using attention/activity placebo controls ($k = 7$, SMD = −0.82, 95% CI = −1.05 to −0.59). Dropout was 11% across physical activity arms and equivalent in controls ($k = 12$, RD = −0.01, 95% CI = −0.04 to 0.03, $p = 0.70$). However, the quality of RCT-level evidence contributing to the primary analysis was downgraded two levels to LOW (trial-level risk of bias, suspected publication bias), suggesting uncertainty in the size of effect and caution in its interpretation. While physical activity appears to be a promising and acceptable intervention for adolescents and young adults experiencing depression, robust clinical effectiveness trials that minimise risk of bias are required to increase confidence in the current finding. The specific intervention characteristics required to improve depression remain unclear, however best candidates given current evidence may include, but are not limited to, supervised, aerobic-based activity of moderate-to-vigorous intensity, engaged in multiple times per week over eight or more weeks. Further research is needed. (Registration: PROSPERO-CRD 42015024388).

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Introduction

Depression affects an estimated one in five people over the lifetime with most cases beginning during the adolescent to young adult period (Kessler *et al.* 2005, 2007). It is often a chronic and recurring condition (Wilson *et al.* 2015) associated with high levels of psychological distress, impairments in functioning and poor physical health (Lewinsohn *et al.* 1998, 2003; Brent & Birmaher, 2002; Thapar *et al.* 2012), and is the leading contributor to the global burden of disease in young people under the age of 25 (Gore *et al.* 2011).

Established, guideline recommended treatments for depression such as cognitive behavioural therapy (CBT) and antidepressants (e.g., fluoxetine) are at best only modestly effective (Weersing & Brent, 2006; Weisz *et al.* 2006; Hetrick *et al.* 2012; Cipriani *et al.* 2016), with significant proportions of recipients either non-responsive or continuing to experience symptoms (Andrews *et al.* 2000; March *et al.* 2004; TADS Team, 2007). Alternative interventions are therefore indicated to support full recovery, either as stand-alone or adjunct treatment strategies. Lifestyle medicine is one such alternative strategy increasingly implicated in the management of mental ill-health, particularly the use of physical activity to treat depression (Sarris *et al.* 2014).

The mechanisms through which physical activity exerts influence on depression are largely understudied,

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however they are likely complex and multifaceted, involving synergies of neurobiological and psychosocial factors. These may include processes that are both disrupted or dysregulated in depression and potentially modulated by physical activity including inflammatory and oxidative stress responses, neurogenesis, modulation of monoamines (e.g., serotonin), and HPA axis regulation, among others (see Deslandes *et al.* (2009); Wegner *et al.* (2014); Schuch *et al.* (2016a) for review). In terms of proposed psychosocial processes, physical activity may have a general behavioural activation effect though activity scheduling and positive reinforcement, and may provide opportunities for mastery or achievement, thus improving self-efficacy. It may also afford opportunities for social interaction and potentially provide distraction from negative thoughts, mood states or ruminative cognitions (Salmon, 2001; Craft & Perna, 2004; Veale, 2008).

Recent meta-analytic reviews of adult trials have demonstrated that physical activity interventions can reduce depression symptoms, with moderate to large effects (Cooney *et al.* 2013; Stubbs *et al.* 2016a; Kvam *et al.* 2016; Schuch *et al.* 2016b). Meta-analyses of child and adolescent trials have identified small to moderate effects on mental health outcomes, including reducing depression (Larun *et al.* 2006; Brown *et al.* 2013; Carter *et al.* 2016). However, these analyses have relied upon trials where physical activity was delivered either to healthy samples, samples with primary conditions other than depression (e.g., anxiety, obesity, autism), or to children (under 12 years). The efficacy of physical activity for young people (aged 12–25) who are experiencing depression, particularly at clinical levels, is yet to be established.

We performed a meta-analysis on all available randomised controlled trials (RCT) where physical activity was delivered as an intervention to participants aged 12–25 years, experiencing a diagnosis or symptoms of depression. The primary aim was to estimate the effect of physical activity on depression symptoms, with secondary aims to examine intervention acceptability using dropout as a proxy, and whether trial-level characteristics such as age group, diagnostic status, depression severity, clinical *v.* non-clinical samples and type of control group, modified the treatment effect. We also aimed to investigate the effect of different physical activity intervention characteristics on depression symptoms.

Method

The methods described in the Cochrane Handbook of Systematic Reviews (Higgins & Green, 2011a) were used and reporting is according to the PRISMA guidelines

(Moher *et al.* 2009, 2015). The review was prospectively registered with PROSPERO (CRD42015024388).

Trial eligibility criteria

Types of studies

RCTs were eligible. Only published, peer-reviewed English-language trials were considered.

Types of participants

Trials recruiting adolescents and/or young adults (mean age ≥ 12 and < 26 years) experiencing depression as determined by (a) meeting diagnostic criteria according to established nosology or (b) an explicitly stated minimum threshold (defined by trial authors) on a self-report or observer-rated symptom measure indicating presence of depression symptoms. Trials that recruited participants without depression or where depression was secondary to another disorder or health condition were excluded.

Types of interventions

All physical activity interventions were eligible. We used the American College of Sports Medicine definition of physical activity, which is 'any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels' (Garber *et al.* 2011).

Types of control/comparison groups

Control groups included no-treatment (NT), wait-list (WL) and attention/activity placebo (AP) conditions. AP was defined as a condition that could reasonably be considered to control for non-specific intervention group factors and was not an established treatment for depression (Lindheimer *et al.* 2015). Comparison treatments could include psychological therapy, medication and treatment as usual (TAU).

Outcome measures

The primary outcome was depression symptoms as assessed with a validated symptom scale at the post-intervention time-point. Where a trial reported more than one depression outcome, the following hierarchy was used: (1) Observer-rated depression, (2) Self-report depression.

Search strategy

Electronic database searches were conducted for the period January 1980 to September 2016 using PsycINFO, Medline, Embase and the Cochrane Central Register of Controlled Trials. Search terms for

depression, physical activity/exercise and controlled trials are available in Supplementary Material. This strategy was supplemented by an ancestry search of the included trials and recently published systematic reviews (Larun *et al.* 2006; Rethorst *et al.* 2009; Brown *et al.* 2013; Cooney *et al.* 2013; Rosenbaum *et al.* 2014; Wegner *et al.* 2014; Nyström *et al.* 2015). A two-stage screening process was conducted using the eligibility criteria defined above. One author conducted first stage screening based on title and abstract. A second author screened 10% of these references to ensure consistency. Independent second stage screening was conducted on the full-text of all references identified in the first stage. Discrepancies were resolved by discussion of full-text.

Data extraction

Data were extracted using a previously piloted, standardised extraction template and targets included sample, intervention (e.g., type, frequency, duration and intensity of physical activity) and control/comparison group characteristics, and outcome data at post-intervention and follow-up. Where outcome data were reported in graphical format, trial authors were contacted requesting numeric data. Where it could not be obtained, the WebPlotDigitizer application (Rohatgi, 2013; Tsafnat *et al.* 2014) was used to convert graphical to numeric data. This process was used to reduce potential bias in the meta-analysis if these trials were excluded (Higgins & Green, 2011a; Vučić *et al.* 2015). A second author independently extracted outcome data for meta-analysis. Discrepancies were discussed and checked against the trial publication.

Risk of bias and GRADE

Bias within trials was assessed using the Cochrane Collaboration's risk of bias tool (Higgins *et al.* 2011b). We examined selection bias (random sequence generation, allocation concealment), performance bias (blinding of participant and personnel), detection bias (outcome assessor blinding), attrition bias (handling of incomplete outcome data), and other bias including baseline imbalance on the primary outcome and selective reporting. Risk of bias assessments were rated independently by two authors. Discrepancies were resolved in consultation with a third author. The GRADE criteria were used to rate overall quality of the evidence contributing to the primary meta-analysis (Balsheem *et al.* 2011; Schünemann *et al.* 2013). GRADE criteria included limitations of study design (risk of bias across trials), indirectness of evidence, inconsistency of results, imprecision of results and probability of significant publication bias.

Data analysis

The primary outcome was depression symptoms at post-intervention. Data were entered in RevMan® (The Cochrane Collaboration, 2014) as mean, standard deviation and number of participants for both intervention and control groups, and pooled for meta-analysis using a random-effects model due to expected between-trial heterogeneity (as trials likely employed different physical activity interventions). The effect was estimated as standardised mean difference (SMD) using Hedges' *g* (adjusted for small sample size bias) with 95% Confidence Intervals (CI) to allow pooling of data from different depression symptom scales. The magnitude of estimated SMD was categorised as small (0.2), medium (0.5) or large (0.8) (Cohen, 1988). Heterogeneity was assessed using standard I^2 statistic parameters (Higgins *et al.* 2011a). Publication bias was assessed by funnel plot inspection, use of the trim-and-fill method to adjust the pooled effect (Duval & Tweedie, 2000) and estimation of the fail-safe *N* (Rosenthal, 1979).

Sensitivity analyses were based on the primary meta-analysis and targets included risk of bias domains (sequence generation, allocation concealment, outcome assessor blinding and incomplete outcome data were selected as these have been shown to bias effect estimates towards the intervention (Schulz *et al.* 1995; Wood *et al.* 2008; Bell *et al.* 2013)), source of depression symptom rating, and review-level decisions including pooling of activity arms and inclusion of potentially heterogeneous forms of activity intervention or control.

The secondary outcome was intervention acceptability, which was assessed using dropout rates. Where dropout and missing data could not be distinguished, missing data at post-treatment was used. These data were pooled for meta-analysis and the risk difference (RD) with 95% CI was estimated using the Mantel-Haenszel method with random-effects.

