Child and Adolescent Mental Health

Child and Adolescent Mental Health Volume **, No. *, 2020, pp. **–** doi:10.1111/camh.12438

Review: Exercise for depression in children and adolescents – a systematic review and meta-analysis

Brynhildur Axelsdóttir[1,2], Sølvi Biedilæ[1,2], Åse Sagatun[1], Lena V. Nordheim[2] & Lillebeth Larun[3]

[1]*Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, Oslo,*
[2]*Department of Health and Functioning, Western Norway University of Applied Sciences, Bergen,*
[3]*Division of Health Services, Norwegian Institute of Public Health, Oslo, Norway*

Background: The objective of this systematic review was to examine the treatment effects of exercise on children and adolescents with depression compared to either other nonexercise treatments or no treatment. A study protocol was registered in PROSPERO (CRD42018101982). **Method:** Cochrane Central Register of Controlled Trials (CENTRAL), Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), AMED (Ovid), SPORTDiscus, PEDro, CINAHL (EBSCO), ERIC (EBSCO), Web of Science, and databases for grey literature and dissertations were searched from their inception through 30 August 2020 for randomized controlled trials. Varieties of search terms for depression, children and adolescents, exercise, and study design were applied. No limits were placed on publication year, language or publication type. Registers for ongoing trials were also searched. Two authors independently screened references, extracted data and assessed risk of bias in the included trials. The effect sizes for depression postintervention were pooled in a meta-analysis, and the certainty of the evidence was assessed using GRADE (Grading of Recommendations Assessments, Development, and Evaluation). **Results:** 13,307 references were screened. Four trials were included (n = 159). Participants were between 12 and 18 years old, and predominantly female. A meta-analysis with a random-effects model was performed, and a moderate effect in favour of exercise on postintervention depression severity was identified (SMD = −0.59, 95% CI = −1.08 to −0.10, p = .02). However, the overall certainty of the evidence for this outcome was low. One trial found a nonsignificant decrease in depression severity at six-month follow-up (n = 42, SMD = −0.59, 95% CI = −1.22 to 0.04, p = 0.07), and the overall certainty of the evidence for this outcome was very low. One trial found no statistically significant differences between the exercise and control groups on quality of life. Other outcomes, including adverse events, psychological well-being and social functioning, were not evaluated. **Conclusion:** Low certainty evidence suggests that exercise interventions may be associated with a decrease in adolescent depression severity. However, our confidence in the effect estimate is limited, and the true effect may be substantially different. Thus, large, high-quality trials including follow-up periods are needed.

Key Practitioner Message

- Depression is a major public health problem and depression in childhood, and adolescence can disturb social functioning, familial connections and educational attainment.
- This systematic review suggests that exercise interventions may be associated with a decrease in adolescent depression severity. However, due to low certainty evidence, the true effect may be substantially different.
- Based on the current findings, group-based exercise activity with supervision is a seemingly manageable intervention to improve the health of children and adolescents with depression.
- Large, high-quality trials that include follow-up periods are needed to provide more robust conclusions about the efficacy of exercise for this population.

Keywords: Depressive disorder; adolescent; child; exercise; systematic review; meta-analysis

Introduction

Depression is a mental disorder characterized by persistent sadness and a loss of interest in and ability to carry out daily activities (World Health Organization, 2020b). Depression is a major public health problem and is one of the most common psychiatric disorders in children and adolescents (Dunn & Weintraub, 2008; Pan & Brent, 2018). Worldwide, depression is the leading cause of years lost due to disability (YLDs) for females aged 15–24 years old and is the third leading cause for adolescent males (Mokdad et al., 2016). The one-year prevalence rate of adolescent depression is estimated to be 5.6%, and 2.8% for children below the age of thirteen (Costello, Erkanli, & Angold, 2006). Depression is more common in girls than in boys (Costello et al., 2006; Thapar, Collishaw, Pine, & Thapar, 2012).

Brynhildur Axelsdóttir and Sølvi Biedilæ are joint first authors.

Published by John Wiley & Sons Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main St, Malden, MA 02148, USA

Depression in childhood and adolescence can disturb social functioning, familial connections and educational attainment, all of which have lifelong effects on employment and social status (Clayborne, Varin, & Colman, 2019; Kessler & Bromet, 2013; Sagatun, Wentzel-Larsen, Heyerdahl, & Lien, 2016). Severe depression can also lead to suicide (World Health Organization, 2020a).

Established treatments for child and adolescent depression are psychological therapies, and in severe cases, antidepressant medications (Cheung, Zuckerbrot, Jensen, Laraque, & Stein, 2018; NICE, 2019; Pan & Brent, 2018). These treatments, however, have modest effects, high relapse rates, and are not acceptable or available to all patients (Cipriani et al., 2016; Cox et al., 2012, 2014; Hetrick, McKenzie, Cox, Simmons, & Merry, 2012; Weisz et al., 2017; Zhou et al., 2015). Furthermore, antidepressant medications have adverse effects such as suicidal behaviour and ideation (Cipriani et al., 2016; Cox et al., 2012, 2014; Hetrick et al., 2012; Weisz et al., 2017). It is therefore important to investigate alternative or adjunct treatments.

Exercise is a promising treatment for adults with depression (Ashdown-Franks et al., 2020; Morres et al., 2019; Schuch et al., 2016). There are indications of exercise having antidepressant effects partly by increasing the synthesis of new neurons in the brain (Ernst, Olson, Pinel, Lam, & Christie, 2006).

The social aspects of group-based exercise may also have positive effects (Lam & Riba, 2016). Other aspects of exercise that may influence depression include improved self-esteem and self-efficacy, and it may also serve as a diversion from negative thoughts (Biddle, Ciaccioni, Thomas, & Vergeer, 2019; Cooney et al., 2013; Lam & Riba, 2016). In addition, sleep problems are common in people with depression, and many experience improved sleep quality after exercise (Lam & Riba, 2016).

Two systematic review of reviews (Hu et al., 2020; Wegner et al., 2020) and five systematic reviews on the effects of exercise on depressive symptoms in children, adolescents and young people have been published over the past few years (Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2017; Brown, Pearson, Braithwaite, Brown, & Biddle, 2013; Carter, Morres, Meade, & Callaghan, 2016; Oberste et al., 2020; Radovic, Gordon, & Melvin, 2017). Additionally, a Cochrane review was published in 2006 (Larun, Nordheim, Ekeland, Hagen, & Heian, 2006). Wegner et al. (2020) included four reviews (Bailey et al., 2017; Brown et al., 2013; Carter, Morres, Meade, et al., 2016; Larun et al., 2006), and Hu et al. (2020) included three reviews on children and adolescents (Brown et al., 2013; Carter, Morres, Meade, et al., 2016; Larun et al., 2006).

