



Høgskulen på Vestlandet

Masteroppgaue

MAKP601

Predefinert infor	masjon			
Startdato:	08-05-2019 09:00	Termin:	2019 VÅR	
Sluttdato:	15-05-2019 14:00	Vurderingsform:	Norsk 6-trinns skala (A-F)	
Eksamensform:	Masteroppgaue	Studiepoeng:	45	
SIS-kode:	203 MAKP601 1 MG 2019 VÅR			
Intern sensor:	(Anonymisert)			
Deltaker				
Kandidatnr.:	417			
Informasjon fra d	eltaker			
Antall ord *:	18599			
Egenerklæring *:	Ja	Inneholder besvarelsen Nei		
		konfidensiell materiale?:		
Jeg bekrefter at jeg har	Ja			
på norsk og engelsk i				
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denne vil stå på				
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Gruppe				
Gruppenavn:	(Anonymisert)			
Gruppenummer:	1			
Andre medlemmer i	418			
gruppen:				

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Western Norway University of Applied Sciences



MASTER'S THESIS

A Systematic Review on the Effect of Exercise for Depression in Children and Adolescents

Sølvi Biedilæ and Brynhildur Axelsdottir

Master in Evidence-Based Practice in the Health Sciences Faculty of Health and Social Sciences Centre for Evidence-Based Practice Supervisor Lillebeth Larun Submission Date: May 15th 2019

We confirm that the work is self-prepared and that references/source references to all sources used in the work are provided, cf. Regulation relating to academic studies and examinations at the Western Norway University of Applied Sciences (HVL), § 10.

Erklæring

Denne masteroppgaven er en systematisk oversikt basert på en protokoll publisert i det internasjonale PROSPERO-registeret 20.07.2018, hvor Brynhildur Axelsdottir og Sølvi Biedilæ står oppført som forfattere. Selv om protokollen har flere medforfattere erklærer vi herved at masteroppgaven er et selvstendig arbeid hvor vi har hatt ansvar for utforming, gjennomføring og rapportering av den systematiske oversikten.

Oslo, 8. mai 2019

Studentenes signatur:

Sølvi Biedilæ og Brynhildur Axelsdottir

SplviBiedilæ Bynlifd-Axelsdotti

A Systematic Review on the Effect of Exercise for Depression in Children and Adolescents

(Title in English)

En systematisk oversikt over effekten av trening for depresjon hos barn og unge

(Title in Norwegian)

Master's students: Sølvi Biedilæ and Brynhildur Axelsdóttir Main supervisor: Lillebeth Larun Co-supervisor: Lena Victoria Nordheim Submission date: May 15th 2019 Total number of words: 13889

Preface

We have worked as librarians at the Centre for Child and Adolescents Mental Health (RBUP) for several years. Working alongside many talented researchers, teachers, and practitioners inspired us to want to learn more about evidence-based practice and research methodology. Our director Arild Bjørndal and his passion for evidence-based practice has been a major inspiration for us. During our studies at Høgskulen på Vestlandet, our interest in systematic reviews has grown. When the suggestion of doing a systematic review on the topic of exercise for children and adolescents with depression came along, we decided that this was a perfect project for us. Luckily our employer agreed, and we could use one working day a week on the project. For that, we are were grateful to our supervisor Astrid Dahlgren and RBUP. Working on this thesis has been challenging, sometimes hard, but mainly rewarding and educational. And we are still friends! Everything we have learned while writing this systematic review will hopefully be useful both to our professional development and future projects at RBUP.

We have many people we would like to thank. First and foremost, our fantastic supervisors Lillebeth Larun and Lena Victoria Nordheim for all your help, support, cheering and for always replying to our emails faster than the speed of light. Big thanks to Astrid Dahlgren for believing in us and inspiring us on a daily basis. Your feedback has significantly improved this thesis. Thanks to Åse Sagatun for interesting discussions about exercise interventions and their potential mechanisms for depression. We are also grateful for your feedback on the study protocol and the article manuscript. We thank our fellow librarians Marte Ødegaard and Mari Elvsåshagen for helping with peer-reviewing the search strategy. Statistician Tore Wentzel-Larsen helped us with assessing the randomization in one of the trials. We appreciate that researchers Simon-Peter Neumer and Parvin Kiamanesh helped us with reading a few articles in German and Persian. We will thank Ragnar Gunnarsson for feedback on the article manuscript and his support. Also, thanks to Ove Dale for encouragement including cinnamon buns when most needed. Last, but not least, thanks to all our wonderful colleagues at RBUP for your support, interest in our project and encouragement.

Abstract

Background

Depression is a common mental health problem in adolescents with a one-year prevalence estimate of 5.6% among 13-18-year olds. It can cause problems at school, with friends, and in the family and may have adverse effects on educational attainment and later employment status.

Objective

The objective of this systematic review was to examine the effects of exercise interventions as treatment of depression in children and adolescents compared to other treatments or no treatment.

Methods

The bibliographic databases 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 inception to December 2018, in addition to grey literature, ongoing and unpublished trials. Trials were included if they were randomized controlled trials of exercise interventions for children and adolescents 6-18 years with depression. Two authors independently screened references, extracted data and assessed the quality of the included trials with the Cochrane Risk of Bias tool. The certainty of the evidence was assessed using GRADE.

Results

Of 11007 retrieved references, four trials were included (n=143). Meta-analysis was conducted using a random-effects model on the outcome of depression post-intervention and found a moderate effect in favour of exercise in adolescents (SMD= -0.59, 95% CI= -1.11, to -0.07). The trials had a low number of participants and were assessed as having an unclear or high risk of bias. The certainty of the evidence was graded as low. None of the trials commented on the presence or absence of adverse events.

Conclusion

Exercise appears to be a promising intervention for children and adolescents with depression. However, large, high-quality trials with longer follow-up time are needed.

Keywords

Depression (MeSH), Depressive Disorder (MeSH), Adolescent (MeSH), Child (MeSH), Exercise (MeSH) Systematic review [Publication Type] (MeSH), Meta-Analysis [Publication Type] (MeSH).

Sammendrag på norsk

Bakgrunn

Depresjon er et vanlig psykisk helseproblem hos ungdom. Forekomst i løpet av et år er estimert til å være 5.6% hos 13-18 åringer. Depresjon kan føre til skoleproblemer og frafall, problemer med venner og i familien og risiko for å falle utenfor arbeidslivet.

Hensikt og problemstilling

Hensikten med denne systematiske oversikten er å undersøke effekten av trening som behandling av depresjon hos barn og unge sammenlignet med andre behandlinger eller ingen behandling.

Metode

De bibliografiske databasene Cochrane Central Register of Controlled Trials (CENTRAL), Medline (Ovid), Embase (Ovid), PsycINFO (Ovid), AMED (Ovid), SPORTDiscus, PEDro, CINAHL (EBSCO), ERIC (EBSCO) og Web of Science ble søkt fra starten til desember 2018, i tillegg til grå litteratur, pågående og upubliserte studier. Studier ble inkludert dersom de var randomiserte kontrollerte forsøk med trening for barn og ungdom mellom 6-18 år med depresjon. To forfattere uavhengig leste gjennom artiklene, trakk ut data og kvalitetsvurderte de inkluderte studiene med Cochrane Risk of Bias verktøyet. Kvaliteten på dokumentasjonen ble vurdert med GRADE.

Resultater

Av 11007 treff ble 4 studier inkludert (n=143). Meta-analyse ble utført med en random-effects modell på utfallet depresjon etter intervensjonen og fant en moderat effekt i favør av trening hos ungdom (SMD= -0.59, 95% CI= -1.11, to -0.07). Studiene hadde få deltakere, og ble vurdert at de hadde uklar eller høy risiko for skjevheter. Kvalitet på dokumentasjonen ble gradert som lav. Ingen av studiene rapporterte om det hadde vært noen uønskede hendelser.

Konklusjon

Trening synes å være en lovende behandling for barn og ungdom med depresjon. Imidlertid behøves større studier med bedre kvalitet og lengre oppfølgingstid.

Nøkkelord

Depresjon (MeSH), Depressiv forstyrrelse (MeSH), Ungdom (MeSH), Barn (MeSH), Trening (MeSH), Systematisk oversikt, publikasjonstype (MeSH), Metaanalyse, publikasjonstype (MeSH)

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Article manuscript

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Introduction and background

This master's thesis is a systematic review of the effects of exercise interventions in children and adolescents with depression.

The thesis has an introduction and a journal article manuscript. In the introduction, we describe in detail the methods we used for conducting the systematic review. Additionally, we discuss the weaknesses and strengths of our methods. We plan to publish the article in a peer-review academic journal.

Background

Depression is one of the most common psychiatric disorders in children and adolescents. (Dunn & Weintraub, 2008; Pan & Brent, 2018). It is characterized by persistent sadness, a loss of interest in and ability to carry out daily activities, fatigue or loss of energy, sleep problems and impairment of functioning (Bonin & Moreland, 2019; World Health Organization, 2017). Depression is highly comorbid with other diseases, both mental disorders such as anxiety, and somatic disorders (Pan & Brent, 2018).

Depression is a chronic and recurrent illness (Pan & Brent, 2018). Childhood depression can lead to social problems, problems in schools, functional impairment, and increases the risk of suicide and substance abuse (Pan & Brent, 2018). Depression in childhood or adolescence often persists into adulthood (Dunn & Weintraub, 2008).

Worldwide, depression is the leading cause of years lost due to disability (YLDs) in females aged 15-24 years, and the third leading cause in males (Mokdad et al., 2016). Prevalence rates are estimated in a meta-analysis of 26 epidemiological studies to be 5.6% among adolescents 13-18 years old, and 2.8% among children under 13 years (Costello, Erkanli, & Angold, 2006). Other studies find higher prevalence rates. In the USA, the 2017 National Survey on Drug Use and Health estimate the past year prevalence of major depressive episode among adolescents to be 13.3% (National Institute of Mental Health, 2019). In a cross-national survey in Norway among adolescents aged 13-16 years, the prevalence of boys with high levels of depressive symptoms was 5.8% and among girls as high as 17.1% (Abebe, Froyland, Bakken, & von Soest, 2016). Depression is more common in children with a chronic medical illness (Pinquart & Shen, 2011).