Observational subgroup analysis was used to investigate whether the effect of physical activity on depression was modified by certain factors. Pre-specified targets for subgrouping were type of control group (WL/NT *v.* AP), trial sample characteristics including age group (<18 *v.* ≥18 years), depression severity (mild, moderate, severe), diagnostic criteria (diagnosis *v.* threshold symptoms), sample recruitment (clinical *v.* non-clinical) and physical activity intervention characteristics including intensity (light, moderate, vigorous) and activity type (aerobic *v.* resistance). Meta-regression was used to examine whether continuous variables (mean age and mean baseline depression symptom severity) were associated with effect size.

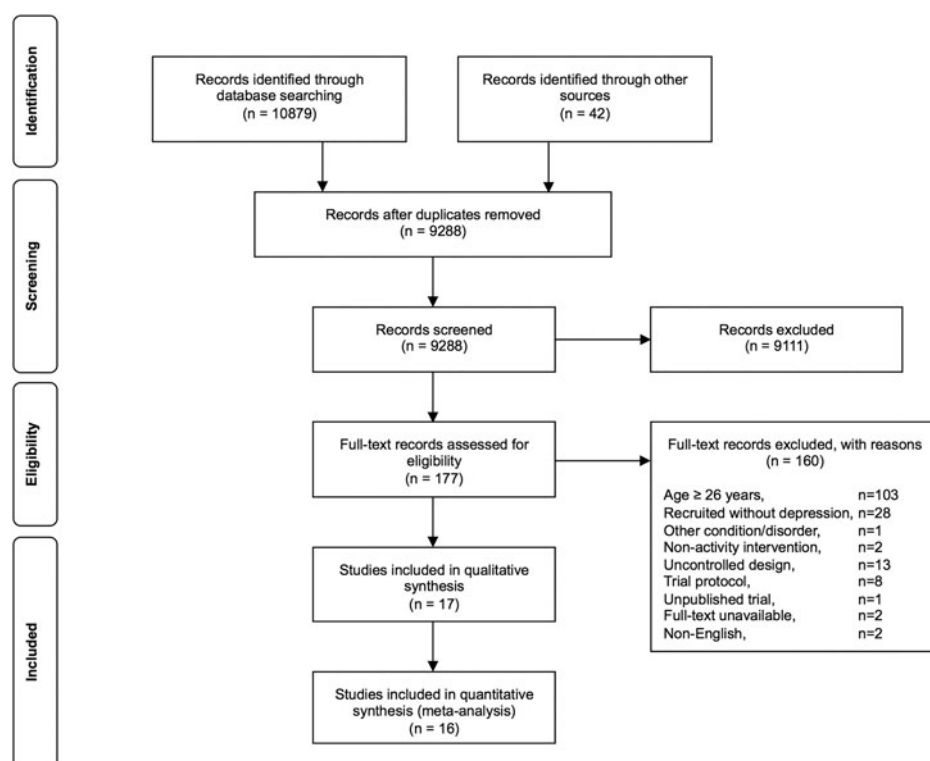


Fig. 1. PRISMA flow diagram of studies retrieved and screened.

Unit of analysis issues

Where a trial used a cross-over design, outcome from the first phase prior to cross-over was selected. Where a trial reported more than one physical activity arm compared with a control condition, the physical activity arms were pooled. This was done to avoid data loss and potential unit of analysis problems (Higgins *et al.* 2011a). Where a trial utilised more than one control arm (e.g., WL and AP), the more rigorous control was selected (see Lindheimer *et al.* 2015). These approaches were taken to ensure the treatment effect was not inflated.

Results

We retrieved 9288 unique publications (see Fig. 1), of which 17 trials were eligible for inclusion (McCann & Holmes, 1984; Woolery *et al.* 2004; Jeong *et al.* 2005; Nabkasorn *et al.* 2006; Yavari, 2008; Chu *et al.* 2009; Mohammadi, 2011; Roshan *et al.* 2011; Hemat-Far *et al.* 2012; Moghaddam *et al.* 2012; Hughes *et al.* 2013; Noorbakhsh & Alijani, 2013; Legrand, 2014; Carter *et al.* 2015; Cecchini-Estrada *et al.* 2015; Balchin *et al.* 2016; Sadeghi *et al.* 2016). Of these, 16 trials provided data for the primary meta-analysis. The characteristics of the included trials are presented in Table 1 and briefly summarised below.

Characteristics of included trials

Participants

Trial sample sizes ranged from 20 to 106 participants (median = 47, IQR = 41). Mean age ranged from 15.4 to 25.8 years. Eight trials were conducted with female participants only. Five trials recruited clinical samples (from inpatient/outpatient treatment services or having a clinician confirmed diagnosis) and 12 trials recruited non-clinical samples. Most trials recruited participants with elevated depression symptoms above a specified threshold ($n=13$), while four used a clinician confirmed diagnosis of depression. Baseline depression severity ranged from mild ($n=4$) to moderate ($n=10$) to severe ($n=2$) (see Supplementary Material for categories). Ten trials recruited an inactive sample, while seven did not report baseline activity level.

Interventions and controls

The characteristics of the physical activity interventions delivered in each trial are summarised in Table 2. Most trials used aerobic-based physical activity ($n=12$), and there was considerable variation in the type of activity. The intensity of activity was estimated by converting reported activity type or intensity into metabolic equivalents (METs) (Norton *et al.* 2010; Ainsworth *et al.* 2011). Most trials involved moderate

Table 1. Included trial characteristics

Trial ID	Country	N	Age, mean (range)	Gender, % female	Recruitment setting	Depression inclusion criteria	Baseline depression severity	Baseline activity threshold for inclusion	Depression outcome measures
Balchin <i>et al.</i> (2016)	South Africa	33	25.4 (18–42)	0	University	Elevated symptoms, HAM-D ≥ 14 , ≤ 18	Moderate, HAM-D = 16.5	No prior high-intensity exercise ($<70\%$ HRR 3/wk)	Observer-rated: HAM-D, MADRS
Carter <i>et al.</i> (2015)	UK	87	15.4 (14–17)	78	Community clinic referral	Elevated symptoms, CDI-2 > 14	Severe*, CDI-2 = 28.7	60% insufficiently active	Self-report: CDI-2
Cecchini-Estrada <i>et al.</i> (2015)	Spain	106	19.6 (18–30)	64	University	Elevated symptoms, 6-item depression scale ≥ 29	Moderate*, score = 30.73	Sedentary (<20 min vigorous activity 3/wk)	Self-report: 6-item depression scale
Chu <i>et al.</i> (2009)	USA	54	25.8 (18–43)	100	University	Elevated symptoms, BDI ≥ 14	Moderate, BDI = 22.5	Sedentary (<20 min exercise 3/wk)	Self-report: BDI
Hemat-Far <i>et al.</i> (2012)	Iran	20	– (18–25)	100	University	Diagnosis, psychiatry review/BDI	Moderate, BDI = 24.4	No sports history	Self-report: BDI
Hughes <i>et al.</i> (2013)	USA	30	17 (12–18)	58	Outpatient clinic referral	Diagnosis, DSM. CDRS-R ≥ 35 , ≤ 70	Moderate*, CDRS-R = 52.1	No current exercise (<30 min vigorous activity 5/wk)	Self-report: QIDS-A-SR Observer-rated: CDRS-R, QIDS-A-C17
Jeong <i>et al.</i> (2005)	Korea	40	16 (–)	100	High-school	Elevated symptoms, BDI = mild depression	Mild*, –	No regular exercise in past 6 months	Self-report: SCL-90-R, depression subscale
Legrand (2014)	France	44	– (19–30)	100	Low SES housing project	Elevated symptoms, BDI ≥ 14	Moderate, BDI = 19.5	Not physically active (<30 min moderate activity 2/wk)	Self-report: BDI
McCann & Holmes (1984)	USA	47	Student, university	100	University	Elevated symptoms, BDI > 11	Mild, BDI = 15.35	–	Self-report: BDI
Moghaddam <i>et al.</i> (2012)	Iran	60	Student, high-school	0	High-school	Elevated symptoms, BDI = ‘moderate to deep depression’	–	–	Self-report: BDI
Mohammadi (2011)	Iran	100	Student, high-school	–	High-school	Elevated symptoms, BDI = ‘borderline to severe depression’	Moderate, BDI = 20.46	No regular exercise or sport activities	Self-report: BDI
Nabkasorn <i>et al.</i> (2006)	Thailand	59	– (18–20)	100	University	Elevated symptoms, CES-D ≥ 16	Mild, CES-D = 19.4	No regular vigorous sports activity in past 6 months	Self-report: CES-D
Noorbakhsh & Alijani (2013)	Iran	75	18.8 (18–20)	100	University	Elevated symptoms, BDI = ‘mild-to-moderate depression’	Moderate, BDI = 19.8	–	Self-report: BDI

Table 1 (cont.)

Trial ID	Country	N	Age, mean (range)	Gender, % female	Recruitment setting	Depression inclusion criteria	Baseline depression severity	Baseline activity threshold for inclusion	Depression outcome measures
Roshan <i>et al.</i> (2011)	Iran	24	16.9 (15–18)	100	High-school	Diagnosis, DSM. HAM-D ≥ 18	Severe, HAM-D=29.9	-	Observer-rated: HAM-D
Sadeghi <i>et al.</i> (2016)	Iran	46	21 (18–25)	22	University counselling centre	Diagnosis, DSM. BDI ≥ 13 , ≤ 28	Moderate, BDI = 22.8	-	Self-report: BDI
Woolery <i>et al.</i> (2004)	USA	28	21.5 (18–29)	79	University	Elevated symptoms, BDI ≥ 10 , ≤ 15	Mild, BDI = 12.4	Not practicing yoga	Self-report: BDI
Yavari (2008)	Iran	74	– (19–22)	0	University	Elevated symptoms, BDI > 19	Moderate, BDI = 24.2	-	Self-report: BDI

BDI, Beck Depression Inventory; CDI-2, Children's Depression Inventory-2; CES-D, Centre for Epidemiological Studies Depression scale; CDRS-R, Childs Depression Rating Scale – Revised; DSM, Diagnostic & Statistical Manual of Mental Disorders; HAM-D, Hamilton Depression Rating Scale; N, total participants randomised; QIDS-A-C17, Quick Inventory of Depression Symptomatology – Adolescent – Clinician Rated; QIDS-A-SR, Quick Inventory of Depression Symptomatology – Adolescent – Self-report; *, author reported severity category; –, not-reported or unclear.