All the reviews listed above found that exercise had a small to moderate effect on the reduction of depression. However, these reviews are limited with regard to the selection criteria and methods they employed. Some reviews included trials with participants both with and without depression (e.g. whole school classes or at-risk participants that did not have depression) (Brown et al., 2013; Carter, Morres, Meade, et al., 2016; Larun et al., 2006; Radovic et al., 2017).

Some reviews also included trials where the comparison group received another type or intensity of exercise (Bailey et al., 2017; Carter, Morres, Meade, et al., 2016; Oberste et al., 2020; Radovic et al., 2017). None of the reviews addressed the important 'quality of life' outcome, and only one of the reviews examined adverse events despite their vital importance in this population. Furthermore, four of the reviews included studies published only in peer-reviewed journals and excluded non-English language studies (Bailey et al., 2017; Brown et al., 2013; Carter, Morres, Meade, et al., 2016; Radovic et al., 2017). These exclusions can lead to biased results (Sterne, Egger, & Moher, 2011).

In this systematic review, we attempted to overcome these limitations. Trials were included only if all participants had depression, as we wanted to investigate whether exercise could be a potential treatment for children and adolescents with depression. Trials were included if the intervention was explicitly defined as exercise, and if the control groups received a nonexercise treatment or no treatment. Adverse events and quality of life outcomes were also included. Trials published in all languages, and all publication types, as well as nonpublished trials, were considered for inclusion to reduce the risk of biased results.

The objective of this systematic review was to determine the treatment effects of exercise on children and adolescents with depression compared to other nonexercise treatments or no treatment.

Methods

The Cochrane Collaboration methodology for conducting systematic reviews was followed (Higgins & Green, 2011), and PRISMA guidelines were utilized during the reporting process (Moher, Liberati, Tetzlaff, & Altman, 2009). The PRISMA checklist is available in Appendix S1. The protocol for this systematic review is registered in the PROSPERO International Prospective Register of Systematic Reviews (identification number CRD42018101982) (Centre for Reviews & Dissemination, 2017).

Eligibility criteria

We included randomized controlled trials (RCTs) that evaluated the effects of any type of individual or group exercise intervention for children and adolescents with depression between 6 and 18 years of age. Detailed inclusion and exclusion criteria are presented in Table 1.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL), Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), AMED (Ovid), SPORTDiscus, PEDro, CINAHL (EBSCO), ERIC (EBSCO) and Web of Science were searched from their inception through 30 August 2020. Open Grey was searched for grey literature, Dissertations and Theses (ProQuest) for dissertations and theses, and Papers First (OCLC) for conference abstracts. The trial registers ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) were also searched for ongoing and unpublished trials.

The search strategy was developed using a wide range of search terms including both index terms and text words for depression, children and adolescents, exercise, and study design. No limits were applied on publication year, language or publication type. The search strategy was peer-reviewed using the PRESS checklist (McGowan et al., 2016) and adapted to each database. Complete search strategies are available in Appendix S2.

The bibliographies of all included studies and previous systematic reviews were also searched for relevant studies.

Table 1. Selection criteria for including and excluding studies

Inclusion criteria	
Study design	Randomized controlled trials (RCTs), that is parallel, cluster or individual RCTs, or the first phase of cross-over trials.
Setting	Any, for example schools, primary care settings, hospitals (including inpatients), in high-, middle- and low-income countries.
Participants	Children and adolescents between 6 and 18 years old with depression, defined by any method of diagnosis and with any degree of severity.
Intervention	Interventions that fell within the American College of Sports Medicine's definition of exercise (2017): 'planned, structured and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness', including: • All types of exercise (aerobic, anaerobic, resistance, flexibility and mixed fitness training) • Group-based or individual exercise • Supervised or unsupervised programs; the programs could be a prescribed (fixed) intensity or a preferred intensity (e.g. the participants chose the intensity themselves)
Comparison	• Nonexercise interventions, for example psychological therapies, pharmacological treatments alone or in combination, treatment as usual or other alternative treatments • No treatment, for example waiting list or a nonintervention group
Outcomes	Standard set of outcomes as recommended by the International Consortium for Health Outcomes Measurement (ICHOM) Depression and Anxiety Working Group (Obbarius et al., 2017). Primary outcomes: • Any measure of depression reported as a continuous or dichotomous outcome, measured by self-report, health personnel report, parent report or teacher report • Adverse events (any unwanted effects of the intervention)Secondary outcomes: • Psychological well-being • Social functioning • Quality of life • Acceptability measured by dropout rateData for each outcome at the end of treatment and, if possible, at the end of long-term follow-up were extracted.
Exclusion criteria	Trials: • with children and adolescents with psychotic or borderline conditions, autism, physical handicaps, eating disorders, and/or chronic or serious somatic diseases • where exercise was one component of a combination treatment (not possible to separate the effect of exercise alone) • in which the exercise intervention was comprised of a single session only or lasted less than a week (unlikely to have any lasting effects on depression)

Study selection and data extraction

Two reviewers (SB and BA) independently screened the identified references and extracted the data from the included studies. Titles and abstracts were screened using the Covidence Systematic Review Software (Veritas Health Innovation, 2019). Any references considered relevant by one or both reviewers were obtained in full-text and screened independently. Disagreements were resolved by discussion, and if needed, a third author was consulted to reach a final decision.

The data extraction form in RevMan (The Cochrane Collaboration, 2014) was used and pilot tested with one of the included studies. The following items were extracted from the included studies: participant characteristics, setting, intervention characteristics, type of outcome, measurement tools, effect estimates, measures of uncertainty and study design. The web-based TIDieR template (Template for Intervention Description and Replication) (Hoffmann et al., 2014) was used to describe the study interventions.

Assessment of study quality

Two review authors (SB and BA) independently assessed risk of bias in the included studies using the Cochrane Collaboration Risk of Bias Tool (Higgins, Altman, & Sterne, 2011, chapter 8.5.1). The following criteria were assessed: sequence generation, allocation concealment, blinding of participants and care providers, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. Each criterion was evaluated as either 'high', 'unclear' or 'low' risk of bias according to the Cochrane Handbook (Higgins et al., 2011, figure 8.6.a and figure 8.6.c).