The clinical guideline on depression in children and adolescents from the National Institute for Health and Care Excellence (NICE) recommends psychological therapies for mild depression, supplemented with antidepressant medications for moderate and severe depression (2005). Even though psychological therapies are recommended, many patients do not have access to it. There can be long waiting lists, and those who have mild depression are often not prioritized in the health care system. There can also be practical problems, patients can live remotely and far from qualified therapists, and in some countries, there are patients who are not able to pay for treatment. Also, not all patients want therapy, due to stigma and prejudice (Mohr et al., 2010). Antidepressant medications can have adverse effects, and many patients do not want to take them (Pan & Brent, 2018). Both of these treatments unfortunately have modest effects and high rates of relapse (Cipriani et al., 2016; Cox et al., 2014; Cox et al., 2012; Hetrick, McKenzie, Cox, Simmons, & Merry, 2012; Weisz et al., 2017).

Exploring alternative or adjunct treatments, to be used either instead of, or in addition to established treatments, or while waiting for help, is essential. Exercise is one such treatment option. Exercise is recommended as a health-promoting strategy to supplement the standard treatment of depression in children and adolescents in the NICE guideline (NICE, 2005). Many people experience improved mood while and after exercise (American College of Sports Medicine, 2014, p. 255). Exercise is accessible and feasible and has several health benefits (American College of Sports Medicine, 2017, pp. 8-10; Carter, Morres, Repper, & Callaghan, 2016; Dopp, Mooney, Armitage, & King, 2012; Peterson, 2017).

It has been suggested that the physiological changes in the body during and after exercise such as changes in the monoamine systems, and β -endorphin levels, may have an impact on depression and mood (American College of Sports Medicine, 2014, p. 255).

The social aspects of group-based exercise may also have a positive effect on depression. People with depression often isolate themselves, and an intervention that helps them to socialize with peers, and perhaps make new friends may improve their mood (Lam & Riba, 2016, p. 31).

Other aspects of exercise that may influence depression include improved self-esteem and self-efficacy, and exercise can be a diversion from negative thoughts (Biddle & Asare, 2011; Cooney et al., 2013; Lam & Riba, 2016, p. 31). Sleep problems are common in people with depression, and many people find that they sleep better after exercise (Lam & Riba, 2016, p. 31).

Previous research

Observational studies show that those who participate in exercise have a lower prevalence of depression (Dale, Vanderloo, Moore, & Faulkner, In press). However, people with depression are much less likely to exercise since depression leads to low energy levels, and less interest and ability to participate in daily activities, including exercise (World Health Organization, 2017). Observational studies are therefore unable to conclude about the effect of exercise in this population.

In the last few years, four systematic reviews have been published that cover the effect of exercise or physical activity on depression or depressive symptoms in children, adolescents and young people (Bailey, Hetrick, Rosenbaum, Purcell, & Parker, 2017; H. E. Brown, Pearson, Braithwaite, Brown, & Biddle, 2013; Carter, Morres, Meade, & Callaghan, 2016; Radovic, Gordon, & Melvin, 2017). These four systematic reviews excluded non-English language studies, and studies not published in peer-reviewed journals.

In their systematic review, H. E. Brown et al. (2013) included nine studies and found a small overall effect for physical activity on depression. They, however, included and combined studies on both clinical and non-clinical populations, i.e., participants with and without a diagnosis of depression. The synthesis of results was for this reason based on studies both on treatment as well as on prevention. Furthermore, several of the included studies were non-randomised controlled trials. The participants in the intervention and control groups could, therefore, be different regarding, e.g., the motivation for exercise or severity of depression.

Radovic et al. (2017) included eight studies and found a moderate effect of exercise on the reduction of depressive symptoms. This systematic review also included studies where the participants were not randomized. Contradictory to their stated inclusion criteria, they included at least two studies where the participants were not diagnosed with depression, again mixing treatment and prevention studies (S. W. Brown, Welsh, Labbe, Vitulli, & Kulkarni, 1992; Hilyer et al., 1982). Also, the participants in one of the included studies were adolescents diagnosed with chronic fatigue syndrome (Gordon, Knapman, & Lubitz, 2010).

Carter, Morres, Meade, et al. (2016) performed a sensitivity analysis of a clinical sample in their systematic review and found a moderate effect of exercise for depression in adolescents. However, one of the included studies compared one type of exercise to another type of exercise. Also, in one study the intervention was dance movement therapy, a type of psychotherapy, not exercise.

Bailey et al. (2017) included five trials on adolescents under 18 years old, both with and without depression, in their systematic review and found a moderate effect of physical activity on depression. Similar to Carter, Morres, Meade, et al. (2016) they included a study comparing exercise to another type of exercise, and a study where the intervention was dance movement therapy.

In this systematic review, we wanted to investigate the effect of exercise on children and adolescents with depression and not on the general population. We included trials where the intervention was exercise, and the control groups received a non-exercise treatment or no treatment. We wanted to include a wider range of important outcomes than the earlier reviews. Additionally, we included trials in all languages, all publication types and non-published trials to reduce the risk of biased results.

Objectives and research question

The objective of this systematic review is to summarize studies on the effects of exercise interventions as treatment of depression in children and adolescents compared to other treatments or no treatment. The research question is: "What are the effects of exercise interventions in children and adolescents with depression?".

Methods

A systematic review attempts to summarize all empirical evidence that fits pre-specified eligibility criteria. It involves an explicit, reproducible methodology, a systematic search to attempt to identify all relevant studies, an assessment of the risk of bias of the included studies and a systematic synthesis and presentation of the findings (Green et al., 2011, chapter 1.2.2).

In this review, we followed the Cochrane Collaboration methodology for conducting systematic reviews (Higgins & Green, 2011). We have also followed the PRISMA guidelines for the reporting (see Appendix I) (Moher, Liberati, Tetzlaff, & Altman, 2009). Additionally, we have written the article and the introduction according to the structure of IMRAD

(International Committee of Medical Journal Editors, 2010), and the author guideline for PLOS One, the journal we are planning to submit the article. Our methods are described and discussed in this section.

Ethical considerations

This project does not require ethical approval from the Regional Committees for Medical and Health Research Ethics (REC) since this is not research on humans, human biological material or personal health information (REK (Regional Committees for Medical and Health Research Ethics), 2012).

Preliminary searches

Before starting the work on this systematic review, we searched for other reviews on the subject. It is important to identify existing or ongoing reviews on the same subject to avoid unnecessary duplication, and waste time and resources (Moher, 2013).

We did a scoping search in various databases that index systematic reviews, Epistemonikos, MEDLINE, PsycINFO. We also checked PROSPERO to see if any other reviews on this subject were ongoing.

We identified reviews that partially overlap the subject of this systematic review. Details about these reviews are covered above in the section "Previous research".

Protocol

The next step was to develop a protocol for our systematic review. It is important to have a detailed protocol that describes the aim of the review and a plan for the methods, e.g., inclusion and exclusion criteria, a plan for the literature search, data selection, quality assessment, and data extraction and analysis (Moher et al., 2015). A carefully planned protocol promotes explicit and transparent decisions. It is also important to have clear criteria to ensure consistency and avoid problems while deciding to include or exclude studies and during the data extraction and analysis process. The review team can avoid having to make ad

hoc decisions because they have (hopefully) anticipated possible problems in advance (Moher et al., 2015).

We registered the protocol in PROSPERO, an international prospective register for systematic review protocols, CRD42018101982 (Centre for Reviews and Dissemination, 2017). It is important to prospectively register review protocols to avoid unplanned duplication of work since other research teams can see that there is already a review ongoing when planning a new review. Registration can also lead to less reporting bias and ad hoc changes during the review process since journals, and peer reviewers have access to the original protocol (PROSPERO, 2019). (See study protocol in Appendix II).

Selection criteria

Deciding eligibility criteria is an essential part of the systematic review process. Inclusion and exclusion criteria must be described clearly and detailed (O'Connor, Green, & Higgins, 2011, chapter 5.1.2). When defining the inclusion and exclusion criteria, The Cochrane Handbook recommends using the PICOS framework for specifying the population, intervention, control, outcome, and study design (O'Connor et al., 2011, chapter 5.1.1). See Table 1 for PICOS for this systematic review. More details and rationale behind these decisions will be described in the next section.

P (Participants)	Children and adolescents (6-18 years) with depression		
I (Intervention)	Exercise interventions, e.g., running, circuit training or weight lifting		
C (Comparison)	Other treatments: Psychological therapies, pharmacological treatments,		
	alone or in combination, treatment as usual or other alternative		
	treatments.		
	No treatment: Waiting list or a non-intervention group		
O (Outcome)	Primary outcomes: Depression. Adverse events		
	Secondary outcomes: Psychological well-being. Social functioning.		
	Quality of life		
S (Study design)	Randomized controlled trials		

Table 1. PICOS

Participants

Age

Previous systematic reviews on the same subject have different inclusion criteria for age. The Cochrane Review by Larun, Nordheim, Ekeland, Hagen, and Heian (2006) included children and young people from 0 up to 20 years. Carter (2016) included adolescents aged 13 to 17 years, while Bailey (2017) included adolescents and young people 12-25 years. Radovic (2017) chose participants between 12 and 18 years old, while Brown (2013) included children and adolescents between 5 and 19 years.

After consulting with experts on depression in children we decided to set 6 years old as our lowest age limit. This is the lowest age children are diagnosed for depression, and several of the measurement tools are validated for children six or seven years and older (APA, 2013).

We decided to set our upper age limit at 18 years old for two reasons. First, there already exists a Cochrane review (Cooney et al., 2013) that covers adults aged 18 and above. Second, life for many young people change around that age and they meet new challenges and opportunities. Many start university or college, or start working, and move away from their parents and family and have to create their own lives.

Diagnosis

In this systematic review, we decided only to include studies where the participants had depression. There are different ways of diagnosing depression, either using the criteria in the international diagnostic classification systems DSM (the most recent version is DSM-5 (APA, 2013)) or ICD (current version is ICD-10 (World Health Organization, 2011)), or screening using various measurement tools.