(3–6METs, $n=6$) to vigorous activity (>6 METs, $n=4$). All trials prescribed either the type or intensity of activity, although four incorporated participant preference. Intervention periods ranged from 5 to 12 weeks (median = 8, IQR = 4) with one to five activity sessions per week (median = 3, IQR = 1). Session duration ranged from 30 to 90 min (median = 60, IQR = 15). Most trials used supervised activity sessions ($n=11$), with seven using trained and qualified professionals. Eight trials implemented interventions in group settings, one of which combined group and individual components. Three additional trials were done with individuals. Control groups were no-treatment (NT, $n=5$), wait-list (WL, $n=5$), and attention/activity placebo (AP, $n=7$). Placebo conditions consisted of stretching/flexibility ($n=3$), relaxation ($n=1$), a physical education class ($n=1$), very light activity ($n=1$) and an unguided group meeting ($n=1$). Eight trials had multiple intervention arms. Six contained two or more physical activity arms *v.* control. These multiple activity arms were collapsed within trials for the primary meta-analysis (Chu *et al.* 2009; Mohammadi, 2011; Noorbakhsh & Alijani, 2013; Cecchini-Estrada *et al.* 2015; Balchin *et al.* 2016). One trial was physical activity *v.* AP *v.* WL and the comparison against AP was selected for meta-analysis (McCann & Holmes, 1984). One trial was physical activity *v.* CBT *v.* control and another trial added physical activity to TAU compared with TAU alone. No trials were identified comparing physical activity to medication.

Outcomes

Fifteen trials used self-report measures, most commonly the Beck Depression Inventory (BDI) ($n=9$), and three reported observer-rated depression symptom measures.

Risk of bias

Risk of bias assessments within and across trials is displayed in Fig. 2a and b. Generation of the randomisation sequence was adequate in only five trials. Four trials adequately concealed allocation. Blinding of intervention personnel and participants to group allocation cannot be adequately achieved in physical activity trials. Blinding of outcome assessor cannot be achieved for self-report outcome measures. Two of three trials using an observer-rated outcome measure masked assessors to group allocation. Six trials were rated as low risk of bias for handling of incomplete post-treatment data. Baseline imbalance on the primary outcome was not detected in 15 trials. Protocols were identified for only three trials resulting in a low risk of bias rating for selective reporting. Overall, selection bias could not be ruled out in 88% of trials, performance bias was likely present in 100% of trials,

Table 2. Characteristics of physical activity interventions from included trials

Trial ID	Physical activity arms and content	Setting	Aerobic/ resistance	Duration (weeks)	Session (min)	Sessions per week	Intensity (MET)*	Activity protocol adherence	Control arm
Balchin <i>et al.</i> (2016)	1. High Intensity: stationary cycling @ 70–75% HR reserve 2. Moderate intensity: stationary cycling @ 45–50% HR reserve	S – I	Aerobic	6	60	3	1. Vig (6–9) 2. Mod (3–6)	64% completed all sessions	1. AP = walking/very light cycling control
Carter <i>et al.</i> (2015)	1. TAU + preferred intensity circuit training: strength + aerobic exercise	S Q G	Mixed	6	60	2	–	Ave. sessions attended = 66%	1. TAU = psychological therapy/medication
Cecchini-Estrada <i>et al.</i> (2015)	1. Physical activity program with motivation enhancement 2. Physical activity program without motivation enhancement 3. Physical activity done individually	S Q G – U – I	–	8	60	3	–	100% completed ≥ 22 of 24 sessions	1. AP = stretching, flexibility control
Chu <i>et al.</i> (2009)	1a. High intensity: treadmill exercise @ 65–75% MaxVO ₂ reserve	S – I	Aerobic	10	30–40	1	1. Vig (6–9)	Ave. sessions attended: 1. 87%	1. AP = stretching control
	1b. +exercise in own time @ 65–75% MaxVO ₂ reserve (EEG = 1000 kcal/wk)	U			–	3–4			
	2a. Low intensity: treadmill exercise @ 40–55% MaxVO ₂ reserve	S			30–40	1	2. Mod (3–6)	2. 77%	
	2b. +exercise in own time @ 40–55% MaxVO ₂ reserve (EEG = 1000 kcal/wk)	U			–	3–4			
Hemat-Far <i>et al.</i> (2012)	1. Running, 3 × 6–13 min sets @ 60–65% HR max, 3 min rest between sets	S – –	Aerobic	8	40–60	3	Mod (3–6)	–	1. NT = no physical activity control
Hughes <i>et al.</i> (2013)	1a. Treadmill/stationary bike exercises @ 1/4 to 1/3 of EEG	S Q I	Aerobic	12	30–40	1	Mod (3–6)	Ave. adherence to EEG = 77%	1. AP = stretching control
	1b. +exercise in own time @ 1/4 to 1/3 of EEG (=12 kcal/kg/week)	U	–		–	2–3			

Table 2 (*cont.*)

Trial ID	Physical activity arms and content	Setting	Aerobic/ resistance	Duration (weeks)	Session (min)	Sessions per week	Intensity (MET)*	Activity protocol adherence	Control arm
Jeong <i>et al.</i> (2005)	1. Dance movement therapy	– – – –		12	45	3	–	–	1. WL
Legrand (2014)	1. Jogging @ 65–80% HR max + zumba dance class + calisthenics	S Q G	Mixed	7	60	2	Vig (6–9)	68% attended all sessions	1. WL
McCann & Holmes (1984)	1a. Aerobics class = dance, jogging, running 1b. +exercise in own time	S – G U I	Aerobic	10	60	2	–	–	1. AP = relaxation control; 2. WL
Moghaddam <i>et al.</i> (2012)	1. Swimming 2. Football 3. Athletics	– – –	Aerobic	12	90	2	–	–	1. NT
Mohammadi (2011)	1. Team sport (soccer or volleyball) 2. Individual sport (table tennis or badminton)	– – G I	Aerobic	8	75	3	–	–	1. NT = prevented from doing sports
Nabkasorn <i>et al.</i> (2006)	1. Self-paced jogging @ <50% maximal HR reserve	S Q G	Aerobic	8	50	5	Mod (3–6)	Ave. sessions attended = 78%	1. WL = daily activity monitoring
Noorbakhsh & Alijani (2013)	1. Aerobics 2. Swimming	– – –	Aerobic	6	60	3	–	–	1. AP = phys. ed. class control
Roshan <i>et al.</i> (2011)	1. Pool walking exercise @ 60– 70% HR max	S – G	Aerobic	6	–	3	Mod (3–6)	–	1. NT = no exercise control
Sadeghi <i>et al.</i> (2016)	1. Aerobic exercise @ 60–80% HR reserve	S Q –	Aerobic	8	45–60	3	Vig (6–9)	–	1. AP = unguided group meeting control; 2. CBT
Woolery <i>et al.</i> (2004)	1. Iyengar yoga classes (Hatha yoga)	S Q G	Resistance	5	60	2	Light (2.5)	–	1. WL = no yoga control, maintain routine activity
Yavari (2008)	1. Swimming	– – –	Aerobic	12–15	–	1	–	–	1. NT = no swimming control

Supervised (S) or unsupervised (U), qualified instructor (Q), group (G) or individual (I); EEG, energy expenditure goal; AP, attention/activity placebo; NT, no-treatment control; WL, wait-list control; TAU, treatment as usual; HR, heart rate; MaxVO₂, maximal oxygen uptake; *MET, metabolic equivalent estimate (based on Ainsworth *et al.* 2011 and Norton *et al.* 2010); (Ainsworth). –, not reported or unclear.