Synthesis of results

The effect sizes for postintervention depression were pooled in a meta-analysis using RevMan (The Cochrane Collaboration, 2014). A random-effects model was used since heterogeneity across the included studies was expected (Sterne et al., 2011). Statistical heterogeneity was assessed using the I^2 statistic. Heterogeneity is considered 'moderate' if I^2 exceeds 50% and 'high' if exceeding 75% (Higgins, Thompson, Deeks, & Altman, 2003).

Depression was measured with a variety of measurement tools across the included studies. We therefore pooled the results by calculating standardized mean differences (SMD) using Hedges (adjusted) g (Deeks, Higgins, & Altman, 2011). The effect size is considered 'small' if SMD is between 0.2 and 0.5, 'medium' if it is between 0.5 and 0.8, and 'large' if it is above 0.8 (Cohen, 1988). Outcomes were reported with 95% confidence intervals (CI).

Other outcomes, including adverse events, psychological well-being, social functioning, quality of life, acceptability and

follow-up, were not possible to pool in a meta-analysis and are therefore narratively described.

Preplanned subgroup analyses to explore differences in treatment effects for type and intensity of exercise were not possible to undertake due to the limited number of included trials.

Certainty of the evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to assess the overall certainty of the evidence for depression at postintervention and follow-up (Guyatt et al., 2011). Risk of bias across studies, directness of the evidence, consistency and precision of the effect estimates, and risk of publication bias were considered. A 'Summary of findings' table was created using the GradePro software (McMaster University & Evidence Prime Inc, 2015; Schünemann et al., 2011, chapter 12.2.1).

The number of included studies was insufficient (requirement of 10 or more) to visually inspect funnel plots for asymmetry and publication bias (Sterne et al., 2011, chapter 10.4). However, to lower the risk of publication bias, a comprehensive literature search was performed, grey literature was included, and we did not exclude studies based on language. In addition, this is an intervention with low risk of industry influence.

Results

The literature searches retrieved 13,307 unique records. 12,955 records were excluded after screening titles and abstracts. Of the 352 full-text articles assessed, 348 were excluded. Four trials were ultimately included (Beffert, 1993; Burrus, 1984; Carter et al., 2015; Roshan, Pourasghar, & Mohammadian, 2011). Details of the study selection process and reasons for exclusion are provided in Figure 1. Further descriptions are available in Appendix S5. List of trials across other systematic reviews and Appendix S6. List of excluded trials with reason for exclusion.

All included trials were published in English. Two were peer-reviewed journal articles (Carter et al., 2015; Roshan et al., 2011), and two were doctoral dissertations (Beffert, 1993; Burrus, 1984).

Participants and settings

The total number of participants across trials was 159; sample sizes ranged from 24 to 64 per trial. Participants were between 12 and 18 years old, and predominantly female.

Two trials were conducted in the United States (Beffert, 1993; Burrus, 1984), one in the UK (Carter et al., 2015) and one in Iran (Roshan et al., 2011).

In three of the trials, all high school students enrolled at a participating school were screened for depression. Students who scored above the criterion level were invited to participate in the trial (Beffert, 1993; Burrus, 1984; Roshan et al., 2011). In the fourth trial, participants were recruited from Child and Adolescent Mental Health Services (Carter et al., 2015).

The characteristics of the included trials are summarized in Table 2. More detailed descriptions of the trials are available in Appendix S3.

Interventions and comparisons

The four trials evaluated different types of group-based exercise including: circuit-training (Carter et al., 2015), interval pool walking (Roshan et al., 2011) and walking–running training (Beffert, 1993). One trial included two intervention groups; one did walk–jog–run (aerobic arm), and the other did weight training and team activities including volleyball and softball (anaerobic arm) (Burrus, 1984). These two intervention groups were pooled using RevMan (The Cochrane Collaboration, 2014). This decision was based on our inclusion criteria of all types of exercise, and there was no strong evidence of one type of exercise over another.

Intervention periods ranged from 6 to 9 weeks, with 2-4 sessions per week. The duration of sessions varied between 20 and 45 minutes in three trials; the fourth trial did not report duration (Roshan et al., 2011). Three trials had a certified physical education instructor, or exercise therapist, to supervise each session (Beffert, 1993; Burrus, 1984; Carter et al., 2015). The fourth trial did not report whether trainers were certified or experienced in their respective fields (Roshan et al., 2011). For further intervention details, see TIDieR tables in Appendix S4.

The comparison groups in the included trials either received treatment as usual (Carter et al., 2015), a first aid and personal safety course (Burrus, 1984), waiting list (Beffert, 1993) or no treatment (Roshan et al., 2011).

In one of the included trials (Carter et al., 2015), exercise was an adjunct treatment. The intervention group received exercise + treatment as usual (TAU), while the control group received TAU.

Outcomes

All trials reported the severity of depression as a continuous outcome; however, all used different measurement tools (Table 2). Three of the measurement tools utilized self-report, and one was clinician-rated. None of the included trials commented on the presence or absence of adverse events.

As for secondary outcomes, quality of life was evaluated in one trial (Carter et al., 2015) where EQ-5D, a standardized measure of health-related quality of life, was used (Herdman et al., 2011). None of the trials evaluated psychological well-being or social functioning.

All trials reported outcomes measured at the end of the intervention period, and only one trial included follow-up data (six-months) beyond the end of treatment (Carter et al., 2015).

Risk of bias in included studies

All included trials had either a 'high' or 'unclear' risk of bias. Random sequence generation and allocation concealment were 'adequate' in only one trial (Carter et al., 2015), and 'unclear' in the other three trials. Blinding of participants and personnel was not possible due to the nature of the intervention (exercise); we therefore rated all trials as having a 'high' risk of bias in this domain. Blinding of outcome assessment was rated 'high' in three trials (Beffert, 1993; Burrus, 1984; Carter et al., 2015) and 'unclear' in one trial (Roshan et al., 2011). This was mainly due to the self-reported measures used. Selective reporting and other bias were satisfactorily reported in only one trial (Carter et al., 2015); the reporting on these domains was inadequate in the remaining trials and thus rated as 'unclear.' Risk of bias due to incomplete outcome data was 'low' in one trial (Burrus, 1984) and 'unclear' in the other three trials (Beffert, 1993; Carter et al., 2015; Roshan et al., 2011). See the Risk of bias graph in Figure 2.