Since we expected that the included studies would have used different diagnostic methods, we decided to use the same criterion as the Cochrane review on adults (Cooney et al., 2013). Studies were thus included if the author defined the trial participants as having depression (by any method of diagnosis and with any severity of depression).

Some of the previous reviews mentioned above have included and pooled both studies where all the participants had depression, and studies on general populations (e.g., whole school classes). We wanted to explore the effect of exercise on children and adolescents with depression, and therefore excluded studies on general populations unless they reported effect sizes for participants with depression separately.

We excluded trials that include children and adolescents with psychotic or borderline conditions, autism, physical handicaps, eating disorders and/or chronic or serious somatic diseases. Exercise interventions for these populations require individual adjustments due to health risks or limitations.

Interventions

Physical activity and exercise are terms that are often used interchangeably. The American College of Sports Medicine defines physical activity as "any bodily movement produced by the contraction of skeletal muscles that results in a substantial increase in caloric requirements over resting expenditure" (American College of Sports Medicine, 2017, p. 1). Exercise is a type of physical activity, defined as "planned, structured and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness" (American College of Sports Medicine, 2017). Components of physical fitness are health related such as, e.g., cardiorespiratory endurance, muscular strength, and endurance and flexibility, or skill-related such as, e.g., agility, balance, and speed (American College of Sports Medicine, 2017, p. 2). Exercise contains purpose and intention. These definitions are based on the work of Caspersen, Powell, and Christenson (1985).

In this systematic review, we only included trials on exercise, not all physical activity. We used the definition of the American College of Sports Medicine mentioned above (2017). This is a very commonly used definition and is the same criteria used by the Cochrane review on exercise for depression in adults (Cooney et al., 2013), and the Cochrane review on exercise for chronic fatigue syndrome (Larun, Brurberg, Odgaard-Jensen, & Price, 2017). Within this definition falls both aerobic, anaerobic, resistance, flexibility, and mixed fitness training exercise. Types of exercise that are often low intensity, e.g., yoga and tai chi, may also be included in this definition. Trials on dance movement therapy were excluded since it is a type of psychotherapy and different from exercise in its purpose and goal. It is also the subject of a separate Cochrane review (Meekums, Karkou, & Nelson, 2015).

Trials that measured outcomes immediately before and after a single exercise session and trials which provided less than a week of exercise were excluded. This criterion is similar to Cooney et al. (2013). A single session of exercise is unlikely to have any long-lasting effects

on the body. Depression scores after just one session have no practical significance and are probably not indicative of the real effects of exercise.

Exercise is a low-cost intervention that requires minimal equipment and can be done at the community level, requiring only minimal cultural adaptation. We considered it to be an intervention that has approximately the same effect irrespective of the cultural or socioeconomic background of the participants, or developmental level of the country where the intervention takes place. We included all settings since exercise can probably be executed in similar ways irrespective of setting, whether it is in schools, primary care settings, or hospitals.

Comparisons

We only included studies that compared an exercise intervention to a non-exercise intervention or no intervention. We decided to exclude trials that compared either two types of exercise or intensities of exercise because those trials explore which type of exercise is most effective, not whether exercise is effective.

Outcomes

We chose a wider range of outcomes than the previous reviews on this subject, which mainly looked at the outcome of depression. We also wanted to investigate other outcomes that are important and relevant to patients, and not only to researchers or clinicians.

Core outcome sets (COS) are an agreed standardized set of outcomes that are important to patients, carers and health personnel. COSes are developed in a consensus process where these stakeholders participate (Williamson et al., 2017). There are currently two ongoing projects that work on producing a core outcome set (COS) for depression in children and/or adolescents for depression (Comet Initiative, 2019a, 2019b). There is a core outcome set for depression and anxiety in adults (including adolescents above the age of 14 years) (Obbarius et al., 2017). The working group behind this COS agreed on four general treatment outcomes: Symptom burden, functioning, disease progression and treatment sustainability, and potential side effects of treatment. We chose outcomes based on these recommendations. These are also the same outcomes as in the Cochrane review on exercise for depression in adults (Cooney et al., 2013).

Primary outcomes

Depression: The primary outcome was a measure of depression, either as a continuous measure or as a dichotomous outcome. Depression could be measured by self-report, health personnel report, parent report and/or teacher report with a standardized procedure. A variety of assessment tools are used to measure depression in children and adolescents. Examples of validated and commonly used tools are Beck Depression Inventory (BDI) (Stockings et al., 2015) and Children's Depression Inventory (CDI) (Kovacs, 1992).

Adverse events reported in any way (e.g., using reporting systems such as Serious adverse reactions (SARs) (European Union Clinical Trials Directive 2001)) was also considered a primary outcome since it is important to investigate whether exercise can harm this population. When choosing an intervention in clinical practice, one must balance benefits and harms (Reeves, Deeks, Higgins, & Wells, 2011, chapter 13.2.1.2). Adverse events in exercise interventions can include musculoskeletal injury, musculoskeletal pain or fatigue, and in rare cases cardiac events or death (American College of Sports Medicine, 2017, pp. 10-16; Peterson).

Secondary outcomes

Psychological well-being measured using any validated scale (e.g., KIDSCREEN (Ravens-Sieberer et al., 2014) and Child Health Questionnaire (CHQ) (Hullmann, Ryan, Ramsey, Chaney, & Mullins, 2011)).

Social functioning measured using any validated scale (e.g., Child and Adolescents Social and Adaptive Functioning Scale (CASAFS) (Price, Spence, Sheffield, & Donovan, 2002)).

Quality of life (QOL): measured using any validated scale (e.g., The Pediatric Quality of Life Inventory (PedsQL) (Varni, Sherman, Burwinkle, Dickinson, & Dixon, 2004).

Acceptability measured as dropouts. This is an important outcome because it does not matter if an intervention is effective, if the participants do not want to, or are able to participate.

Timing of outcome assessment

We included data from both the end of treatment and if available, any follow-up. Long-term effects are important to investigate (Obbarius et al., 2017).

Types of studies

We only included randomized controlled trials (RCTs). The research question in this systematic review is about the effects of an intervention, and RCTs are the best study design for answering effects questions. Randomization minimizes the risk of systematic baseline differences between the intervention and control groups (O'Connor et al., 2011).

Language, publication year and publication status

Trials published in any language were included. Systematic reviews that are based on only English-language trials can miss trials, and therefore be biased. Some research indicates that negative results are more often published in local, non-English journals, while positive results are more frequently published in international, English-language journals (Sterne, Egger, & Moher, 2011). No limitations on publication year were applied since neither the intervention (exercise) nor the definition of depression has changed considerably. This also makes older studies interesting, and fairly similar to current studies. We applied no limitations on publication status either. In addition to journal articles, we wanted to include grey literature such as dissertations, theses, and reports, as well as unpublished trials. By doing this, we hoped to find a more complete picture of the research, in contrast to the previous systematic reviews on the same topic that only included articles in peer-reviewed journals (O'Connor et al., 2011). Searching for and including grey literature decreases the risk of publication bias in systematic reviews. Trials that have not been published might have negative results (Sterne et al., 2011).

Search methods for identification of studies

Systematic reviews require an exhaustive, unbiased and reproducible literature search in a range of sources to identify as many relevant studies as possible (Lefebvre, Manheimer, & Glanville, 2011, chapter 6.1.1.2). In systematic reviews, the literature search is a key component. The quality and scope of the literature search is an important factor in the quality of the systematic review. A comprehensive search minimizes the risk of bias in the systematic review (Lefebvre et al., 2011). It is necessary to identify all of the evidence before we can synthesize and assess it (Levay & Craven, 2019, p. 2). Finding all trials, however, is often

only theoretically possible. The goal should be to find as many relevant studies as possible within the resource limits (Lefebvre et al., 2011). These limits can be time, both for doing the literature searches and study selection, access to databases, the functionality of the databases and how they are indexed, and knowledge and skills of the person who do the searches (Levay & Craven, 2019, p. 52).

Cochrane recommends having an experienced information specialist doing the literature searches for systematic reviews (Lefebvre et al., 2011). Both authors are librarians, so we performed the searches ourselves.

The first step in a literature search process for a systematic review consists of deciding where and how to search for evidence (Levay & Craven, 2019, p. 53). Choosing where to search depends on the research question, how much time is available, and which databases we have access to (Levay & Craven, 2019, pp. 74-77). Our research question is multidisciplinary, and of interest to several different research fields. We, therefore, decided to search a wide range of bibliographic databases within medicine, psychology, healthcare and sports science. We decided which databases to search based on advice in the Cochrane handbook, the Campbell Methods guide and previous systematic reviews on this subject (Kugley et al., 2017; Lefebvre et al., 2011). In this project, we had access to all the major bibliographic databases we needed, either through Høgskulen på Vestlandet or through our place of work.

We expected that trials could be published not only as journal articles, but also as dissertations and theses, reports and other grey publications, and therefore included databases that index those publication types in our search. Trials registers were also searched because they can be important sources of unpublished and ongoing trials since many journals and research funders require pre-registration of trials (Dwan, Gamble, Williamson, & Altman, 2008).

When designing a search strategy, the first step is to translate the research question into searchable concepts (Levay & Craven, 2019, p. 59). The PICOS for the research question is a helpful guide when deciding these concepts. Each part of the PICOS may be one concept or be split into two or more concepts. It is not necessary to include every part of the PICOS in the search strategy. Abstracts and titles might have limited details, making it difficult to find all potential trials if one uses too many concepts in a search strategy. In systematic reviews on the effects of an intervention, it is often recommended to use only P, I and S (Lefebvre et al., 2011).

In our PICOS, the P (population) could be split into two different concepts, "children and adolescents" and "depression". For each of these concepts, we found search terms (both index terms and text words), and combined them with the boolean operator OR. The I (intervention), exercise, is one concept. We found a wide range of search terms for exercise and combined them with OR. The C (comparison) is all non-exercise interventions or no intervention. Since the search terms for these interventions can be unlimited, we decided not to include this concept in the literature search since we did not want to miss any relevant trials. The O (outcome) was also excluded from the literature search since, according to our experience, outcomes are often poorly reported or reported in many different ways in the titles or abstracts of studies on mental health. In this research field, it is often implied, but not explicitly, that the outcome is symptom severity, measured using one of the numerous different measuring tools.