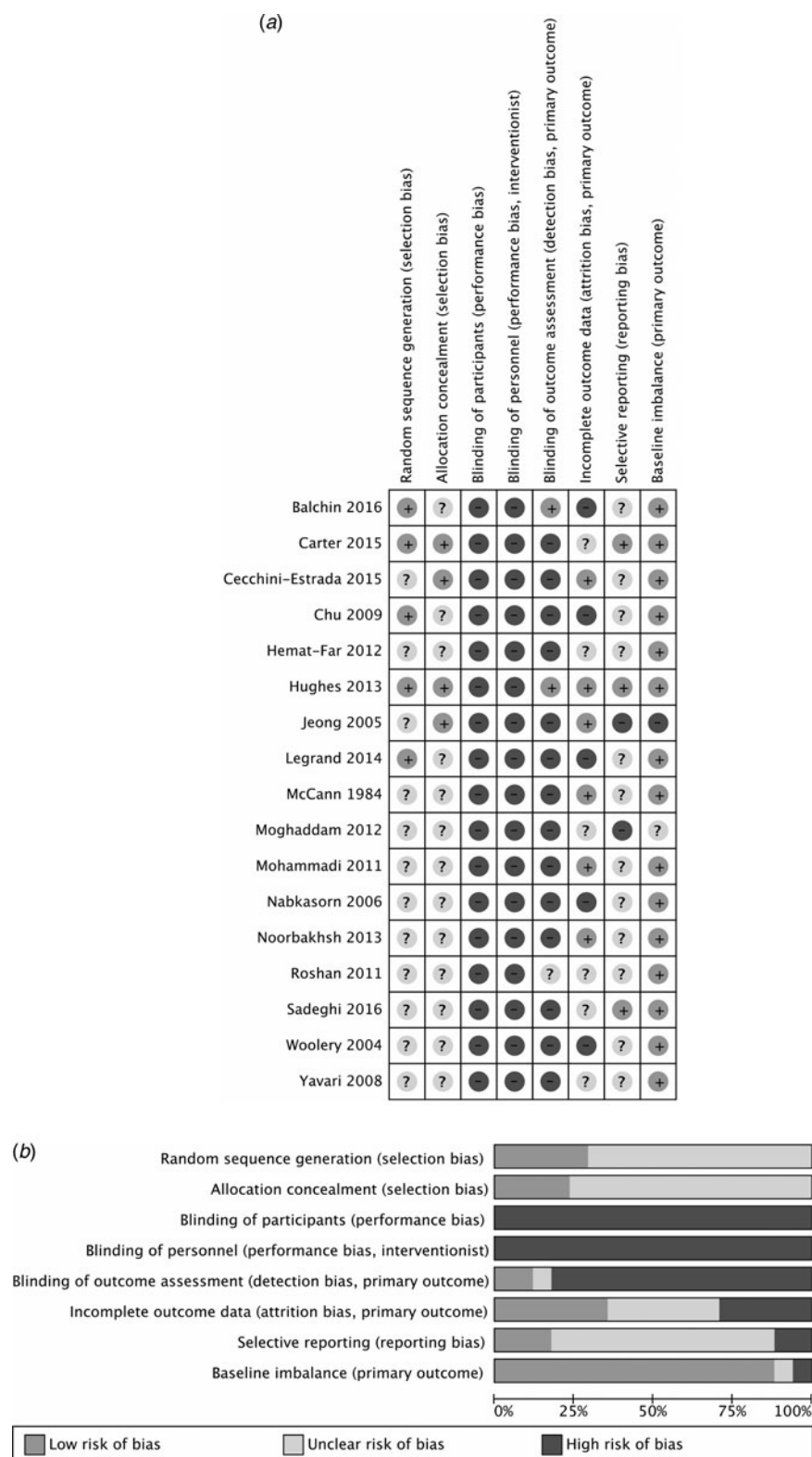


Fig. 2. (a) Risk of bias ratings. (b) Risk of bias graph: percentage of trials receiving low, unclear or high risk of bias rating for each domain.

detection bias was present or could not be ruled out in 88% of trials and attrition bias was present or could not be ruled out in 59% of trials.

Intervention adherence

Seven trials reported intervention adherence or attendance data. Three reported that on average 66% to 87% of intervention sessions were attended, one reported an average energy expenditure target adherence of 77%, two reported that 64% and 68% of participants completed all activity sessions and one trial reported that all participants attended at least 22 of 24 sessions.

Imputation of trial outcome data

Two trials reported graphical outcome data which we converted to numerical format as described above (McCann & Holmes, 1984; Nabkasorn *et al.* 2006). One trial did not report an estimate of variability (McCann & Holmes, 1984), therefore we imputed the missing standard deviation with an estimate pooled[†] from the eight included trials that had used the same outcome measure (BDI) at post-intervention, based on the recommendations by Furukawa *et al.* (2006) and in the Cochrane Handbook (Higgins *et al.* 2011a). One trial did not report extractable outcome data and is therefore not included in meta-analysis (Moghaddam *et al.* 2012).

Meta-analysis results

The primary meta-analysis pooled 16 trials ($n=771$) testing the effect of physical activity on depression symptoms at post-intervention compared with a control condition (Fig. 3), finding a large effect in favour of physical activity (SMD = -0.82 , 95% CI = -1.02 , to -0.61 , $p < 0.05$, $I^2 = 38\%$).

Publication bias

Estimation of the fail-safe N suggests that 430 trials with no effect would be needed before the pooled effect was no longer statistically significant. The fill-and-trim analysis suggests four trials may be missing from the right side of the funnel plot (see Supplementary Material Fig. S2). Imputing these missing trials produced an adjusted pooled effect in favour of physical activity of -0.69 (95% CI = -0.90 to -0.48).

Sensitivity analysis (Table 3)

We were unable to conduct a sensitivity analysis restricted to better quality trials as there were not enough available trials at low risk of bias across all or most domains of bias. Therefore we conducted

four separate sensitivity analyses excluding trials that were rated as either unclear or high risk of bias for sequence generation, allocation concealment, outcome assessor blinding and incomplete outcome data. The pooled effect remained in favour of physical activity for trials at low risk of bias for sequence generation ($k=5$, SMD = -0.63 , 95% CI = -0.97 to -0.29), for blinding of outcome assessor ($k=2$, SMD = -0.90 , 95% CI = -1.47 to -0.32) and for incomplete outcome data ($k=6$, SMD = -0.72 , 95% CI = -1.03 to -0.40), but not for allocation concealment ($k=4$, SMD = -0.48 , 95% CI = -1.02 to 0.05). When multiple activity and control arms were available within a trial, the comparison identified as producing the largest effect size was selected for sensitivity analysis. This was in contrast to the primary analysis where a more conservative approach was taken by pooling activity arms within trials and selecting the more rigorous control group for comparison. This sensitivity analysis produced a larger effect (SMD = -1.00) when compared with the primary analysis (SMD = -0.82), however heterogeneity was substantially increased ($I^2 = 38\%$ to 61%). Four trials appeared to categorically differ from the others and therefore may have introduced heterogeneity to the primary analysis; two employed alternative intervention modalities (yoga in Woolery *et al.* (2004); dance movement therapy in Jeong *et al.* (2005)), and two used control conditions, which may not be equivalent to NT, WL or AP (physical activity + TAU *v.* TAU in Carter *et al.* (2015); the AP control group engaged in significant levels of activity in Balchin *et al.* (2016)). Removal of these trials reduced heterogeneity ($I^2 = 0\%$), but did not substantially alter the pattern of results (SMD = -0.92). Similar magnitudes of effect were found when the analysis was restricted to either observer-rated or self-report depression symptom measure outcomes and when trials with imputed data from graphical representations were removed from the analysis.

Analysis of dropout

Dropout rate from randomisation to post-intervention was 11% (95% CI = 4.8 – 17.6) in physical activity arms and 18% (95% CI = 9.5 – 27.8) in control arms, however there was no significant difference between arms when trial dropout was pooled ($k=12$, RD = -0.01 , 95% CI = -0.04 to 0.03 , $p = 0.70$) (Fig. 4).

Subgroup analyses

The observational results in Table 4 show that in these included trials, the effect sizes did not significantly differ by type of control group (WL/NT *v.* AP), age group (<18 *v.* ≥ 18), diagnostic status (diagnosis *v.* threshold symptoms), sample recruitment (clinical *v.* non-clinical), depression severity category (mild, moderate, severe),

[†] The notes appear after the main text.

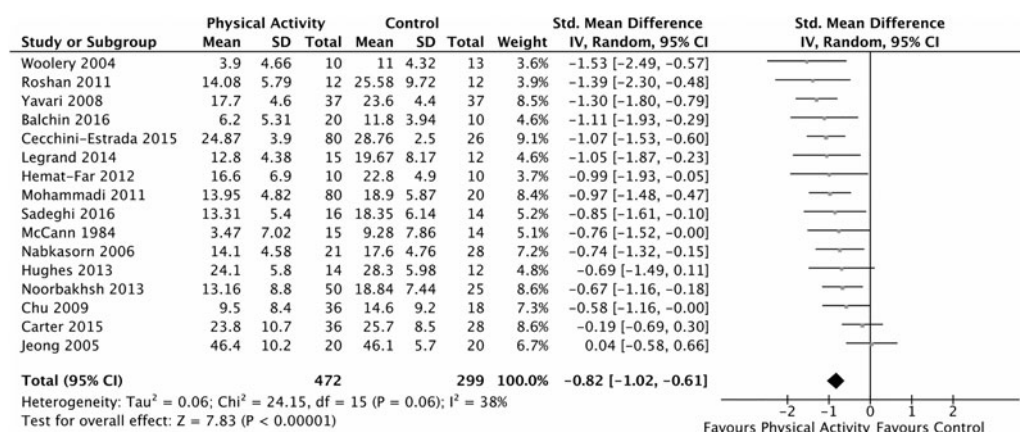


Fig. 3 Primary meta-analysis forest plot: physical activity *v.* control at post-intervention, depression symptom measure.

Table 3. Sensitivity analyses

Sensitivity analyses	k	n	SMD	95% CI	p value	Heterogeneity
Primary meta-analysis	16	771	-0.82	-1.02 to -0.61	$p < 0.00001$	$\chi^2 = 24.15$, $df = 15$ ($p = 0.06$); $I^2 = 38\%$
Selection of largest effect size when multiple arms available	16	624	-1.00	-1.28 to -0.72	$p < 0.00001$	$\chi^2 = 38.55$, $df = 15$ ($p = 0.0007$); $I^2 = 61\%$
Randomisation sequence generation: low risk of bias	5	201	-0.63	-0.97 to -0.29	$p < 0.001$	$\chi^2 = 5.18$, $df = 4$ ($p = 0.27$); $I^2 = 23\%$
Allocation concealment: low risk of bias	4	236	-0.48	-1.02 to 0.05	$p = 0.08$	$\chi^2 = 10.28$, $df = 3$ ($p = 0.02$); $I^2 = 71\%$
Outcome assessor blinding: low risk of bias	2	56	-0.90	-1.47 to -0.32	$p < 0.001$	$\chi^2 = 0.52$, $df = 1$ ($p = 0.47$); $I^2 = 0\%$
Incomplete outcome data: low risk of bias	6	376	-0.72	-1.03 to -0.40	$p < 0.00001$	$\chi^2 = 8.83$, $df = 5$ ($p = 0.12$); $I^2 = 43\%$
Self-report depression symptom measure	14	717	-0.77	-0.99 to -0.55	$p < 0.00001$	$\chi^2 = 22.19$, $df = 13$ ($p = 0.05$); $I^2 = 41\%$
Observer-rated depression symptom measure	3	80	-1.03	-1.52 to -0.55	$p < 0.00001$	$\chi^2 = 1.33$, $df = 2$ ($p = 0.52$); $I^2 = 0\%$
Excluding trials with heterogeneous control groups ^a	14	677	-0.86	-1.06 to -0.67	$p < 0.00001$	$\chi^2 = 17.23$, $df = 13$ ($p = 0.19$); $I^2 = 25\%$
Excluding trials with heterogeneous physical activity groups ^b	14	708	-0.85	-1.02 to -0.67	$p < 0.00001$	$\chi^2 = 14.66$, $df = 13$ ($p = 0.33$); $I^2 = 11\%$
Excluding trials with heterogeneous physical activity & control groups	12	614	-0.92	-1.09 to -0.74	$p < 0.00001$	$\chi^2 = 6.95$, $df = 11$ ($p = 0.80$); $I^2 = 0\%$
Excluding trials with graphical/imputed data	14	693	-0.83	-1.07 to -0.60	$p < 0.00001$	$\chi^2 = 24.07$, $df = 13$ ($p = 0.03$); $I^2 = 46\%$

k, number of trials; n, number of participants; SMD, standardised mean difference; CI, confidence interval.