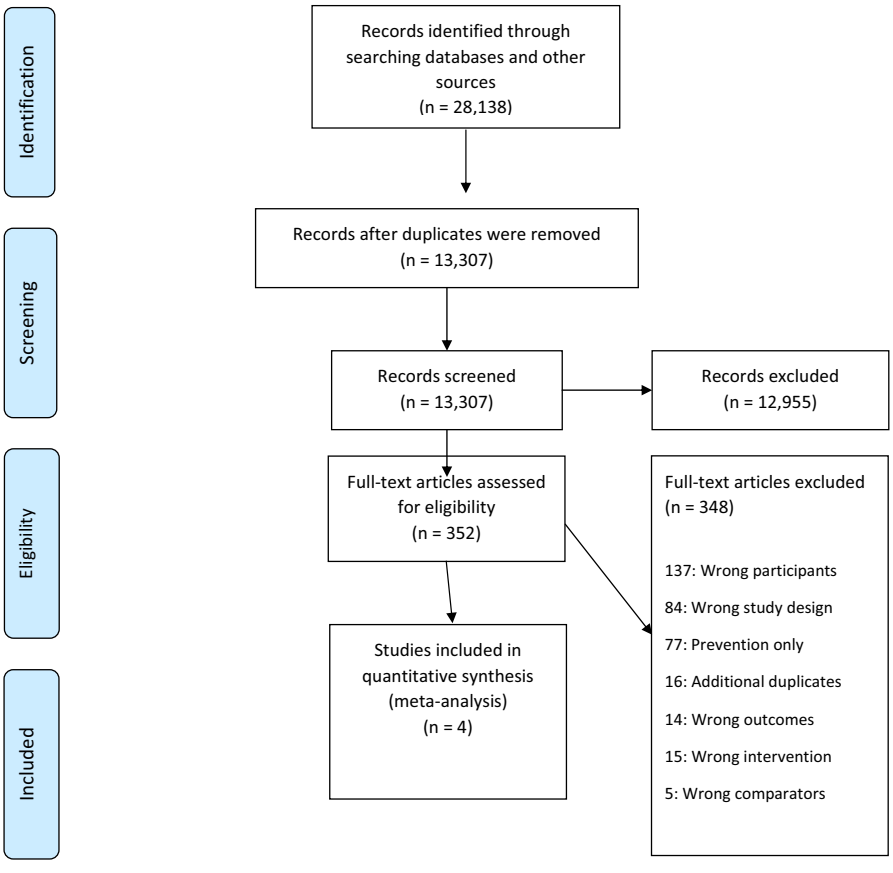

Figure 1. PRISMA flow chart of the search results and screening process

Table 2. Characteristics of included trials

Intervention (exercise component)								
Study, year	Participants	Country, Setting	Type	Dose	Control	Outcome measures (depression)	Baseline severity of depression mean (*SD*)	Results (lower score is better) SMD (CI)
Carter et al., 2015	*n* = 64 14–17 years *M* = 15.4 years 78% females	UK Community-centres	Circuit-training (aerobic and strengthening exercises) adjunct to TAU	45 min 2 times/week 9 weeks	Treatment as usual	CDI-2 Self-report	I: 29.1 (9.4) C: 28.2 (6.8)	−0.19 (−0.69, 0.30)
Roshan et al., 2011	*n* = 24 15–18 years *M* = 16.9 years 100% females	Iran High school	Pool-walking program	3 times/week 6 weeks	No treatment	Ham-D Clinician-rated	I: 30.15 (7.62) C: 29.58 (7.25)	−1.39 (−2.30, −0.48)
Beffert, 1993	*n* = 26 12–15 years M = N/A 83% females	USA High school	Walking–running (aerobic exercises) and weight training and team sports (anaerobic exercises)	20 min 3 times/week 6 weeks	Waitlist	RADS Self-report	I: 122.53 (6.03) C: 124.91 (6.92)	−0.85 (−1.66, −0.03)
Burrus, 1984	*n* = 45 15–18 years *M* = N/A 60% females	USA High school	1. Walk–jog–run (aerobic running program) 2. Weight training and anaerobic team activities	45 min 4 times/week 9 weeks	Red Cross First Aid and Personal Safety Class	DACL Self-report	I 1.: 19.14 (3.73) 2.: 19.31 (4.61) C: 19.33 (3.71)	−0.33 (−0.95, 0.29)

All trials were RCTs (randomized controlled trials).
All interventions were group-based and supervised.
CDI-2, Children's Depression Inventory; DACL, Depression Adjective Checklist; Ham-D, Hamilton Rating Scale for Depression; RADS, Reynolds Adolescent Depression Scale; TAU, Treatment as usual.

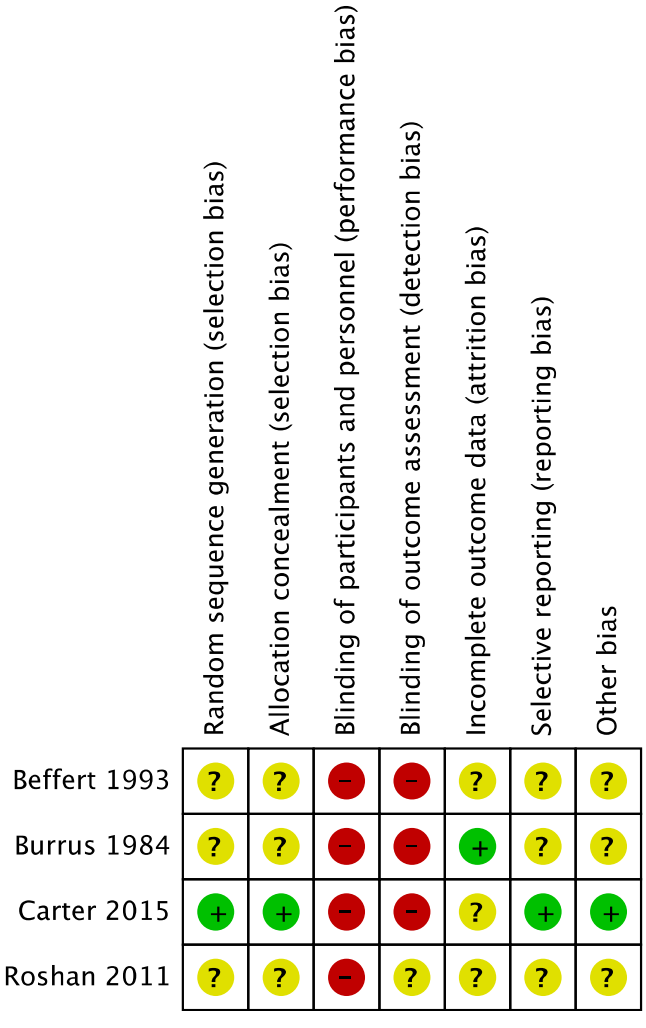

Figure 2. Risk of bias graph

Effects of interventions

Depression (postintervention). For the primary outcome, change in depression postintervention, the results of all four trials (n = 159) were pooled in a meta-analysis. Results show a moderate effect in favour of exercise (SMD = −0.59, 95% CI = −1.08 to −0.10, p = .02). See forest plot in Figure 3.