The S (study design) is randomized controlled trials. We applied a search filter with search terms for randomized controlled trials in databases where the number of references would have been unmanageable without adding such a filter. We used validated RCT filters in the databases where available (The InterTASC Information Specialists' Sub-Group Search Filter Resource, 2017).

Finally, we combined all included search concepts ("children and adolescents", "depression", "exercise" and "randomized controlled trials") using the boolean operator AND since we wanted to find references where all of these concepts were present.

When searching for a systematic review, it is recommended to search with both index terms and text terms to get a comprehensive search that finds as many studies as possible that fits the eligibility criteria (Lefebvre et al., 2011). Finding search terms for the different concepts in the search strategy can be time-consuming. The goal is to find all, or at least as many as possible, terms that are used in articles that fulfill the inclusion criteria (Lefebvre et al., 2011). On the other hand, a very sensitive literature search can lead to an unmanageable number of references, most of them not relevant, that is not possible to handle within the resources of the review team (Lefebvre et al., 2011, chapter 6.1.1.2).

We started by designing the search strategy for the MEDLINE (Ovid) database. We looked for index terms (MeSH-terms) and text words for every concept of the P and I. To find MeSH-terms we searched the MEDLINE-thesaurus for different synonyms for and types of exercise. We also looked at the search strategies for the previous systematic reviews on this subject and other reviews (especially Cochrane-reviews) where the intervention was exercise. To find text words, we also looked at other reviews. In addition, we browsed the reference lists of these reviews, and primary studies we knew. We also used general thesauri and Google-searches. We found validated search filters for children and adolescents and used terms from them in addition to the ones we found via other sources (The InterTASC Information Specialists' Sub-Group Search Filter Resource).

We discovered that there is a rich terminology in this field, and the author of trials have used many different terms in their titles and abstracts. We, therefore, used a wide range of search terms to minimize the risk of missing relevant trials. We truncated many of the text words to ensure that we would find all versions of the words. We combined the search terms in accordance with the search functionalities in Ovid.

For the S (study design) we used the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (Lefebvre et al., 2011). See Table 2. for a description of the search strategy.

Торіс	Search line
Participants (P)	
Condition (depression) (MeSH)	1-2
Condition (depression) in title and abstract	3-4
Combined	5
Children and adolescents (MeSH)	6
Children and adolescents (6-18 years) in title and abstracts	7-8
Combined	9
Intervention (I)	
Exercise (MeSH)	10
Exercise (all kinds) in title and abstract	11
Combined	12
Condition + Children and adolescents + Exercise	13
Study design (S)	
Methodological search filter for RCTs (randomized controlled trials)	14-24
P + I + S	25

Table 2. Description of the MEDLINE (Ovid) search strategy

After designing the MEDLINE (Ovid) search strategy, we checked it several times to detect any mistakes or omissions. Small details are important in literature searches. One example is from one of the search strategies where we detected a missing end parenthesis. When it was added, the number of hits decreased from 1488 to 773. Two experienced medical librarians peer-reviewed the MEDLINE (Ovid) search strategy using the PRESS checklist (McGowan, Sampson, Cogo, Foerster, & Lefebvre, 2016). When we were satisfied with the MEDLINE (Ovid) search strategy was translated to the other databases. Each database has slightly different ways of searching, different index terms (or no index terms) and their quirks.

Study selection

References from the electronic searches were exported to an EndNote library (Clarivate Analytics, 2017). Duplicates were removed with a de-duplication method (Bramer, Giustini, de Jonge, Holland, & Bekhuis, 2016), and the remaining references were exported to Covidence (Veritas Health Innovation, 2019). More duplicates were removed in the duplicate removal process in Covidence.

The two authors independently screened all articles for eligibility, as recommended by the Cochrane Handbook (Higgins & Deeks, 2011). Title and abstracts were screened. All references that one or both of us had selected "include" on was ordered in full text, and the PDFs were imported into Covidence. We then screened the full texts independently. There were a few conflicts after the full-text screening, that was resolved by consulting a third reviewer. The web-based tool Covidence was used to screen articles at the title/abstract-level and full text (Veritas Health Innovation, 2019). Several different tools have been developed to help with the screening process in systematic reviews. We chose Covidence because our place of work has a subscription, we have considerable experience in using it from previous projects, and we find Covidence to be user-friendly.

A few studies in German and Persian appeared to be eligible for inclusion based on the English language title and abstract. We were helped by two native speakers (both are experienced researchers) who read the full text, and we decided that none of these articles were eligible for inclusion.

A PRISMA flowchart was created for the visualization of the study selection process (Moher et al., 2009).

Data extraction

We made a data extraction form based on the recommendations in the Cochrane Handbook (Higgins & Green, 2011, chapter 7.3). We extracted the following data from the included studies:

- Methods: study design
- Participants: number (randomized and analyzed), drop-outs, age, gender, recruitment, baseline severity of depression, inclusion and exclusion criteria, location.
- Interventions: type of exercise, intensity, intervention provider, modes of delivery, duration of the trial, frequency, number of sessions, duration of each session, setting, control intervention(s).
- Outcomes: primary and secondary outcomes, measurement tools and timing of measurement
- Notes: publication type, funding, conflicts of interest, trial registration, intention to treat analysis, sample size calculation

The data extraction form was pilot tested using one of the included studies (Higgins & Deeks, 2011, chapter 7.6.3). We then independently completed the data extraction from the other trials.

For descriptions of the interventions in the included trials, we used the Template for Intervention Description and Replication (TIDieR) checklist and guide (Hoffmann et al., 2014). TIDieR was developed to improve the completeness of reporting of interventions. We used TIDier to ensure that we extracted the recommended items for describing an intervention. See the TIDieR checklist below in Table 3, and the TIDieR tables in Appendix III.

Table 3. TIDieR checklist

T DieR Template for Intervention

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item	Item	Where located **	
number		Primary paper	Other † (details)
		(page or appendix	
		number)	
	RRIEE NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those		
	provided to participants or used in intervention delivery or in training of intervention providers.		
	Provide information on where the materials can be accessed (e.g. online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention,		
	including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their		
	expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or		
	telephone) of the intervention and whether it was provided individually or in a group.		
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary		
	infrastructure or relevant features.		

TIDieR checklist

	WHEN and HOW MUCH		
в.	Describe the number of times the intervention was delivered and over what period of time including		
	the number of sessions, their schedule, and their duration, intensity or dose.		
	TAILORING		
).	If the intervention was planned to be personalised, titrated or adapted, then describe what, why,		
	when, and how.		
	MODIFICATIONS		
0.*	If the intervention was modified during the course of the study, describe the changes (what, why,	0	<u>.</u>
	when, and how).		
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any		
	strategies were used to maintain or improve fidelity, describe them.		Sec. 111-11
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the	N	0
	intervention was delivered as planned.		

** Authors - use N/A if an item is not applicable for the intervention being described. Reviewers - use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).
If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a randomised trial is being reported, the TIDIER checklist should be used in conjunction with the CONSORT statement (see <u>www.consort-statement.org</u>) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is being reported, the TIDIER checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013** Statement (see <u>www.spirit-statement.org</u>). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

TIDieR checklist

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. doi:10.1136/

We planned to contact the authors of the included trials in the case of missing data (Moher et al., 2009). However, no data were missing for completing the analyses and the data extractions.

Risk of Bias assessments in included studies

Despite the highest methodological standards when conducting a trial, it still may have biases. Bias is a systematic error that can threaten the true effect of an intervention and can raise questions about the internal validity of the trial. Evaluating the validity of the included trials with a risk of bias tool is an important factor when conducting a systematic review and should be taken into consideration in the analysis and the conclusions of the review (Higgins, Altman, & Sterne, 2011, chapter 8.4).

Risk of bias assessments requires two persons to evaluate each trial independently, and because of subjectivity in each decision, they may come to a different conclusion. Discrepancies should be resolved by consensus or by consulting a third reviewer (Higgins & Deeks, 2011, chapter 7.6.5).

We independently assessed the quality of the included trials with the Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011), using the following criteria: 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, and presented in a table and as a figure, according to the Cochrane Handbook (Higgins et al., 2011, figure 8.6.a and figure 8.6.c).

Sequence generation is a domain which addresses the process of random assignment of participants in either an intervention or a control group. Assignment, when it is done randomly and properly, secures that each participant has the same opportunity to be assigned to either an intervention or a control group. Random assignment increases the likelihood of similarity between the groups at the start of the trial. It also makes potentially confounding factors balanced between the groups and may reduce systematic errors. Random assignment can be achieved by using a published list of random numbers or to a list of random assignments generated by a computer (Higgins et al., 2011, chapter 8.9.2).

Allocation concealment is a domain which refers to the random assignment being concealed from the person recruiting participants, to prevent selective enrolment. There are different methods used to conceal allocation. A proper method is when the allocation is done by a third party and involves using sequentially numbered, opaque, sealed envelopes. It is essential that researchers make sure the envelopes are opened sequentially after the envelope has been assigned to the participant and cannot change the result of the assignment (Higgins et al., 2011, chapter 8.10.2).

Blinding of participants and personnel means that participants or personnel are unaware of group allocation. Blinding reduces the risk introduced when a participant or investigator know which intervention a participant received, which in turn may affect the outcomes. Blinding can be impossible in some interventions; such is the case in this review, where the intervention is exercise and both participants and personnel know if they have participated in an exercise group. However, other measures could be taken to reduce the risk of bias, for example, using a strict protocol to reduce the risk of differential behaviours by participants and personnel (Higgins et al., 2011, chapter 8.11.2).

Blinding of outcome assessors is a domain which refers to the person who assesses the outcome data being unaware of the intervention allocations. This is particularly important when the outcome is subjective, as with self-reported outcome measures (Higgins et al., 2011, chapter 8.12.1). It can affect the outcome assessment and bias the result of the trial. Outcome assessments may be made by the participants themselves, by their personnel or by independent assessors. Cochrane handbook recommends to group outcomes with similar risks of bias, instead of assessing the risk of bias for each outcome separately. For example, assessment of the risk of bias for all subjective outcomes separate from assessment of blinding for all objective outcomes (Higgins et al., 2011, chapter 8.12.2).