^a Excluded from analysis are Carter *et al.* (2015) and Balchin *et al.* (2016).

^b Excluded from analysis are Jeong *et al.* (2005) and Woolery *et al.* (2004).

type of physical activity (aerobic *v.* resistance) and intensity (light, moderate, vigorous). Meta-regression analyses found no relationship between physical activity's observed effect and either of the two continuous variables (mean age and standardised mean depression symptoms at baseline, both $p > 0.1$).

Grade

Overall quality of the evidence contributing to the primary meta-analysis was rated as LOW to VERY LOW. Serious or very serious limitations in study design and suspected publication bias led to a downgrading of the

Table 4. Subgroup analyses based on the primary meta-analysis

Subgroup analysis	<i>k</i>	<i>N</i>	SMD	95% CI	<i>p</i> value	Heterogeneity	Test for subgroup difference
Primary meta-analysis	16	771	−0.82	−1.02 to −0.61	$p < 0.00001$	$\chi^2 = 24.15$, df = 15 ($p = 0.06$); $I^2 = 38\%$	
Sample recruitment							
Clinical	5	164	−0.72	−1.16 to −0.29	$p < 0.01$	$\chi^2 = 6.62$, df = 4 ($p = 0.16$); $I^2 = 40\%$	$\chi^2 = 0.29$, df = 1,
Non-Clinical	11	607	−0.86	−1.09 to −0.63	$p < 0.00001$	$\chi^2 = 16.05$, df = 10 ($p = 0.10$); $I^2 = 38\%$	($p = 0.59$); $I^2 = 0\%$
Diagnostic status							
Diagnosis	4	100	−0.95	−1.37 to −0.53	$p < 0.00001$	$\chi^2 = 1.37$, df = 3 ($p = 0.71$); $I^2 = 0\%$	$\chi^2 = 0.40$, df = 1,
Threshold symptoms	12	671	−0.79	−1.04 to −0.55	$p < 0.00001$	$\chi^2 = 22.25$, df = 11 ($p = 0.02$); $I^2 = 51\%$	($p = 0.53$); $I^2 = 0\%$
Depression symptom severity (baseline)							
Mild	4	141	−0.68	−1.26 to −0.10	$p < 0.05$	$\chi^2 = 8.05$, df = 3 ($p = 0.04$); $I^2 = 63\%$	$\chi^2 = 0.75$, df = 2,
Moderate	10	542	−0.94	−1.13 to −0.74	$p < 0.05$	$\chi^2 = 5.56$, df = 9 ($p = 0.78$); $I^2 = 0\%$	($p = 0.69$); $I^2 = 0\%$
Severe	2	88	−0.73	−1.89 to 0.42	$p = 0.21$	$\chi^2 = 5.03$, df = 1 ($p = 0.02$); $I^2 = 80\%$	
Age group							
Mean age < 18	5	254	−0.59	−1.08 to −0.11	$p < 0.05$	$\chi^2 = 11.50$, df = 4 ($p = 0.02$); $I^2 = 65\%$	$\chi^2 = 1.67$, df = 1,
Mean age ≥ 18	11	517	−0.94	−1.13 to −0.74	$p < 0.00001$	$\chi^2 = 7.32$, df = 10 ($p = 0.70$); $I^2 = 0\%$	($p = 0.20$); $I^2 = 40.2\%$
Type of control							
PA v. NT/WL	8	357	−0.95	−1.30 to −0.60	$p < 0.00001$	$\chi^2 = 14.41$, df = 7 ($p = 0.04$); $I^2 = 51\%$	$\chi^2 = 0.35$, df = 1,
PA v. attention/activity placebo	7	350	−0.82	−1.05 to −0.59	$p < 0.00001$	$\chi^2 = 2.73$, df = 6 ($p = 0.84$); $I^2 = 0\%$	($p = 0.55$); $I^2 = 0\%$
Type of activity							
Aerobic	13	657	−0.84	−1.04 to −0.64	$p < 0.00001$	$\chi^2 = 15.47$, df = 12 ($p = 0.22$); $I^2 = 22\%$	$\chi^2 = 2.42$, df = 2,
Resistance	1	23	−1.53	−2.49 to −0.57	$p < 0.01$	NA	($p = 0.30$); $I^2 = 17.5\%$
Mixed	2	91	−0.56	−1.39 to 0.28	$p = 0.19$	$\chi^2 = 3.11$, df = 1 ($p = 0.08$); $I^2 = 68\%$	
Intensity							
Light	1	23	−1.53	−2.49 to −0.57	$p < 0.05$	NA	$\chi^2 = 2.87$, df = 2
Moderate ^a	6	176	−0.76	−1.09 to −0.43	$p < 0.00001$	$\chi^2 = 5.48$, df = 5 ($p = 0.36$); $I^2 = 9\%$	($p = 0.24$); $I^2 = 30.2\%$
Vigorous ^a	4	112	−1.04	−1.44 to −0.64	$p < 0.00001$	$\chi^2 = 0.39$, df = 3 ($p = 0.94$); $I^2 = 0\%$	

k, number of trials; *n*, number of participants; SMD, standardised mean difference; CI, confidence interval; PA, physical activity; NT, no-treatment; WL, wait-list.

^a Two trials (Chu *et al.* 2009; Balchin *et al.* 2016) have multiple physical activity arms of differing intensity and thus contribute non-independent effects to the intensity sub-group analysis.

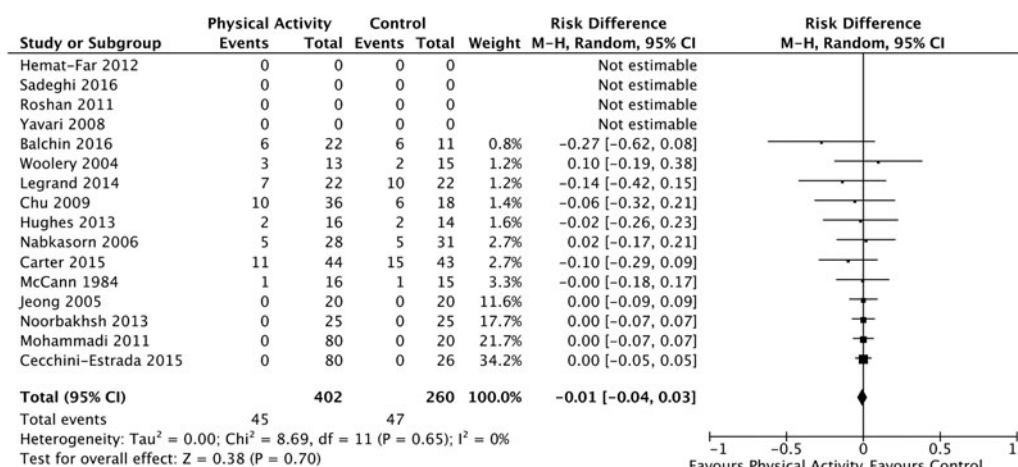


Fig. 4. Acceptability forest plot: physical activity *v.* control, number of participants dropping out of intervention and control arms (Events) from number randomised (Total).

evidence by two to three levels (See Supplementary Material for GRADE ratings). The level of evidence was not downgraded for either imprecision, inconsistency, or indirectness.

Discussion

Main findings

Physical activity appears to show efficacy for improving depression symptoms in adolescents and young adults experiencing a diagnosis or threshold symptoms of depression. However the risk of bias within included trials and the low quality of the overall evidence base limit our confidence in this finding. None-the-less, physical activity does appear to be an acceptable and feasible intervention modality for young people experiencing depression given the low dropout rate. Subgroup and meta-regression analyses suggest that the treatment effect may not be modified by characteristics such as age, depression severity, diagnostic status, physical activity type or intensity, however these analyses are observational, likely underpowered to detect effects and should be interpreted with caution. While we do not yet know the specific intervention characteristics required to bring about symptom improvement, we identify a number of characteristics common across trials that may inform future research agendas and the implementation of physical activity interventions.

Context of main findings

To provide a clinical interpretation of the large pooled effect, the SMD (-0.82) was back-transformed into units of the BDI (Higgins *et al.* 2011a), showing that those receiving a physical activity intervention would

score, on average, 5.38 (95% CI = 4.00–6.69) points lower on the BDI than those in a control condition². The minimal clinically important difference on the BDI has been estimated at between three and five points (Hiroe *et al.* 2005) and elsewhere as a 17.5% reduction from baseline (Button *et al.* 2015). This suggests that physical activity may produce a clinically significant reduction in depression symptoms. Furthermore, the effect was robust when restricting the analysis to the seven trials comparing physical activity to attention/activity placebo controls (-0.82 , $I^2 = 0\%$). Importantly this provides some indication that the effect estimate may be due to the physical activity intervention rather than the non-specific factors that cannot be controlled in comparison with no-treatment/wait-list controls (Lindheimer *et al.* 2015; Stubbs *et al.* 2016a). However further research is needed to establish this finding given the observational nature of the analysis, the small number and the low quality of included trials.