Heterogeneity across the four trials was moderate (I^2 = 51%), which may be explained by the variety of control interventions and measurement tools used. However, we decided to undertake a meta-analysis on this outcome, as the participants and interventions were sufficiently similar to pool the results.

We decided to pool the one trial of exercise as an adjunct treatment (Carter et al., 2015) with the trials where exercise was a stand-alone treatment. This decision might have underestimated the effect of exercise as a stand-alone treatment since Carter et al. (2015) had a lower, and nonsignificant effect size (SMD −0.19, 95% CI = −0.69, 0.30) than the pooled result.

Depression (follow-up). Depression at six-month follow-up was reported in one trial (n = 42); however, 22 were lost to follow-up from postintervention (Carter et al., 2015). This trial found a moderate, nonsignificant effect in favour of exercise (SMD = −0.59, 95% CI = −1.22 to 0.04, p = .07).

Quality of life. Postintervention quality of life was reported in one trial (n = 64) (Carter et al., 2015). There was no statistically significant difference between the exercise and control groups (SMD = 0.27, 95% CI = −0.35 to 0.89, p = .39).

Acceptability measured as dropouts. It was not possible to pool data on this outcome due to unclear reporting. Burrus (1984) reported that one participant withdrew from the intervention group due to medical reasons; however, the other trials did not provide detailed reports. Roshan et al. (2011) did not report dropout information, and precise dropout numbers were not reported in Beffert (1993). In Carter et al. (2015), the total loss to follow-up was 25% postintervention and 51% at 6 months follow-up, and there were no statistically significant differences in dropout rates between the intervention and the control groups.

Certainty of the evidence (GRADE)

We graded the overall certainty of the evidence for exercise on changes in depression at postintervention and at six-month follow-up as 'low' and 'very low', respectively. We downgraded the evidence due to the 'high' or 'unclear' risk of bias ratings for the trials, as well as imprecision due to a limited number of participants (<400 in total) and wide confidence intervals.

Further details of the grading are provided in the Summary of findings table (Table 3).

Discussion

Four trials that assessed the effects of exercise interventions on children and adolescents with depression were included in this systematic review. The pooled effect estimate showed a moderate decrease in depression severity postintervention, in favour of exercise. However, the

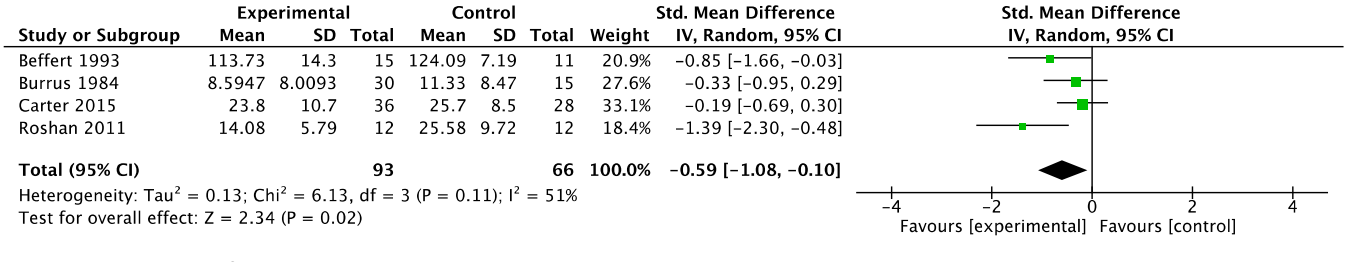

Figure 3. Forest plot of comparison: exercise versus control, outcome: change in depression postintervention

Table 3. Summary of findings

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with Exercise			
Change in depression postintervention		SMD 0.59 lower (1.08 lower to 0.10 lower)		159 (4 RCTs)	⊕⊕⊖⊖ LOW[a,b]
Change in depression follow-up (6 months)		SMD 0.59 lower (1.22 lower to 0.04 higher)		42 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Lack of blinding probably increased effect sizes. Sequence generation was considered unclear in three studies.
[b]Imprecision (total number of participants less than 400). The 95% CI around the estimate of effect of all studies included in the meta-analysis was very wide.
[c]The confidence interval encompasses benefit and harm

overall certainty of the evidence for this outcome was graded 'low.' Thus, our confidence in the effect estimate is limited, and the true effect of exercise may be substantially different from the estimate of the effect reported in this review. The severity of depression at six-month follow-up was reported in only one trial; thus, we cannot draw conclusions regarding the long-term effects of exercise. None of the included trials commented on the presence nor absence of adverse events of exercise.

The majority of the participants in the trials were female, and the effect of exercise is even more uncertain in males.

Possible mechanisms

Given the complexity of both physical activity and mental health, mental health effects are unlikely to be explained by a single process (Faulkner & Taylor, 2009). Several biological, psychological and social factors serve as plausible explanations for the effects of exercise on depression.

One probable biological explanation is the exercise-induced increased capability of the human brain to generate new neurons. There is mounting evidence that neurogenesis in the adult hippocampus is needed for specific memory processes and in mood regulation (Kozareva, Cryan, & Nolan, 2019). This has also been demonstrated by antidepressant therapy in humans (Gheorghe, Qiu, & Galea, 2019; Micheli, Ceccarelli, D'Andrea, & Tirone, 2018) and in studies on laboratory mice by aerobic exercise (Duman, Schlesinger, Russell, & Duman, 2008).

The importance of the suggested explanations may vary depending on the age of the population. Adolescence is a phase of life where the importance of peers increases, and developmental tasks, such as gaining independence from parents and developing a sense of identity and self-acceptance, takes shape (Shaffer & Kipp, 2014). Furthermore, all exercise interventions included in the current study were group-based and supervised. Thus, one of the plausible explanations for the identified effect may be due to social interaction and support. Social isolation is considered a contributing and sustaining factor in depression, however, being physically active with peers may demonstrate to an adolescent that he or she is important to others as well as a part of a community (Coatler, 2005). Indeed, participants in one of the included trials (Carter et al., 2015) were interviewed, and most emphasized that being with peers was a positive and valuable experience (Carter, Morres, Repper, & Callaghan, 2016).