The domain of incomplete outcome data refers to outcome data being missed due to attrition (drop-out) or participants being excluded from analysis from different reasons. Incomplete outcome data can bias the effect estimate. The Cochrane handbook recommends an intention-to-treat (ITT) analysis as the least biased way to estimate intervention effects. The method includes analyzing the participants within the groups they were allocated to regardless of the intervention they received (Higgins et al., 2011, chapter 8.13.2).

Selective outcome reporting occurs when researchers select one type of data for an outcome, or they select which outcomes to report. If that selection is made based on the results, the

concern is that statistically non-significant results may be withheld from publication. If a study protocol is available, outcomes in the protocol should be compared to those in the published article. If not, the outcomes listed in the methods section of an article can be compared with those results reported. These methods can indicate whether selective reporting has occurred (Higgins et al., 2011, chapter 8.14.2).

Other sources of bias are a domain where other potential threats to validity in a trial are assessed, for example, design-specific risks of bias, sources of funding, or any other sources of bias that should be investigated. Finally, we assessed the overall bias for each included trial.

Data analysis

A meta-analysis is a statistical method which summarizes the effectiveness of the experimental intervention compared with a control intervention (Deeks, Higgins, & Altman, 2011, chapter 9.4.1). The possible advantage of a meta-analysis is increased power and improved precision. Authors of systematic reviews should reflect on if it is appropriate to combine the results, from all or some of the included trials in a meta-analysis. Only when the trials are sufficiently homogeneous in terms of participants, interventions, and outcomes should they be combined statistically to provide a meaningful summary. If inappropriate to conduct a meta-analysis because of heterogeneity, a narrative synthesis is a proper method. (Deeks et al., 2011).

The trials were assessed as similar enough to be appropriate to synthesize the results of the outcome depression severity at post-intervention in a meta-analysis. We used the software RevMan to perform the meta-analysis and to create forest plots that visually present the effect estimates for each outcome (The Cochrane Collaboration, 2014). We started by identifying the data for the outcome measures from the included studies. Continuous outcomes were reported as standardized mean difference (SMD) since the outcomes were measured using different instruments across the included studies. We reported 95% confidence intervals and p-values (Deeks, Higgins, & Altman, 2011, chapter 9.2).

We interpreted the heterogeneity results of the I² statistic according to the Cochrane Handbook: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Deeks et al., 2011, chapter 9.5.2). We expected that there would be heterogeneity between the studies, e.g., different types and doses of exercise, or that the participants would be different at baseline and react differently to the intervention due to depression severity, gender or motivation to exercise. We used a random effects model since it is recommended over a fixed effects model when there is heterogeneity (Deeks et al., 2011, chapter 9.5.4).

Subgroup analysis and investigation of heterogeneity

There is a risk of heterogeneity when different trials are pooled together in a systematic review (Deeks et al., 2011). We, therefore, planned to perform subgroup analyses for the variables: type and intensity of the exercise interventions. The advice for undertaking subgroup analyses is that at least ten studies are included in a meta-analysis. Not enough number of trials met our inclusion criteria, and we were, therefore, unable to investigate if the heterogeneity was affected by these variables.

Sensitivity analysis

In the study protocol, we planned to perform sensitivity analyses for the primary outcomes by removing trials with high or unclear risk of bias. Methodological differences across the trials, such as concealment allocation, blinding of outcome assessor and the dropout rate was to be used to conduct the analyses. However, none of the included trials were assessed as having a low risk of bias, and therefore, we were unable to perform a sensitivity analysis.

Assessment of publication bias

The reasons for assessing publication bias is the concern that statistically non-significant results may be selectively not published. This can lead to overestimating intervention effects and pose a threat to the validity of the review (Higgins et al., 2011, chapter 10.2.2.5). Negative results in trials can be unpublished because authors may think journal editors do not want to publish negative results (Sterne et al., 2011). The most common approach to assess publication bias is by visually examining funnel plots for asymmetry; the required number is at least ten trials. We included only four trials which made it impossible to assess publication bias in this way. However, we attempted to search as widely as possible, for published, unpublished and ongoing trials. We searched for grey literature, conference abstracts, and

dissertations databases and in trials register. There is, however, always a possibility to miss out on publications.

Certainty of the evidence (GRADE)

To assess the certainty of the evidence for each outcome, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and the GradePro software to create a "Summary of findings"-table (McMaster University and Evidence Prime Inc., 2015; Schünemann et al., 2011, chapter 12.2.1).

GRADE is a framework to present summaries of evidence with a systematic approach to making clinical practice recommendations (Guyatt et al., 2008). GRADE provides explicit criteria for rating the certainty of evidence. The criteria include study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of the effect. GRADE has four levels of evidence: very low, low, moderate, and high (see further description for the domains below and the GRADE criteria for assessing certainty of evidence in table 4).

The study design is the start point for grading. Randomized controlled trials start at high certainty and are either downgraded or upgraded. Observational studies start at low certainty (Guyatt et al., 2011).

The overall risk of bias is assessed and downgraded by one level for serious limitations, and by two levels for very serious limitations. Inconsistency is assessed and downgraded by one level if there are unexplained variations in the results of the trials (high heterogeneity) and downgraded by two levels where there is serious unexplained variability. Indirectness is assessed and downgraded by one level if there is a wide variation of the population, intervention, control groups, and outcomes. It can affect the generalizability of the results. For very serious indirectness is downgraded by two levels. Imprecision is assessed and downgraded by one level if confidence intervals affect the quality of the data. For very serious imprecisions is downgraded by two levels. Publication bias refers to when trials with "negative" findings remain unpublished and can bias the review outcome. For the likelihood of publication bias is downgraded by one level and if publication bias is very likely, it is downgraded by two levels. Table 4. the GRADE criteria for assessing certainty of evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias	Large effect
	~	-1 Serious	+1 Large
		-2 Very serious	+2 Very large
	Moderate	_ Inconsistency	Dose response
		-1 Serious	+1 Evidence of a gradient
		-2 Very serious	100
			All plausible confounding
Observational study	Low	Indirectness	+1 Would reduce a
		-1 Serious	demonstrated effect or
		-2 Very serious	
			+1 Would suggest a
		Imprecision	spurious effect when
	Verylow	-1 Serious	results show no effect
	,	-2 Very serious	
		Publication bias	
		-1 Likely	
		-2 Very likely	

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., . . . Schunemann, H. J. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, 64(4), 383-394. doi:10.1016

Results

The comprehensive literature search retrieved a total of 15869 records from all bibliographic databases. The initial search in March 2018 retrieved 13079 records, the update search in December 2018 retrieved 2464 records. Searching for grey literature and ongoing trials identified 538 records, of which 212 were manually screened. After removing duplicate records, 11007 remained for screening. We excluded 10698 references based on the title and abstract screening. We assessed 309 full-text articles and excluded 301 references.

We identified four ongoing trials (De Volder, 2018; Dopp, 2018; Lin, 2018; Oberste et al., 2018). Three of the four trials were located in ClinicalTrials.gov, and one trial was published as a study protocol in a journal (Oberste et al., 2018). Further description of ongoing trials is in Appendix IV.

Completing the study selection process, four trials (n=143) met the inclusion criteria. Details of the study selection process and reasons for exclusions are given in the PRISMA flow diagram (figure 1) and a list of excluded trials with the primary reason for exclusion in Appendix V.



PRISMA 2009 Flow Diagram


Included studies

Two of the four included trials were articles published in peer-reviewed journals and performed in the UK (Carter et al., 2015) and Iran (Roshan, Pourasghar, & Mohammadian, 2011). Moreover, two trials were doctoral dissertations, both performed in the USA (Beffert, 1993; Burrus, 1984). All included trials were published in English.

The four trials were randomized controlled trials. Carter et al. (2015) implemented a pragmatic randomized controlled trial design. Pragmatic trials are designed to show the reallife effectiveness of the intervention and are useful in trials with small samples, because such trials may overestimate benefits and underestimate harm (Patsopoulos, 2011). Burrus (1984) used a stratified random sampling procedure due to the variance found in levels of depression and cardiovascular fitness among participants. Both variables were stratified and statistically analyzed to ensure that the groups were equivalent. Stratified randomization is performed separately within strata and generates separate randomization for subsets of participants. (Higgins et al., 2011, chapter 8.9.2.1). Roshan et al. (2011) and Beffert (1993) had no reporting of adjustments to the study design in their trials.

The age of participants in the trials was similar and ranged from 12 and 18 years of age. The only trial that included participants below the teenage was Beffert (1993), which included children from 12 to 15 years. The other three trials included participants from the age of 14 or 15 years.

The four trials consisted of different types of exercises and comparisons. All interventions were group-based training, and all except one trial were supervised by experienced instructors or therapists (Roshan et al., 2011). By using the TIDieR framework (Hoffmann et al., 2014), we have described the interventions in detail (see TIDieR tables in Appendix III). The TIDieR tables show the difference in duration, intensity, and mode of delivery of the exercises. The interventions in the included trials are adequately described. The time period of the interventions was similar, six weeks in three trials (Beffert, 1993; Carter et al., 2015; Roshan et al., 2011) and nine weeks in one trial (Burrus, 1984). The intensity was slightly different across studies; in three trials the maximum heart rate was between 60-85%, while in Carter et al. (2015) the participants could choose the level of intensity.

The comparison groups consisted of no exercise (Roshan et al., 2011), or waitlist (Beffert, 1993). Burrus (1984) implemented two comparison groups, one with medium physiological

activity based on anaerobic exercise and one with low physiological activity based on first aid and personal safety class. However, only the non-exercise comparison group was included in the analysis for this systematic review. That decision was based on the inclusions criteria of not including trials comparing exercise with a different type of exercise. Carter et al. (2015) however, compared to treatment as usual which consisted of psychological therapies and medications.

All four trials evaluated depression as the primary outcome. Three trials used self-reported outcome measurement tools (Beffert, 1993; Burrus, 1984; Carter et al., 2015) and one used a clinician-rated outcome measurement tool (Roshan et al., 2011).