The large effect generated from this meta-analysis is consistent in size with meta-analytic findings of physical activity for depression in adults (Cooney *et al.* 2013; Kvam *et al.* 2016; Schuch *et al.* 2016b). In terms of previous child and adolescent meta-analyses, these have included trials of healthy young people, those with other medical or mental health conditions or children under 12 years, potentially complicating the generalisability of their findings to the treatment of depression (Larun *et al.* 2006; Brown *et al.* 2013; Carter *et al.* 2016). The current meta-analysis synthesised only trials of adolescents and young adults with either a diagnosis or threshold symptoms of depression highlighting its relevance to young people needing treatment, particularly as our subgroup analysis suggests a robust effect size in trials that recruited clinical samples. We

also identified and included seven RCTs that had not appeared in any previous adult or child-adolescent review.

In the context of established treatments for youth depression, psychological interventions demonstrate small-to-moderate treatment effects (Weisz *et al.* 2006, 2017; Watanabe *et al.* 2007). While our meta-analysis generated a large preliminary effect size, physical activity is considerably less researched than established psychotherapies and we have limited information regarding head-to-head comparisons. Only one trial to date has compared physical activity with CBT for depression in young people, finding equivalent treatment effects in comparison with control (Sadeghi *et al.* 2016). Physical activity interventions may exert some influence on depression via a general behavioural activation effect, an often-utilised treatment component of CBT. This is potentially relevant to youth depression given that behavioural-based interventions may be better suited to younger age groups (Hetrick *et al.* 2015). Preliminary work is exploring the use of physical activity-based interventions delivered via behavioural activation frameworks for depression in both young people and adults (Parker *et al.* 2016; Euteneuer *et al.* 2017).

Our investigation of attrition rates as a proxy for intervention acceptability showed that dropout across physical activity arms was 11%, which did not differ from controls. This rate is comparable with that established in a recent meta-analysis of dropout from physical activity trials in adults with depression (15.2%, (Stubbs *et al.* 2016b)). It is also equivalent to pooled attrition rates observed from psychotherapy trials for depression in young people (12%, (Weisz *et al.* 2006)) and substantially better than rates identified for antidepressant medication (19% to 38%, (Hetrick *et al.* 2012)), suggesting that physical activity is at least as acceptable as psychotherapy and may be more acceptable than medication. Additionally, young people appear more likely to endorse physical activity as a helpful intervention for depression, than either medication or psychotherapy (Jorm & Wright, 2007; Reavley & Jorm, 2011), further highlighting the potential acceptability and feasibility of employing this intervention modality with young people.

Quality of evidence

The overall quality of evidence contributing to the meta-analysis is low, suggesting the current findings should be interpreted with caution. We were unable to undertake an analysis restricted to high quality trials, because there are currently not enough available trials at low risk of bias across all or most domains, to do so. While the effect sizes from three of our four sensitivity

analyses by individual risk of bias domain remained largely unchanged compared with the overall effect, each analysis was restricted to a very small number of trials meaning we cannot rule out bias from the overall effect size. This uncertainty is likely a result of inadequate reporting of trial methods, particularly as many domains (e.g., selection and attrition bias) received unclear ratings across trials. Both trial-level selection and attrition bias have been shown to impact the size of effect estimate (Schulz *et al.* 1995; Bell *et al.* 2013). Of particular concern to the internal validity of the current finding is that physical activity is an unblinded intervention (risk of performance bias), and in the context of a self-report outcome measure (risk of detection bias), there is the potential to inflate the effect in favour of the intervention. Large, robust, adequately reported trials that attempt to reduce the risk of bias in their methodologies are therefore needed to increase confidence in the current finding. Publication bias cannot be ruled out given the small attenuation of effect size using the trim and fill method, however its potential effect appears small given the adjusted effect size (after imputing potentially suppressed trials) was moderate and remained significant, coupled with the large observed fail-safe *N*. Ratings for two of the five GRADE domains (limitations of study design, publication bias) resulted in a downgrading of the current RCT-generated evidence from HIGH to LOW or VERY LOW, suggesting that confidence in the effect is limited and the effect size may be substantially different from the estimate presented (Balslem *et al.* 2011; Schünemann *et al.* 2013).

Implementation and further research

We do not yet know the specific characteristics or type of young people who might be suited to, or benefit most from a physical activity intervention. Our analysis suggests that in these trials, physical activity may produce a similar, large magnitude of effect for young people irrespective of whether they were recruited with a diagnosis or threshold symptoms of depression, and appears unchanged when restricted to trials conducted with clinical samples. Similarly, the treatment effect does not appear to be associated with baseline depression symptom severity, however given the small number of clinical-based trials, further work is needed to confirm these findings. While appearing consistent with a recent adult level moderator analysis of physical activity trials (Schuch *et al.* 2016c), caution should still be taken when interpreting these subgroup analyses as they are likely underpowered and only observational in nature. All but two included trials in this analysis were in the mild and

moderate severity range suggesting that physical activity may be clinically relevant for young people experiencing this symptom severity, and that further research is needed to explore the benefits for severe depression. Current treatment guidelines recommend providing general advice on the benefit of physical activity, alongside first-line interventions (e.g., CBT), to all young people presenting with depression, regardless of severity (NICE, 2015). While the current finding highlights the potential of physical activity as stand-alone intervention, larger scale replication trials, particularly with clinical samples, are needed before this work can be used to inform treatment guidelines.

Common intervention characteristics were observed across trials that may guide further research and the clinical implementation of physical activity protocols, including the use of supervised group sessions of moderate or vigorous intensity aerobic activity over 60 min sessions, multiple times per week, over at least an 8-week period. Adult-level syntheses have identified a similar pattern of common characteristics that may lead to symptom improvement (Perraton *et al.* 2010; Silveira *et al.* 2013; Stanton & Reaburn, 2014; Nyström *et al.* 2015). Our observational subgroup analyses suggest that the intervention characteristics we investigated may not have modified the treatment effect in the included trials. However, caution should be taken when interpreting this finding given the small number of trials in subgroups leaving analyses underpowered to detect differences if they exist. The current evidence base is therefore limited to the characteristics common in the small number of trials published to date, with further work needed to determine the component ingredients required to bring about improvement in depression and if identified, how best to implement them in clinical settings.

To date, an optimum dose of activity for depression cannot be recommended due to a lack of available trial data. Only two trials with young people have directly tested the effect of differing intensities of aerobic activity (Chu *et al.* 2009; Balchin *et al.* 2016), with equivocal findings. Pooling of included trials according to intensity appeared to suggest that those implementing moderate and vigorous intensity activities produced large effects, however there were too few trials of low intensity activity to allow meaningful comparison, requiring further investigation. Two highly cited trials in adults suggest that more physical activity, whether in the form of higher intensity or overall energy expenditure may produce better results for the treatment of depression (Dunn *et al.* 2005; Trivedi *et al.* 2011). While the dose-response relationship looks promising, further trials are required, particularly in young people. Investment in dose-response trials needs to be considered alongside an alternative treatment option that

focuses less on minimum thresholds and more on promoting incidental physical activity and reducing sedentary behaviour (Vancampfort *et al.* 2015; Parker *et al.* 2016).

Our pooled effect was based on variable types of physical activity, yet it remained unchanged when trials that differed substantially were removed (e.g., yoga, dance movement therapy), suggesting that the type of activity may not be important. Although the type was variable, most interventions consisted of an aerobic-based activity, with only one trial using resistance-based activity (Woolery *et al.* 2004) and two others using a combination (Legrand, 2014; Carter *et al.* 2015). In adults, resistance-based activity has produced reductions in depression symptoms and direct comparison suggests both modalities perform equally well (Doyle *et al.* 1987; Martinsen *et al.* 1989; Krogh *et al.* 2009; Cooney *et al.* 2013). Further investigation of resistance-based activity in young people is warranted, particularly as some may show preference for this modality (Firth *et al.* 2016).

Supervision is a common feature of physical activity protocols (Perraton *et al.* 2010), and may lead to lower dropout, particularly when delivered by a qualified professional (e.g., exercise physiologist or physiotherapist) (Stubbs *et al.* 2016b). Conversely, a lack of supervision may contribute to poor engagement and compliance (Knapen *et al.* 2015), and is a likely factor in null findings in some adult level trials (Chalder *et al.* 2012; Pfaff *et al.* 2014). Most trials in this review utilised supervision, with seven employing a qualified professional, potentially contributing to the positive pooled effect.

Strengths and limitations

The rigour of this review is enhanced by the inclusion of RCTs, the use a comprehensive and exhaustive search, systematic methodology to identify trials and extract data, and the use of systematic tools to assess bias and overall evidence quality. Additionally the requirement of a diagnosis or threshold depression symptoms for trial inclusion highlights the potential clinical applicability of the findings. This is the first meta-analysis to examine the effects of physical activity interventions for depression spanning the adolescent-young adult period, providing valuable knowledge about a period that overlaps with the peak onset of depression.

A number of factors may limit the generalisability of the findings, including the overall low quality of the evidence base contributing to the main analysis, overrepresentation of female-only samples, use of potentially heterogeneous activity protocols, small sample sizes and the limited number of available trials,

particularly those recruiting from clinical settings. Our subgroup findings are limited by being observational in nature and underpowered due to the small number of trials in many subgroupings. We were unable to investigate a number of important factors due to the paucity of available trials, including the effect of physical activity over longer-term follow-up (as maintenance of post-intervention benefit is often an important clinical goal) and the relative benefits of physical activity compared with established depression treatments such as medication and psychotherapy. Determining whether these interventions are equivalent may provide young people who do not want, are not suited for or do not benefit from established therapies, a viable and effective treatment option. Exploring the mechanisms by which physical activity improves depression is also needed to better understand the necessary ingredients for symptom change and to inform the design of more targeted intervention strategies. Also missing from the current evidence base is an investigation of the effect that physical activity interventions have on physical health outcomes in depression, particularly given the risk that both depression and low activity levels confer to negative health consequences (Lee *et al.* 2012; Goldstein *et al.* 2015).