Another plausible explanation may be that exercise interventions serve as a diversion from negative thoughts and feelings. In addition, the professional and interpersonal skills of the supervisors, including their ability to motivate the participants, may also have influenced the results of the trials.

Strengths and limitations

A strength of this review is the use of standardized and transparent methods for identifying trials, screening references, extracting data, assessing risk of bias and evaluating the certainty of the evidence, as recommended by Cochrane Collaboration. However, although a comprehensive and systematic literature search was performed, there is always a risk of missing relevant trials. The most recent previous systematic review is based on a literature search from January 2019 (Oberste et al., 2020) while the literature search in the current study was updated as late as in August 2020.

The small number of included trials is a significant limitation, especially considering the heterogeneity (51%) and the inability to examine it properly. Furthermore, due to the low number of included trials, we were unable to estimate the risk of publication bias.

The decision to pool the trial where exercise was an adjunct treatment (Carter et al., 2015) with trials of stand-alone exercise may have underestimated the effects of stand-alone exercise and over-estimated the effects of exercise as an adjunct treatment. Ekkekakis (2015) demonstrated this moderating effect in trials of exercise for depression in adults. If there had been a larger number of included trials in our review, it would have

been interesting to investigate this in trials with children and adolescents.

Comparison with other systematic reviews

Due to differences in inclusion criteria, previous reviews on this topic have included more trials. The main result in our review, a moderate effect in favour of exercise on postintervention depression, is consistent with the results of previous reviews even though they have included trials where not all the participants had depression. Our results are also consistent with the results of recent systematic reviews of exercise for depression in adults (Ashdown-Franks et al., 2020; Morres et al., 2019; Schuch et al., 2016).

Implications for practice

Evidence suggests that exercise interventions may be associated with a decrease in adolescent depression severity. However, limitations in the existing evidence prevent us from making definitive conclusions, especially regarding long-term effects. Despite the low certainty of the effect of exercise on depression, there are legitimate reasons to recommend regular exercise to this group. Adolescents with depression are generally less active than their nondepressed peers, and they are also commonly less involved in sports (Guddal et al., 2019; Long, Rogers, & Gjelsvik, 2019). However, the dose of exercise in the evaluated interventions was below the WHO's recommended daily 60 min of moderate to vigorous physical activity for positive health outcomes (World Health Organization, 2010). Thus, for practitioners, the question is not whether they should recommend exercise, but rather, what type or mode they should recommend, and how it should be implemented in this population. Based on the current findings, group-based exercise activity with supervision is a seemingly manageable intervention to improve the health of children and adolescents with depression.

Implications for future research

There is a need for high-quality trials evaluating the effect of exercise in children and adolescents with depression. Adequate numbers of participants should be recruited to detect a difference between groups.

Since depression is often a chronic and recurring illness (Wesselhoeft, Sorensen, Heiervang, & Bilenberg, 2013), future trials need longer follow-up periods to investigate whether exercise has long-lasting effects. For ethical and clinical reasons, it is important to evaluate how new treatments compare with established treatments (Stang, Hense, Jöckel, Turner, & Tramèr, 2005). Thus, the comparison groups in future trials should be offered either treatment as usual or other recommended treatments for depression (e.g. cognitive behaviour therapy). A wider range of outcomes should be measured in future trials, including quality of life, social functioning and psychological well-being, and the choice of these outcomes should be based on agreed standardized outcome sets (Core Outcome Sets) (Williamson et al., 2017). Furthermore, safety is a major issue. Accordingly, better recording and reporting of adverse events is vital to ascertain knowledge as to whether exercise may be harmful for this population.

Acknowledgements

No external funding was received for this study. The authors wish to thank Astrid Dahlgren, Ph.D. and Ragnar Gunnarsson, MD. Ph.D. for feedback on the article manuscript. Information specialists Marte Ødegaard, MSc. and Mari Elvsåshagen, M.A. peer-reviewed the Medline search strategy with the PRESS checklist. Simon-Peter Neumer, Ph.D. and Parvin Kiamanesh, Ph.D. helped with reading articles in German and Persian, respectively, and statistician Tore Wentzel-Larsen, Ph.D. helped assess the randomization in one of the trials. The authors thank Pamela Marie Waaler, M.A., MSc. for the final editing and text correction, and Ingrid Borren, Ph.D. for text correction. The authors have declared that they have no competing or potential conflicts of interest.

Ethical information

No ethical approval was required for this review article.

Correspondence

Brynhildur Axelsdóttir and Sølvi Biedilæ, Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, Gullhaugveien 1-3, 0484 Oslo, Norway; Email: ba@r-bup.no; sb@r-bup.no

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PRISMA 2009 checklist.
Appendix S2. Search strategies.
Appendix S3. Detailed characteristics of included studies.
Appendix S4. TIDieR tables.
Appendix S5. List of trials across other systematic reviews
Appendix S6. List of excluded trials with reason for exclusion.

References

American College of Sports Medicine (2017). *ACSM's guidelines for exercise testing and prescription* (10th edn). Philadelphia: Wolters Kluwer.

Ashdown-Franks, G., Firth, J., Carney, R., Carvalho, A.F., Hallgren, M., Koyanagi, A.I., … & Stubbs, B. (2020). Exercise as medicine for mental and substance use disorders: A meta-review of the benefits for neuropsychiatric and cognitive outcomes. *Sports Medicine*, *50*, 151–170.

Bailey, A.P., Hetrick, S.E., Rosenbaum, S., Purcell, R., & Parker, A.G. (2017). Treating depression with physical activity in adolescents and young adults: A systematic review and meta-analysis of randomised controlled trials. *Psychological Medicine*, *48*, 1068–1083.

Beffert, J.W. (1993). *Aerobic exercise as treatment of depressive symptoms in early adolescents*. Unpublished PhD Dissertation, University of Northern Colorado, Greeley, CO.

Biddle, S.J.H., Ciaccioni, S., Thomas, G., & Vergeer, I. (2019). Physical activity and mental health in children and adolescents: An updated review of reviews and an analysis of causality. *Psychology of Sport and Exercise*, *42*, 146–155.

Brown, H.E., Pearson, N., Braithwaite, R.E., Brown, W.J., & Biddle, S.J.H. (2013). Physical activity interventions and depression in children and adolescents: A systematic review and meta-analysis. *Sports Medicine*, *43*, 195–206.