Another primary outcome in this review was adverse events. However, none of the included trials reported any adverse events. Only one trial (Carter et al., 2015) evaluated quality of life, a secondary outcome in this review. Other secondary outcomes, psychological well-being, and social functioning were not reported in the trials, and drop-out reporting was unclear in several of the trials.

For a further description of the trials that met the inclusion criteria see Table 1. Characteristics of included trials.

Intervention (exercise component)								
Study, year	Participants	Country, Setting	Туре	Dose, Intensity (max. heart rate)	Control	Outcome Measures (depression)	Baseline severity of depression Mean (SD)	Results (lower score is better) SMD (CI)
Carter <i>et al.</i> 2015	n= 64 14-17 years M=15.4 years 78% females	UK Community centres	Circuit-training (aerobic and strengthening exercises)	45 min 2 times/wk 6 weeks Preferred intensity	Treatment as usual	CDI-2 Self-report	I: 29.1 (9.4) C: 28.2 (6.8)	-0.19 (-0.69, 0.30)
Roshan <i>et al.</i> 2011	n=24 15-18 years M=16.9 years 100% females	Iran High school	Pool-walking program	3 times/wk 6 weeks 60-70%	No exercise, no anti- depressant 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)	20 min 3 times/wk 6 weeks 60-85%	Waitlist	RADS Self-report	I: 122.53 (6.03) C: 124.91 (6.92)	-0.85 (-1.66, -0.03)
Burrus 1984	n=29 15-18 years M=N/A 60% females	USA High school	Walk-jog-run (aerobic running program)	45 min 4 times/wk 9 weeks 75%	Anaerobic treatment, Red Cross First Aid and Personal Safety Class	DACL Self-report	I: 19.14 (3.73) C: 19.33 (3.71)	-0.27 (-1.00, 0.46)

*All trials are RCTs (Randomised Controlled Trials)

*All interventions were group-based and supervised. Note: CDI-2= Children's Depression Inventory; Ham-D= Hamilton Rating Scale for Depression; RADS= Reynolds Adolescent Depression Scale; DACL= Depression Adjective Checklist.

Risk of bias in the included studies

We assessed one trial (Carter et al., 2015) as having an overall unclear risk of bias and the other three trials as having an overall high risk of bias (Beffert, 1993; Burrus, 1984; Roshan et al., 2011), (see figure 2 and 3). Mostly all domains across the trials were rated as unclear risk of bias. Blinding of participants and personnel was rated as high risk of bias in all the trials due to the nature of the intervention exercise, as it was not possible to blind neither the participants nor the personnel. The blinding of outcome assessors was also rated as high risk of bias in two of the trials and unclear in the other two trials. For full detail of the risk of bias assessments see Appendix VI.

Figure 2. Risk of bias graph



Figure 3. Risk of bias graph



We assessed the risk of bias due to inadequate *sequence generation* to be low in only one trial (Carter et al., 2015), where the random allocation sequence was computer generated by the trial statistician using permuted block randomization with varying block size. In the other three trials, we assessed this domain as having an unclear risk of bias. In Roshan et al. (2011) the participants were divided randomly into experimental group or control group, without any description of the randomization process. Burrus (1984) attempted assignment to treatment groups to be random, however, due to variance in levels of depression and cardiovascular fitness, both variables were stratified and statistically analyzed to ensure the groups to be equivalent. Beffert (1993) randomly assigned students who scored a 75 or higher on the RADS scale to either a treatment group or a waitlist control group, without describing the process.

We assessed the risk of bias due to *allocation concealment* as low risk in one trial (Carter et al., 2015), who used sequentially numbered opaque sealed envelopes to ensure allocation concealment. Whereas in the other tree trials we assessed the risk as unclear since there was no mention of concealment allocation.

We assessed the risk of bias due to *blinding of participants and personnel* as high risk in all the four trials because of the nature of the interventions; all participants were aware that they participated in the exercise group.

We assessed the risk of bias due to *blinding of outcome assessments* as an unclear risk in two trials (Carter et al., 2015; Roshan et al., 2011) and high risk in two trials, due to self-reported outcomes measurement tools (Beffert, 1993) (Burrus, 1984). Roshan (Roshan et al., 2011) used a tool administered by a health-care professional (HAM-D) and was therefore assessed as unclear risk of bias. Carter et al. (2015, p. 2.) also used a self-rated outcome measurement tool (CDI-2). However, he informed that "outcome assessors, including the data input administrator, were blind to treatment group at both follow-up time points". "The analysis was conducted on a data set in which group allocation was unlabelled". Therefore, it was rated as unclear risk of bias.

We assessed the risk of bias due to *incomplete outcome data* to be unclear in all four trials. In Carter et al. (2015) the description of attrition and lost to follow-up was unclear. Burrus (1984) reports attrition of only one student who, for medical reasons, dropped out of school. (Beffert, 1993) did not report precise numbers for drop-out and Roshan et al. (2011) had no reporting of drop-out at all.

We assessed the risk of bias due to *selective reporting* as low risk in one trial since a published protocol for the study was available at ClinicalTrials.gov, NCT01474837 (Carter et al., 2015). The other three trials were assessed as having an unclear risk of bias, Roshan et al. (2011) had published a retrospective registration of study protocol, and for the other two trials, no published protocol was available.

We assessed the risk of bias due to *other potential sources of bias* as low risk in one trial (Carter et al., 2015) and unclear risk in the other three trials.

Effects of interventions

Meta-analysis results

The four trials used different outcome measurement tools to evaluate depression postintervention. The effect sizes were reported as continuous data. Accordingly, we summarized the results by calculating standardized mean differences (SMD) using Hedges g. in RevMan. Some systematic reviews convert scores from different tools to be able to pool the results from different trials, but since all included trials had different measurement tools we decided to avoid that.

A random-effects model was used since we expected heterogeneity across the trials. We assessed the heterogeneity as being moderate ($I^2=52\%$), using the I^2 statistics. We anticipated that the heterogeneity could be explained by different control interventions and measurement tools, but we decided to go forward with pooling the data. The clinical questions, the participants and the exercise interventions were similar enough to justify pooling the results in a meta-analysis.

Depression (post-intervention)

The primary meta-analysis pooled four trials (n=143) testing the effects of exercise on depression at post-intervention compared with a control, finding a moderate effect in favour of exercise (SMD= -0.59, 95% CI= -1.11, to -0.07, p=0.03, I²=52%), see figure 4.



Figure 4 Forest plot of comparison: exercise versus control, post-intervention, outcome: change in depression

Depression (follow-up)

A meta-analysis of exercise versus control was not possible, as change in depression at follow-up was reported in only one trial (n=42)(Carter et al., 2015). The trial found a moderate effect in favour of exercise (SMD= -0.59, 95% CI= -1.22, to -0.04, p=0.07), see figure 5. With only one trial the test for heterogeneity was not applicable.



Figure 5 Forest plot of comparison exercise versus control, follow-up, outcome: change in depression

Quality of Life

A meta-analysis of exercise versus control was not possible, as quality of life at postintervention was reported in only one trial (n=42)(Carter et al., 2015). The trial found no statistically significant differences (SMD= 0.27, 95% CI= -0.35, to 089, p=0.39), see figure 6. With only one trial the test for heterogeneity was not applicable.



Figure 6 Forest plot of comparison exercise versus control, post-intervention outcome: quality of life

Certainty of the evidence (GRADE)

The GRADE approach was used to assess the certainty of the evidence, and we created a summary of findings table (see table 6) (Schünemann et al., 2011). We independently graded the primary outcome of change in depression, post-intervention and at a follow-up.

Depression, post-intervention

For the domain risk of bias, we downgraded by one level for lack of blinding and sequence generation, which was unclear in three of the trials. Imprecision was downgraded by one level due to a low number of participants. Heterogeneity across the trials was moderate and therefore not downgraded for. Overall certainty of the evidence for the outcome change in depression, post-intervention, was rated as low. Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Depression at follow-up (six months)

For the domain risk of bias, we downgraded by one level for lack of blinding and unclear sequence generation in three of the trials. For imprecision we downgraded by two levels due to a low number of participants in the trials and the width of the confidence interval was consistent with both important benefit and harm. Overall certainty of the evidence for the outcome change in depression at follow-up was rated as very low. We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 6. Summary of findings table.

Outcomes	Anticipated absolute effects [*] (95% CI)		Relative effect (95%	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with Exercise	CI)		
Change in depression post-intervention		SMD 0.59 lower (1.11 lower to 0.07 lower)		143 (4 RCTs)	⊕⊕⊖⊖ LOW ¹²
Change in depression follow-up (6 months)		SMD 0.59 lower (1.22 lower to 0.04 higher)		42 (1 RCT)	$ \begin{array}{c} \bigoplus \ominus \ominus \ominus \\ \text{VERY LOW}^{1} \\ ^{23} \end{array} $

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.

Footnotes

¹ Lack of blinding probably increased effect sizes. Sequence generation was considered unclear in 3 studies.

² 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.

⁷ The width of confidence interval was consistent with both important benefit and harm.

Discussion

The first part of the discussion is a summary of the main results, followed by the

methodological limitations of the included trials, and the strength and limitation of the current

systematic review. Finally, we discuss the implications for practice and future research.

Summary of main results

Our focus was the effect of exercise intervention on depression in children and adolescents. We included four trials with a similar exercise intervention, with exclusively adolescent participants. By pooling the results of the four included trials, we found a moderate effect in favour of exercise on depression post-intervention, with a wide confidence interval. The trials had a low number of participants and were assessed as having an unclear or high risk of bias. The certainty of the evidence of the primary outcome, depression post-intervention, was graded as low. Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

The strengths and limitations of the included studies

In the following section, we will discuss the strengths and limitations of the included studies, and their generalizability to children and adolescents with depression.

Sample sizes

The included studies had a low number of included participants (*n*=24-64). Using small samples increases the chance of having participants who are not representative of the population (Polit & Beck, 2012, p. 284). The effect estimates are less precise, and small studies are underpowered to detect a true difference between the groups. The risk of false positive or false negative findings is increased in underpowered studies (Polit & Beck, 2012, p. 422-423). Only one of the included studies, Carter et al. (2015), performed a sample size calculation before recruitment started. They calculated that to detect a medium effect size they required 158 participants. They were however only able to recruit 87 participants, and only 64 finished the trial. Not even when we pooled all the four included studies (n=143) did we reach the number required according to the study (Carter et al., 2015).