Conclusion

This review indicates that physical activity is a promising primary intervention for adolescents and young adults experiencing a diagnosis or threshold symptoms of depression, however concerns surrounding methodological quality of included trials limit our ability to conclude on its effectiveness. While the effect of physical activity appears large and robust in comparison with attention/activity placebo control conditions, and when restricted to trials in clinical samples, the findings should be interpreted with caution given the quality of the underlying evidence base is currently low. This suggests uncertainty surrounding the size of the effect and indicates that large, well-reported and robust trials conducted with help-seeking clinical samples in real-world treatment settings are required to increase confidence in the current finding. Physical activity appears to be acceptable to young people, suggesting the potential feasibility of incorporating it into the routine clinical treatment of depression, however research is still required to establish the intervention characteristics that are necessary to improve depression.

Notes

¹ Pooled standard deviation = $\sqrt{\sum (n_i - 1)SD_i^2 / (n_i - 1)}$.

² SMD multiplied by the pooled baseline standard deviation of the eight included trials ($n = 424$) reporting the BDI in numerical format.

Supplementary material

The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291717002653>

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Declaration of Interest

None.

References

- Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr. DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS (2011). 2011 compendium of physical activities: a second update of codes and MET values. *Medicine & Science in Sports* **43**, 1575–1581.
- Andrews G, Sanderson K, Corry J, Lapsley HM (2000). Using epidemiological data to model efficiency in reducing the burden of depression. *Journal of Mental Health Policy & Economics* **3**, 175–186.
- Balchin R, Linde J, Blackhurst D, Rauch HL, Schonbachler G (2016). Sweating away depression? The impact of intensive exercise on depression. *Journal of Affective Disorders* **200**, 218–221.
- Balslem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH (2011). GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* **64**, 401–406.
- Bell ML, Kenward MG, Fairclough DL, Horton NJ (2013). Differential dropout and bias in randomised controlled trials: when it matters and when it may not. *British Medical Journal* **346**, e8668.
- Brent DA, Birmaher B (2002). Adolescent depression. *New England Journal of Medicine* **347**, 667–671.
- Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJH (2013). Physical activity interventions and depression in children and adolescents. *Sports Medicine* **43**, 195–206.
- Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ, Ades AE, Lewis G (2015). Minimal clinically important difference on the Beck Depression Inventory – II according to the patient's perspective. *Psychological Medicine* **45**, 3269–3279.

- Carter T, Guo B, Turner D, Morres I, Khalil E, Brighton E, Armstrong M, Callaghan P (2015). Preferred intensity exercise for adolescents receiving treatment for depression: a pragmatic randomised controlled trial. *BMC Psychiatry* 15, 1–12.
- Carter T, Morres ID, Meade O, Callaghan P (2016). The effect of exercise on depressive symptoms in adolescents: a systematic review and meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*. 55, 580–590.
- Cecchini-Estrada J-A, Mendez-Gimenez A, Cecchini C, Moulton M, Rodriguez C (2015). Exercise and Epstein's TARGET for treatment of depressive symptoms: a randomized study. *International Journal of Clinical and Health Psychology* 15, 191–199.
- Chalder M, Wiles NJ, Campbell J, Hollinghurst SP, Haase AM, Taylor AH, Fox KR, Costelloe C, Searle A, Baxter H, Winder R, Wright C, Turner KM, Calnan M, Lawlor DA, Peters TJ, Sharp DJ, Montgomery AA, Lewis G (2012). Facilitated physical activity as a treatment for depressed adults: randomised controlled trial. *British Medical Journal* 344, 1–13.
- Chu IH, Buckworth J, Kirby TE, Emery CF (2009). Effect of exercise intensity on depressive symptoms in women. *Mental Health & Physical Activity* 2, 37–43.
- Cipriani A, Zhou X, Del Giovane C, Hetrick S, Qin B, Whittington C, Coghill D, Zhang Y, Hazell P, Leucht S, Cuijpers P, Pu J, Cohen D, Ravindran A, Liu Y, Michael K, Yang L, Liu L, Xie P (2016). Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 388, 881–890.
- Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum: Hillsdale, NJ.
- Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE (2013). Exercise for depression. *Cochrane Database of Systematic Reviews*, Issue 9. Art. No.: CD004366. doi: 10.1002/14651858.CD004366.pub6.
- Craft LL, Perna FM (2004). The benefits of exercise for the clinically depressed. *Primary Care Companion to the Journal of Clinical Psychiatry* 6, 104–111.
- Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, Pompeu FAMS, Coutinho ESF, Laks J (2009). Exercise and mental health: many reasons to move. *Neuropsychobiology* 59, 191–198.
- Doyne EJ, Ossip-Klein DJ, Bowman ED, Osborn KM, McDougall-Wilson IB, Neimeyer RA (1987). Running versus weight lifting in the treatment of depression. *Journal of Consulting & Clinical Psychology* 55, 748–754.
- Dunn AL, Trivedi MH, Kampert JB, Clark CG, Chambliss HO (2005). Exercise treatment for depression: efficacy and dose response. *American Journal of Preventive Medicine* 28, 1–8.
- Duval S, Tweedie R (2000). Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56, 455–463.
- Euteneuer F, Dannehl K, del Rey A, Engler H, Schedlowski M, Rief W (2017). Immunological effects of behavioral activation with exercise in major depression: an exploratory randomized controlled trial. *Translational Psychiatry* 7, e1132.
- Firth J, Rosenbaum S, Stubbs B, Vancampfort D, Carney R, Yung AR (2016). Preferences and motivations for exercise in early psychosis. *Acta Psychiatrica Scandinavica* 134, 83–84.
- Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N (2006). Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 59, 7–10.
- Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, Nieman DC, Swain DP (2011). American College of Sports Medicine Position Stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine & Science in Sports & Exercise* 43, 1334–1359.
- Goldstein BI, Carnethon MR, Matthews KA, McIntyre RS, Miller GE, Raghuvver G, Stoney CM, Wasiak H, McCrindle BW (2015). Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 132, 965–986.
- Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph VR, Coffey C, Sawyer SM, Mathers CD (2011). Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 377, 2093–2102.
- Hemat-Far A, Shahsavari A, Mousavi SR (2012). Effects of selected aerobic exercises on the depression and concentrations of plasma serotonin in the depressed female students aged 18 to 25. *Journal of Applied Research* 12, 47–52.
- Hetrick S, Cox G, Fisher C, Bhar S, Rice S, Davey C, Parker A (2015). Back to basics: could behavioural therapy be a good treatment option for youth depression? A critical review. *Early Intervention in Psychiatry* 9, 93–99.
- Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN (2012). Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, Issue 11. Art. No.: CD004851. doi: 10.1002/14651858.CD004851.pub3.
- Higgins J, Green S (eds) (2011a). *Cochrane Handbook for Systematic Reviews of Interventions*. [V5.1 updated March 2011], The Cochrane Collaboration: <http://www.cochrane-handbook.org>.
- Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC (2011b). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* 343, d5928.
- Hiroe T, Kojima M, Yamamoto I, Nojima S, Kinoshita Y, Hashimoto N, Watanabe N, Maeda T, Furukawa TA (2005). Gradations of clinical severity and sensitivity to change assessed with the Beck Depression Inventory-II in Japanese patients with depression. *Psychiatry Research* 135, 229–235.
- Hughes CW, Barnes S, Barnes C, DeFina LF, Nakonezny P, Emslie GJ (2013). Depressed Adolescents Treated with Exercise (DATE): a pilot randomized controlled trial to test feasibility and establish preliminary effect sizes. *Mental Health & Physical Activity* 6, 119–131.
- Jeong YJ, Hong SC, Myeong SL, Park MC, Kim YK, Suh CM (2005). Dance movement therapy improves emotional