Burrus, M.J. (1984). *The effects of a running treatment program on depressed adolescents*. Unpublished PhD Dissertation, University of Miami, Coral Gable, FL.

Carter, T., Guo, B., Turner, D., Morres, I., Khalil, E., Brighton, E., … & Callaghan, P. (2015). Preferred intensity exercise for

adolescents receiving treatment for depression: A pragmatic randomised controlled trial. *BMC Psychiatry*, *15*, 247.
Carter, T., Morres, I.D., 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 & Adolescent Psychiatry*, *55*, 580–590.
Carter, T., Morres, I., Repper, J., & Callaghan, P. (2016). Exercise for adolescents with depression: Valued aspects and perceived change. *Journal of Psychiatric and Mental Health Nursing*, *23*, 37–44.
Centre for Reviews and Dissemination (2017). *PROSPERO: International Prospective Register of Systematic Reviews*. Retrieved 21.11.2017, from https://www.crd.york.ac.uk/prospero/
Cheung, A.H., Zuckerbrot, R.A., Jensen, P.S., Laraque, D., & Stein, R.E.K. (2018). Guidelines for Adolescent Depression in Primary Care (GLAD-PC): Part II. Treatment and ongoing management. *Pediatrics*, *141*, e20174082.
Cipriani, A., Zhou, X., Del Giovane, C., Hetrick, S.E., Qin, B., Whittington, C., ... & 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.
Clayborne, Z.M., Varin, M., & Colman, I. (2019). Systematic review and meta-analysis: adolescent depression and long-term psychosocial outcomes. *Journal of the American Academy of Child & Adolescent Psychiatry*, *58*, 72–79.
Coatler, F. (2005). Sport, social inclusion and crime reduction. In G. Faulkner (Ed.), *Exercise, health and mental health: emerging relationships* (pp. 190–210). New York: Routledge.
Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd edn). Hillsdale, NJ: Lawrence Erlbaum.
Cooney, G.M., Dwan, K., Greig, C.A., Lawlor, D.A., Rimer, J., Waugh, F.R., ... & Mead, G.E. (2013). Exercise for depression. *Cochrane Database of Systematic Reviews*, *9*, CD004366.
Costello, J.E., Erkanli, A., & Angold, A. (2006). Is there an epidemic of child or adolescent depression? *Journal of Child Psychology and Psychiatry*, *47*, 1263–1271.
Cox, G.R., Callahan, P., Churchill, R., Hunot, V., Merry, S.N., Parker, A.G., & Hetrick, S.E. (2014). Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database of Systematic Reviews*, *11*, CD008324.
Cox, G.R., Fisher, C.A., De Silva, S., Phelan, M., Akinwale, O.P., Simmons, M.B., & Hetrick, S.E. (2012). Interventions for preventing relapse and recurrence of a depressive disorder in children and adolescents. *Cochrane Database of Systematic Reviews*, *11*, CD007504.
Deeks, J.J., Higgins, J.P.T., & Altman, D.G. (2011). Chapter 9: Analysing data and undertaking meta-analyses. In J.P.T. Higgins, & J.J. Deeks (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*, The Cochrane Collaboration. Version 5.1.0: Cochrane. https://training.cochrane.org/handbook/archive/v5.1/
Duman, C.H., Schlesinger, L., Russell, D.S., & Duman, R.S. (2008). Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *Brain Research*, *1199*, 148–158.
Dunn, A.L., & Weintraub, P. (2008). Exercise in the prevention and treatment of adolescent depression: A promising but little researched intervention. *American Journal of Lifestyle Medicine*, *2*, 507–518.
Ekkekakis, P. (2015). Honey, I shrunk the pooled SMD! Guide to critical appraisal of systematic reviews and meta-analyses using the Cochrane review on exercise for depression as example. *Mental Health and Physical Activity*, *8*(Suppl. C), 21–36.
Ernst, C., Olson, A.K., Pinel, J.P.J., Lam, R.W., & Christie, B.R. (2006). Antidepressant effects of exercise: Evidence for an adult-neurogenesis hypothesis? *Journal of Psychiatry and Neuroscience*, *31*, 84–92.
Faulkner, G.E.J., & Taylor, A.H. (2009). Promoting physical activity for mental health: A complex intervention? *Mental Health and Physical Activity*, *2*, 1–3.
Gheorghe, A., Qiu, W., & Galea, L.A.M. (2019). Hormonal regulation of hippocampal neurogenesis: Implications for depression and exercise. In L.M. Coolen & D.R. Grattan (Eds.), *Neuroendocrine regulation of behavior* (vol. *43*, pp. 380–404). Cham, Switzerland: Springer.
Guddal, M.H., Stensland, S.Ø., Småstuen, M.C., Johnsen, M.B., Zwart, J.-A., & Storheim, K. (2019). Physical activity and sport participation among adolescents: Associations with mental health in different age groups. Results from the Young-HUNT study: a cross-sectional survey. *British Medical Journal Open*, *9*, e028555.
Guyatt, G.H., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., Brozek, J., ... & Schünemann, H.J. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, *64*, 383–394.
Herdman, M., Gudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., ... & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*, 1727–1736.
Hetrick, S.E., McKenzie, J.E., Cox, G.R., Simmons, M.B., & Merry, S.N. (2012). Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, *11*, CD004851.
Higgins, J.P.T., Altman, D.G., & Sterne, J.A.C. (2011). Chapter 8: Assessing risk of bias in included studies. In J.P.T. Higgins, & J.J. Deeks (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0: Cochrane. https://training.cochrane.org/handbook/archive/v5.1/
Higgins, J.P.T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0*. Retrieved 10.08.2017, from http://handbook.cochrane.org/
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., & Altman, D.G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, *327*, 557–560.
Hoffmann, T.C., Glasziou, P.P., Boutron, I., Milne, R., Perera, R., Moher, D., ... & Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, *348*, g1687.
Hu, M.X., Turner, D., Generaal, E., Bos, D., Ikram, M.K., Ikram, M.A., ... & Penninx, B.W.J.H. (2020). Exercise interventions for the prevention of depression: A systematic review of meta-analyses. *BMC Public Health*, *20*, 1255.
Kessler, R.C., & Bromet, E.J. (2013). The epidemiology of depression across cultures. *Annual Review of Public Health*, *34*, 119–138.
Kozareva, D.A., Cryan, J.F., & Nolan, Y.M. (2019). Born this way: Hippocampal neurogenesis across the lifespan. *Aging Cell*, *18*, e13007.
Lam, L.C.W., & Riba, M.B. (2016). *Physical exercise interventions for mental health*. Cambridge: Cambridge University Press.
Larun, L., Nordheim, L.V., Ekeland, E., Hagen, K.B., & Heian, F. (2006). Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database of Systematic Reviews*, *3*, CD004691.
Long, S., Rogers, M.L., & Gjelsvik, A. (2019). The influence of depression status on weekly exercise in children ages 6 to 17 years. *Preventive Medicine Reports*, *13*, 199–204.
McGowan, J., Sampson, M., Salzwedel, D.M., Cogo, E., Foerster, V., & Lefebvre, C.(2016). *PRESS Peer Review of Electronic Search Strategies: 2015 Guidelines Explanation and Elaboration*. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health.
McMaster University, & Evidence Prime Inc (2015). *GRADEpro GDT*. Retrieved 01.10.2019, from https://gradepro.org/
Micheli, L., Ceccarelli, M., D'Andrea, G., & Tirone, F. (2018). Depression and adult neurogenesis: Positive effects of the antidepressant fluoxetine and of physical exercise. *Brain Research Bulletin*, *143*, 181–193.
Moher, D., Liberati, A., Tetzlaff, J., & Altman, D.G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ*, *339*, b2535.
Mokdad, A.H., Forouzanfar, M.H., Daoud, F., Mokdad, A.A., El Bcheraoui, C., Moradi-Lakeh, M., ... & Murray, C.J.L. (2016). Global burden of diseases, injuries, and risk factors for young