Participants

Three of the studies screened high school students for depression (Beffert, 1993; Burrus, 1984; Roshan et al., 2011). In two of the trials students who scored above the cut-off point of the assessment tool, were screened a second time 1-6 months later to ensure that depression

was not short term or situational (Beffert, 1993; Burrus, 1984). Students who scored above the cut-off point in both screenings were invited to participate in the trials. In Carter et al. (2015) the participants were recruited among adolescents receiving treatment from a health or social care professional for depression and scoring above cut off point on the Children's Depression Inventory-2 (Kovacs, 1992). The participants in the included studies were representative of adolescents with depression. That increases the applicability of the included trials for practice.

Exercise interventions

Blinding of participants and personnel is not possible in exercise interventions. In the included trials, as in most studies on exercise interventions, the lack of blinding creates a risk of bias (Higgins et al., 2011, chapter 8.11.1).

Hoffmann et al. (2014) emphasize the importance of a precise description of interventions in trials. If interventions are inadequately described or defined, it inhibits replication and verification of the trial result and makes it impossible to implement the intervention in practice or further research. The interventions are well described in all the included studies. The type of exercise, intensity, frequency, and duration, are reported in detail. This makes it possible for readers to understand what the intervention consists of and researchers would be able to replicate the studies. Practitioners can also implement the interventions in practice based on the information in the published studies.

The types of interventions are sensible, and feasible in practice. Two of the trials use walking/running which is easy to do in practice in most settings (Beffert, 1993; Burrus, 1984). It is a low-cost intervention, requires no or little equipment, and minimal extra training of personnel. A PE teacher, physiotherapist or a sports trainer would be able to organize and implement this intervention easily. In one of the studies, Roshan et al. (2011), the intervention is pool walking, which requires access to a swimming pool. This is not available in all settings, and water-based activities might not be culturally acceptable everywhere. This study, however, included girls in Iran, a conservative country, so with some adaptations, it might be suitable in various cultural settings. In Carter et al. (2015) the intervention is circuit training. This intervention requires some equipment, but can also be done with low-cost equipment.

The dose of the intervention (length of each session and frequency) is according to the recommendations of the American College of Sports Medicine of exercising 3-5 days per week, for 20-60 minutes (American College of Sports Medicine, 2014, p. 468). The length of

the intervention (6-9 weeks) might have been too short to see the full effect of exercise in this population. It is not known if a longer intervention time would have had a different impact. The only trial that measured follow-up data, Carter et al. (2015), did not report how many of the participants they measured after six months had continued to exercise after the intervention stopped. It would have been interesting to investigate if the long-term effect differed among participants who continued to exercise after the intervention, versus those who stopped exercise after the end of the intervention.

Comparisons

The comparison groups in the included trials received different control conditions. In Roshan et al. (2011) the comparison group received no treatment. Since these participants had been diagnosed with depression, it can be considered unethical not to offer them any treatment, or at least refer them to other treatment options (Stang, Hense, Jöckel, Turner, & Tramèr, 2005). In Beffert (1993) the comparison group was on a waitlist and received the exercise intervention later. When comparing an exercise intervention to no treatment or waitlist it is not possible to disentangle the specific effect of exercise from the other factors that are present in the interventions. Such factors include the social aspect of doing activities in a group with other adolescents, the motivational role of the supervisor, diversion from negative thoughts, and the effects of receiving attention (Craft & Perna, 2004).

In Carter et al. (2015) exercise was an adjunct intervention to treatment as usual. This study design could not take into account other factors of exercise intervention. In Burrus (1984) the control group participated in a first aid and personal safety course with similar attention time as the intervention group. In other words, this control group received everything that intervention group received except the exercise. This type of control condition might indicate if it is the exercise part itself that has an effect or if the other factors are more important. However, this study was unfortunately too small to draw any such conclusions.

Outcomes

The core outcome set for depression and anxiety (Obbarius et al., 2017) agreed on four general treatment outcomes: Symptom burden, functioning, disease progression and treatment sustainability, and potential side effects of treatment. Symptom burden (i.e., depression severity) was measured in all the four included trials. Functioning was not measured in any of

the trials, which is unfortunate since it is an essential measure for patients. Disease progression and treatment sustainability requires long term follow up. Only Carter et al. (2015) measured follow up effects, after six months. Long term follow-up trials, preferably longer than six months, are needed since depression is a recurrent disease (Pan & Brent, 2018). Side effects or adverse events of exercise interventions were not reported in any of the trials. There has been an increasing focus on adverse events in all types of interventions. All interventions should attempt not to harm participant, and it should be obligatory to access and report this outcome (Loke, Price, & Herxheimer, 2011). Adverse events can potentially lead to discontinuing further exercise interventions. Carter et al. (2015) also measured Quality of Life which is an important outcome measure. Drop-out was not adequately addressed in the included trials.

Depression severity and quality of life are measured using different measuring tools, either self-report or health personnel report. They are all subjective measures, which is a risk of bias (Higgins et al., 2011, chapter 8.12.1) There is however no objective way of measuring these outcomes (Uher et al., 2012).

Reporting of the studies

It is recommended (and obligatory for publication in high-impact peer-review journals) that study protocols for clinical trials are registered prospectively to avoid the risk of bias (De Angelis et al., 2004). Inconsistent reporting between protocols and published articles are frequent, and prospectively registered study protocols can reveal unpublished results (Li et al., 2018).

Carter et al. (2015) is the only of the studies who registered their trial prospectively. Roshan et al. (2011) registered their trial retrospectively after the journal had received the article manuscript, and just two days before it was accepted for publication (Iranian Registry of Clinical Trials, 2011). Retrospective registration makes it impossible to investigate selective reporting, or if they had followed their study protocol. The other included trials were older and conducted before it was standard practice to register study protocols.

Carter et al. (2015) adhered to and referenced the CONSORT statement for the reporting of trials. Roshan et al. (2011) did not follow this reporting standard. The other two trials were older doctoral dissertations and published before CONSORT was developed.

Methodological strengths and limitations of this systematic review

The main strengths of this systematic review are the standardized methods we have followed, and the comprehensive systematic literature search performed to identify trials.

In the conducting of this systematic review, we followed the methods of the Cochrane Handbook (Higgins & Green, 2011). Cochrane systematic reviews are known for their explicit, transparent and systematic methods, and Cochrane is a leading provider of systematic reviews in health care (Petticrew, Wilson, Wright, & Song, 2002). Additionally, we have reported according to the PRISMA guidelines (preferred reporting items for systematic reviews and meta-analysis) (Moher et al., 2009). PRISMA guidelines and checklist were developed to improve reporting in systematic reviews and meta-analysis. Our efforts of following international quality standards for conducting systematic reviews can nevertheless have been affected by both authors being inexperienced reviewers.

Preliminary searches

Efforts were made to identify other systematic reviews and ongoing reviews on the same topic, to avoid duplication. We searched various databases that index journals with systematic reviews and found reviews that somewhat overlapped. Also, we searched relevant databases for protocols to reveal ongoing systematic reviews. When starting to work on a new systematic review, reviewers should do their best to find existing systematic reviews on the same topic. This attempt has strengthened this project and is the best way to avoid unnecessary duplication (Moher, 2013).

The protocol

In the current project, we developed a pre-specified protocol and published it in the PROSPERO database (see appendix x). Publishing a protocol helps to detect selective reporting bias (Green & Higgins, 2011, chapter 2.1). We followed our protocol with some minor adjustments.

Selection criteria

Participants

Participants, from six to eighteen years old, were included in the review. The main reason for the low number of included trials in our analysis was that we excluded participants older than 18-year-old. During the study selection, we observed several trials with participants older than 18 years. Eighteen-year-old is the legal age in many countries. Before that age, it is mandatory to have consent from parents or guardians to participate in clinical trials, which may complicate the recruitment of younger participants. A difference between a 17-year-old and a 20-year-old may exist. During these years there is often a transition in the life of young people, which may include changing school and environment and even friends. However, the results of the effect of exercise for depression may be transferable across these age groups.

During the study selection process, we discovered that some trials do not report the age of the participants but refer to them as, e.g., college students. We checked the age of college students in the countries involved (e.g., China). In all cases, we classified them as over the age of 18 years, and therefore excluded them.

The included trials had participants with diagnosed depression or participants that reported above a clinical cut-off point for depression. The current inclusion criterion makes the results of our review more applicable to adolescents with depression than if we had also included the general population (participants without depression). However, previous systematic reviews show that exercise also probably decreases depressive symptoms in adolescents who are below the clinical level of depression (Bailey et al., 2017; Carter, Morres, Meade, et al., 2016).

Interventions

A strength of this systematic review was the use of a well-defined and widely used definition of exercise (American College of Sports Medicine, 2014, p. 2.). A clear definition was helpful and resulted in the improved decision process in the study selection. We discovered that several eligible trials had "combination of interventions," where exercise was one component of the combination. For example, exercise and cognitive behaviour therapy. This was something we did not anticipate and is, therefore, missing in the protocol. We decided, however, to exclude trials with "combination of interventions" because we could not separate

the effect of exercise from the effect of the other components. Cooney et al. (2013) have the same exclusion criterion in their Cochrane review.

Comparisons

An additional strength of our review was the exclusion of trials comparing two types of exercise or two different intensities of exercise. Comparing two types of exercise interventions makes it impossible to conclude on the sole effect of exercise. In one of the included trials (Burrus, 1984), one of two control group was another type of exercise, anaerobic treatment consisting of a weight training program. The results from this control group were not included in the meta-analysis in the review.

Despite the differences in the comparisons, we decided to pool the results in a meta-analysis. We reflected on this and are aware of the critics of this practice (Ekkekakis, 2015). Other systematic reviews have come to the same conclusion and have included different control groups in their meta-analyses (Bailey et al., 2017; Carter, Morres, Meade, et al., 2016; Cooney et al., 2013).