- responses and modulates neurohormones in adolescents with mild depression. *International Journal of Neuroscience* **115**, 1711–1720.
- Jorm AF, Wright A** (2007). Beliefs of young people and their parents about the effectiveness of interventions for mental disorders. *Australian and New Zealand Journal of Psychiatry* **41**, 656–666.
- Kessler RC, Angermeyer M, Anthony JC, De Graaf R, Demyttenaere K, Gasquet I, De Girolamo G, Gluzman S, Gureje O, Haro JM** (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* **6**, 168–176.
- Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE** (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593–602.
- Knapen J, Vancampfort D, Moriën Y, Marchal Y** (2015). Exercise therapy improves both mental and physical health in patients with major depression. *Disability and Rehabilitation* **37**, 1490–1495.
- Krogh J, Saltin B, Gluud C, Nordentoft M** (2009). The DEMO trial: a randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. *Journal of Clinical Psychiatry* **70**, 790–800.
- Kvam S, Kleppe CL, Nordhus IH, Hovland A** (2016). Exercise as a treatment for depression: a meta-analysis. *Journal of Affective Disorders* **202**, 67–86.
- Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F** (2006). Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD004691. doi: 10.1002/14651858.CD004691.pub2.
- Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group** (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **380**, 219–229.
- Legrand FD** (2014). Effects of exercise on physical self-concept, global self-esteem, and depression in women of low socioeconomic status with elevated depressive symptoms. *Journal of Sport & Exercise Psychology* **36**, 357–365.
- Lewinsohn P, Rohde P, Seeley J, Klein D, Gotlib I** (2003). Psychosocial functioning of young adults who have experienced and recovered from major depressive disorder during adolescence. *Journal of Abnormal Psychology* **112**, 353–363.
- Lewinsohn PM, Rohde P, Seeley JR** (1998). Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implications. *Clinical Psychology Review* **18**, 765–794.
- Lindheimer JB, O'Connor PJ, Dishman RK** (2015). Quantifying the placebo effect in psychological outcomes of exercise training: a meta-analysis of randomized trials. *Sports Medicine* **45**, 693–711.
- March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J** (2004). Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *Journal of the American Medical Association* **292**, 807–820.
- Martinsen EW, Hoffart A, Solberg Ø** (1989). Comparing aerobic with nonaerobic forms of exercise in the treatment of clinical depression: a randomized trial. *Comprehensive Psychiatry* **30**, 324–331.
- McCann IL, Holmes DS** (1984). Influence of aerobic exercise on depression. *Journal of Personality & Social Psychology* **46**, 1142–1147.
- Moghaddam JB, Hefzollasan M, Salehian MH, Shirmohammadzadeh M** (2012). Effect of different exercises on reducing male students depression. *Annals of Biological Research* **3**, 1231–1235.
- Mohammadi M** (2011). A study and comparison of the effect of team sports (soccer and volleyball) and individual sports (table tennis and badminton) on depression among high school students. *Australian Journal of Basic and Applied Sciences* **5**, 1005–1011.
- Moher D, Liberati A, Tetzlaff J, Altman DG** (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* **339**, b2535.
- Moher D, Shamseer L, Clarke M, Gherzi D, Liberati A, Petticrew M, Shekelle P, Stewart LA** (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* **4**, 1–9.
- Nabkasorn C, Miyai N, Sootmongkol A, Junprasert S, Yamamoto H, Arita M, Miyashita K** (2006). Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. *European Journal of Public Health* **16**, 179–184.
- NICE** (2015). *Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care* (Clinical Guideline 28). National Institute for Health and Care Excellence: United Kingdom.
- Noorbakhsh M, Alijani E** (2013). The effects of physical activity on the level of depression in university female students. *Annals of Biological Research* **4**, 196–200.
- Norton K, Norton L, Sadgrove D** (2010). Position statement on physical activity and exercise intensity terminology. *Journal of Science & Medicine in Sport* **13**, 496–502.
- Nyström MBT, Neely G, Hassmén P, Carlbring P** (2015). Treating major depression with physical activity: a systematic overview with recommendations. *Cognitive Behaviour Therapy* **44**, 341–352.
- Parker AG, Hetrick SE, Jorm AF, Mackinnon AJ, McGorry PD, Yung AR, Scanlan F, Stephens J, Baird S, Moller B, Purcell R** (2016). The effectiveness of simple psychological and physical activity interventions for high prevalence mental health problems in young people: a factorial randomised controlled trial. *Journal of Affective Disorders* **196**, 200–209.
- Perraton LG, Kumar S, Machotka Z** (2010). Exercise parameters in the treatment of clinical depression: a systematic review of randomized controlled trials. *Journal of Evaluation in Clinical Practice* **16**, 597–604.

- Pfaff JJ, Alfonso H, Newton RU, Sim M, Flicker L, Almeida OP (2014). ACTIVEDEP: a randomised, controlled trial of a home-based exercise intervention to alleviate depression in middle-aged and older adults. *British Journal of Sports Medicine* **48**, 226–232.
- Reavley N, Jorm A (2011). Young people's recognition of mental disorders and beliefs about treatment and outcome: findings from an Australian national survey. *Australian and New Zealand Journal of Psychiatry* **45**, 890–898.
- Rethorst C, Wipfli B, Landers D (2009). The antidepressive effects of exercise. *Sports Medicine* **39**, 491–511.
- Rohatgi A (2013). WebPlotDigitizer (<http://arohatgi.info/WebPlotDigitizer/>). Accessed 12 December 2016.
- Rosenbaum S, Tiedemann A, Sherrington C, Curtis J, Ward P (2014). Physical activity interventions for people with mental illness: a systematic review and meta-analysis. *Journal of Clinical Psychiatry* **75**, 1–11.
- Rosenthal R (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin* **86**, 638–641.
- Roshan VD, Pourasghar M, Mohammadian Z (2011). The efficacy of intermittent walking in water on the rate of MHPG sulfate and the severity of depression. *Iranian Journal of Psychiatry & Behavioral Sciences* **5**, 26–31.
- Sadeghi K, Ahmadi SM, Ahmadi SM, Rezaei M, Miri J, Abdi A, Khamoushi F, Salehi M, Jamshidi K (2016). A comparative study of the efficacy of cognitive group therapy and aerobic exercise in the treatment of depression among the students. *Global Journal of Health Science* **8**, 1–8.
- Salmon P (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. *Clinical Psychology Review* **21**, 33–61.
- Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M (2014). Lifestyle medicine for depression. *BMC Psychiatry* **14**, 107.
- Schuch F, Deslandes A, Stubbs B, Gosmann N, da Silva C, Fleck M (2016a). Neurobiological effects of exercise on major depressive disorder: a systematic review. *Neuroscience & Biobehavioral Reviews* **61**, 1–11.
- Schuch F, Vancampfort D, Richards J, Rosenbaum S, Ward P, Stubbs B (2016b). Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. *Journal of Psychiatric Research* **77**, 42–51.
- Schuch FB, Dunn AL, Kanitz AC, Delevatti RS, Fleck MP (2016c). Moderators of response in exercise treatment for depression: a systematic review. *Journal of Affective Disorders* **195**, 40–49.
- Schulz KF, Chalmers I, Hayes RJ, Altman DG (1995). Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* **273**, 408–412.
- Schünemann H, Brożek J, Guyatt G, Oxman A (eds) (2013). *Handbook for Grading the Quality of Evidence and the Strength of Recommendations Using the GRADE Approach*. The Grade Working Group. <http://gdt.guidelinedevelopment.org/app/handbook/handbook.html>.
- Silveira H, Moraes H, Oliveira N, Coutinho ESF, Laks J, Deslandes A (2013). Physical exercise and clinically depressed patients: a systematic review and meta-analysis. *Neuropsychobiology* **67**, 61–68.
- Stanton R, Reaburn P (2014). Exercise and the treatment of depression: a review of the exercise program variables. *Journal of Science & Medicine in Sport* **17**, 177–182.
- Stubbs B, Vancampfort D, Rosenbaum S, Ward PB, Richards J, Ussher M, Schuch FB (2016a). Challenges establishing the efficacy of exercise as an antidepressant treatment: a systematic review and meta-analysis of control group responses in exercise randomised controlled trials. *Sports Medicine* **46**, 699–713.
- Stubbs B, Vancampfort D, Rosenbaum S, Ward PB, Richards J, Soundy A, Veronese N, Solmi M, Schuch FB (2016b). Dropout from exercise randomized controlled trials among people with depression: a meta-analysis and meta regression. *Journal of Affective Disorders* **190**, 457–466.
- TADS Team (2007). The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Archives of General Psychiatry* **64**, 1132–1143.
- Thapar A, Collishaw S, Pine DS, Thapar AK (2012). Depression in adolescence. *Lancet* **379**, 1056–1067.
- The Cochrane Collaboration (2014). *Review Manager (RevMan)*. [V5.1], The Nordic Cochrane Centre: Copenhagen.
- Trivedi MH, Greer TL, Church TS, Carmody TJ, Grannemann BD, Galper DI, Dunn AL, Earnest CP, Sunderajan P, Henley SS (2011). Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *Journal of Clinical Psychiatry* **72**, 677–684.
- Tsafnat G, Glasziou P, Choong MK, Dunn A, Galgani F, Coiera E (2014). Systematic review automation technologies. *Systematic Reviews* **3**, 74.
- Vancampfort D, Stubbs B, Ward PB, Teasdale S, Rosenbaum S (2015). Why moving more should be promoted for severe mental illness. *Lancet Psychiatry* **2**, 295.
- Veale D (2008). Behavioural activation for depression. *Advances in Psychiatric Treatment* **14**, 29–36.
- Vučić K, Jeličić Kadić A, Puljak L (2015). Survey of Cochrane protocols found methods for data extraction from figures not mentioned or unclear. *Journal of Clinical Epidemiology* **68**, 1161–1164.
- Watanabe N, Hunot V, Omori I, Churchill R, Furukawa T (2007). Psychotherapy for depression among children and adolescents: a systematic review. *Acta Psychiatrica Scandinavica* **116**, 84–95.
- Weersing VR, Brent DA (2006). Cognitive behavioral therapy for depression in youth. *Child & Adolescent Psychiatric Clinics of North America* **15**, 939–957.
- Wegner M, Helmich I, Machada S, Nardi A, Arias-Carrion O, Budde H (2014). Effects of exercise on anxiety and depression disorders: review of meta-analyses and neurobiological mechanisms. *CNS & Neurological Disorders Drug Targets* **13**, 1002–1014.
- Weisz JR, Kuppens S, Ng MY, Eckshtain D, Ugueto AM, Vaughn-Coaxum R, Jensen-Doss A, Hawley KM, Krumholz Marchette LS, Chu BC (2017). What five decades of research tells us about the effects of youth psychological therapy: a multilevel meta-analysis and implications for science and practice. *American Psychologist* **72**, 79–117.

- Weisz JR, McCarty CA, Valeri SM** (2006). Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychological Bulletin* **132**, 132–149.
- Wilson S, Hicks B, Foster K, McGue M, Iacono W** (2015). Age of onset and course of major depressive disorder: associations with psychosocial functioning outcomes in adulthood. *Psychological Medicine* **45**, 505–514.
- Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJG, Sterne JAC** (2008). Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *British Medical Journal* **336**, 601–605.
- Woolery A, Myers H, Sternlieb B, Zeltzer L** (2004). A yoga intervention for young adults with elevated symptoms of depression. *Alternative Therapies in Health & Medicine* **10**, 60–63.
- Yavari A** (2008). The effect of swimming in reduction of depression in university male students. *Research Journal of Biological Sciences* **3**, 543–545.