people's health during 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, *387*, 2383–2401.

Morres, I.D., Hatzigeorgiadis, A., Stathi, A., Comoutos, N., Arpin-Cribbie, C., Krommidas, C., & Theodorakis, Y. (2019). Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depression and Anxiety*, *36*, 39–53.

NICE (2019). *Depression in children and young people: identification and management*. NICE guideline. Retrieved 05.02.2020, from https://www.nice.org.uk/guidance/ng134

Obbarius, A., van Maasakkers, L., Baer, L., Clark, D.M., Crocker, A.G., de Beurs, E., … & Rose, M. (2017). Standardization of health outcomes assessment for depression and anxiety: Recommendations from the ICHOM Depression and Anxiety Working Group. *Quality of Life Research*, *26*, 3211–3225.

Oberste, M., Medele, M., Javelle, F., Lioba Wunram, H., Walter, D., Bloch, W., … & Zimmer, P. (2020). Physical activity for the treatment of adolescent depression: A systematic review and meta-analysis. *Frontiers in Physiology*, *11*, 185.

Pan, L., & Brent, D.A. (2018). *Depression in children*. BMJ Best Practice. Retrieved 29.04.2019, from https://bestpractice.bmj.com/topics/en-gb/785/pdf/785.pdf

Radovic, S., Gordon, M.S., & Melvin, G.A. (2017). Should we recommend exercise to adolescents with depressive symptoms? A meta-analysis. *Journal of Paediatrics and Child Health*, *53*, 214–220.

Roshan, D.V., 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 and Behavioral Sciences*, *5*, 26–31.

Sagatun, Å., Wentzel-Larsen, T., Heyerdahl, S., & Lien, L. (2016). Mental health in adolescence and subsequent receipt of medical benefits in young adulthood: The mediating role of upper secondary school completion. *Scandinavian Journal of Public Health*, *44*, 431–438.

Schuch, F.B., Vancampfort, D., Richards, J., Rosenbaum, S., Ward, P.B., & Stubbs, B. (2016). Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. *Journal of Psychiatric Research*, *77*, 42–51.

Schünemann, H.J., Oxman, A.D., Vist, G.E., Higgins, J.P.T., Deeks, J.J., Glasziou, P.P., & Guyatt, G.H. (2011). Chapter 12: Interpreting results and drawing conclusions. In J.P.T. Higgins, & J.J. Deeks (Eds.), *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0: Cochrane.

Shaffer, D.R., & Kipp, K.(2014). *Developmental psychology: Childhood and adolescence* (9th edn). London: Cengage Learning.

Stang, A., Hense, H.-W., Jöckel, K.-H., Turner, E.H., & Tramèr, M.R. (2005). Is it always unethical to use a placebo in a clinical trial? *PLoS Med*, *2*, e72.

Sterne, J.A.C., Egger, M., & Moher, D. (2011). Chapter 10: Addressing reporting biases. In J.P.T. Higgins, & J.J. Deeks (Eds.), *Cochrane Handbook for Systematic Reviews of interventions*. Version 5.1.0: Cochrane.

Thapar, A., Collishaw, S., Pine, D.S., & Thapar, A.K. (2012). Depression in adolescence. *Lancet*, *379*, 1056–1067.

The Cochrane Collaboration. (2014). Review Manager (RevMan) 5.3 [Computer Software].

Veritas Health Innovation. (2019). *Covidence Systematic Review Software [Computer Software]*.

Wegner, M., Amatriain-Fernández, S., Kaulitzky, A., Murillo-Rodriguez, E., Machado, S., & Budde, H. (2020). Systematic review of meta-analyses: Exercise effects on depression in children and adolescents. *Frontiers in Psychiatry*, *11*, 81.

Weisz, J.R., Kuppens, S., Ng, M.Y., Eckshtain, D., Ugueto, A.M., Vaughn-Coaxum, R., … & Fordwood, S.R. (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.

Wesselhoeft, R., Sorensen, M.J., Heiervang, E.R., & Bilenberg, N. (2013). Subthreshold depression in children and adolescents: A systematic review. *Journal of Affective Disorders*, *151*, 7–22.

Williamson, P.R., Altman, D.G., Bagley, H., Barnes, K.L., Blazeby, J.M., Brookes, S.T., … & Young, B. (2017). The COMET Handbook: version 1.0. *Trials*, *18*, 280.

World Health Organization (2010). *Global recommendations on physical activity for health*. Retrieved 03.03.2020, from https://apps.who.int/iris/handle/10665/44399

World Health Organization (2020a). *Depression fact sheet*. Retrieved 03.03.2020, from https://www.who.int/en/news-room/fact-sheets/detail/depression.

World Health Organization (2020b). *Health Topics: Depression*. Retrieved 03.03.2020, from https://www.who.int/health-topics/depression#tab=tab_1

Zhou, X., Hetrick, S.E., Cuijpers, P., Qin, B., Barth, J., Whittington, C.J., … & Xie, P. (2015). Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: A systematic review and network meta-analysis. *World Psychiatry*, *14*, 207–222.

Accepted for publication: 30 October 2020