Outcomes

The process of identifying important outcomes for this review was done in several ways. We checked the core outcome sets (COMET)(Williamson et al., 2017) and looked through other systematic reviews of this population. The choice of including more outcomes than the other systematic reviews has highlighted the lack of important outcomes. This may inspire researchers to address these gaps in future studies (O'Connor et al., 2011). More attention is now given to outcomes that are important to the people involved. Another initiative that involves stakeholders is the James Lind Alliance, which brings patients, carers, and clinicians together in a consensus process to identify and prioritize unanswered questions or evidence uncertainties (Cowan & Oliver, 2018).

The Literature searches

One of the main strengths of this review is the comprehensive systematic literature search. Ten bibliographic databases within medicine, psychology, healthcare, and sports science were searched. The choice of databases was based on recommendations in the Cochrane handbook and the Campbell Methods guide (Kugley et al., 2017; Lefebvre et al., 2011). The search strategies were designed based on the rich terminology of the subject. A wide range of search terms was applied to minimize the risk of missing relevant trials which is also one of the recommendations of the Cochrane Handbook (Lefebvre et al., 2011, chapter 6.4.6). Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivitymaximizing version, was implemented (Lefebvre et al., 2011).

Furthermore, unpublished and grey literature were also searched to minimize publication bias that can threaten the validity of the review (Sterne et al., 2011, chapter 10.3.2). Bibliographies of included trials and previous systematic reviews were screened for relevant trials. The initial MEDLINE search strategy was peer-reviewed by two librarians independently, using the PRESS checklist (McGowan et al., 2016). Peer-reviewing search strategies, especially for systematic reviews, are recommended to identify search errors and improve the selection of search terms (McGowan et al., 2016).

A search update was carried out after the initial search, but no new eligible trials were found. At the time of submission of this thesis, only five months have passed since the update search which is shorter than in most systematic reviews (Beller, Chen, Wang, & Glasziou, 2013). We received e-mail alerts from the main databases when new references that matched our search strategy are added. There is however a chance that we have missed a newly published study.

No language restriction was applied in the searches, and during the study selection process we found several trials on the subject from China, Iran, and Germany. Therefore, we could have considered searching in country-specific databases.

As a sign of the thorough systematic literature search, we included one trial that has not been included in any other systematic review on this topic, as far as we know (Burrus, 1984).

Study selection

The study selection was carried out independently by two review authors, according to the method of systematic reviews (Higgins & Deeks, 2011, chapter 7.2.3). The comprehensive literature search resulted in a very large number of references (11007 records after removal of duplicates) that we screened for eligibility. This was a time-consuming process. All retrieved references were screened in Covidence, a user-friendly web-based screening tool which minimizes the risk of excluding a trial by mistake. Using Covidence is both time saving compared to other screening methods and helps manage the whole screening process,

especially with the high number of references. Having a protocol with clear inclusion and exclusion criteria, eased the study selection process and made it more consistent.

A limitation of this review is that neither of the review authors are professional experts on exercise nor mental health in children and adolescents. We were aware of this limitation and therefore checked more references that we were unsure about in full text rather than excluding them based on title and abstract. Additionally, we received assistance assessing the type of intervention in a few cases from a third reviewer (LL).

Risk of bias assessment

Risk of bias assessments were carried out by two review authors independently, according to the methods (Higgins et al., 2011). Since both authors were inexperienced in the risk of bias assessment, we compensated by independently assessing all the trials. We then discussed the results and resolved the discrepancies by consensus. The assessments were performed with the Cochrane risk of bias tool, and the assessments were also included in the data analyses and the conclusion of the review. Assessing internal validity in included trials and reflect on their impact of the results is essential in conducting a systematic review (Higgins et al., 2011), and strengthens the validity of this systematic review.

Data extraction

Data extraction of the included trials was performed independently by two reviewers. We developed a data extraction form based on the RevMan "characteristics of studies" form (The Cochrane Collaboration, 2014). We pilot tested the form with one of the included trials (Carter et al., 2015). The forms were then checked for compliance, before extracting data from the remaining trials. When preparing for data extraction, Cochrane Handbook recommends that all forms should be pilot tested (Higgins & Deeks, 2011).

Another strength of this review was the use of TIDieR, a standardized template, and checklist for the description of the interventions in included trials (Hoffmann et al., 2014). The TIDieR template consists of 12 items including the procedure, provider, mode of delivery, the adherence and fidelity of the intervention. By filling out the TIDieR tables for the

interventions, comparing the exercise interventions across the trials was more effortless and increased transparency.

Assessment of reporting bias

One limitation was that it was not possible to assess reporting bias in included trials due to a low number of included trials. To test for funnel plot asymmetry, at least ten trials are required (Sterne et al., 2011, chapter 10.4.3.1). Review authors should strive to asses the reporting bias because it can threaten the validity of the review (Sterne et al., 2011). To weigh up for this, we have attempted to search as extensively as possible, for grey literature, conference abstracts, and dissertations in various databases. We also searched trials registers to identify protocols of trials with unpublished results. We assume that the subject of this review is not of a high risk of reporting bias.

Data analysis

We were able to perform a meta-analysis by pooling the results of the primary outcome, postintervention depression, as all the four trials reported this outcome. Even though it was moderate heterogeneity between the studies, we assessed that it was appropriate. The difference of the control groups may explain the moderate heterogeneity in the analysis of this review.

The value of a meta-analysis in a review is an increase in power and the ability to detect if a real effect exists (Deeks et al., 2011, chapter 9.1.3). However, results of a meta-analysis can be misleading, and review authors should evaluate each step of the review process carefully before deciding if the data is appropriate to pool the studies in a meta-analysis (Deeks et al., 2011). Unfortunately, the other outcomes, depression at follow-up and quality of life was only measured in one trial, and we were therefore not able to pool these outcomes.

Certainty of the evidence (GRADE)

For assessing certainty of the evidence, we used the GRADE approach, that is by far the most widely used method (Goldet & Howick, 2013). The GRADE assessments are subjective and challenging. We independently graded all outcomes, discussed and resolved the discrepancies to improve the GRADE assessments.

Comparison with other systematic reviews

The main result of our systematic review is that there is a moderate effect of exercise on depression severity in adolescents with depression. These findings are consistent with the results of the previous systematic reviews, despite the differences in inclusion criteria. Several of the earlier reviews had, e.g., included participants both with and without depression, unlike our review that only included participants with depression. We also identified two dissertations that were not included in any of the earlier reviews.

Implications for future research

Large, high-quality trials including children and adolescents with depression are needed. Adequate numbers of participants should be recruited to detect a difference between the groups and to reduce the risk of bias. The trials need to have a longer follow-up time to assess long-term effectiveness. The comparison groups should be offered either treatment as usual or other recommended treatments for depression (e.g., cognitive behaviour therapy). Studies, where exercise is an add-on to other treatments, are also needed since that is perhaps the most realistic in real-life situations. A wider range of outcomes should be measured in future trials. Adverse effects of exercise interventions and drop-out rate should also be adequately addressed.

Implications for practice

Exercise interventions may have a beneficial effect on the depression severity in adolescents with depression. However, the four included trials had a limited number of participants and had a high or unclear risk of bias. The overall certainty of the evidence is low or very low. The effect of exercise on social functioning or psychological well-being is not known. Adverse events were not addressed in any of the included trials, and it is therefore not known if exercise interventions can be harmful to children and adolescents with depression.

Conflict of interest / Declarations of interest

The authors have no known conflicts of interest to declare.

The authors received no specific funding for this work, but the work on this thesis has partly been done as a part of our work at the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP). The Centre has not influenced objectives, research question, methods or conclusions.

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APPENDIX I

PRESS 2015 Guideline Evidence-Based Checklist

McGowan, J., Sampson, M. S., D.M., Cogo, E., Foerster, V., & Lefebvre, C. (2016). PRESS Peer Review of Electronic Search Strategies : 2015 Guidelines Explanation and Elaboration (PRESS E&E). Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health.

Translation of the research question	Does the search strategy match the research question/PICO?		
	Are the search concepts clear?		
	Are there too many or too few PICO elements included?		
	Are the search concepts too narrow or too broad?		
	Does the search retrieve too many or too few records? (Please show number of hits per line.)		
	Are unconventional or complex strategies explained?		
Boolean and proximity operators (these vary based on search	Are Boolean or proximity operators used correctly?		
service)	Is the use of nesting with brackets appropriate and effective for the search?		
	If NOT is used, is this likely to result in any unintended exclusions?		
	Could precision be improved by using proximity operators (eg, adjacent, near, within) or phrase searching instead of AND?		
	Is the width of proximity operators suitable (eg, might adj5 pick up more variants than adj2)?		
Subject headings (database specific)	Are the subject headings relevant?		
	Are any relevant subject headings missing; for example, previous index terms?		

	Are any subject headings too broad or too narrow?
	Are subject headings exploded where necessary and vice versa?
	Are major headings ("starring" or restrict to focus) used? If so, is there adequate justification?
	Are subheadings missing?
	Are subheadings attached to subject headings? (Floating subheadings may be preferred.)
	Are floating subheadings relevant and used appropriately?
	Are both subject headings and terms in free text (see the following) used for each concept?
Text word searching (free text)	Does the search include all spelling variants in free text (eg, UK vs. US spelling)?
	Does the search include all synonyms or antonyms (eg, opposites)?
	Does the search capture relevant truncation (ie, is truncation at the correct place)?
	Is the truncation too broad or too narrow?
	Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?
	Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?
	Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded (database specific)?

	Should any long strings be broken into several shorter search statements?	
Spelling, syntax, and line numbers	Are there any spelling errors?	
	Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?	
	Are there incorrect line combinations or orphan lines (ie, lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?	
Limits and filters	Are all limits and filters used appropriately and are they relevant given the research question?	
	Are all limits and filters used appropriately and are they relevant for the database?	
	Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?	
	Are sources cited for the filters used?	

PROSPERO APPENDIX II

International prospective register of systematic reviews

Exercise for depression in children and adolescents: a systematic review of randomized controlled trials

Brynhildur Axelsdottir, Solvi Biedilae, Lillebeth Larun, Lena Viktoria Nordheim, Ase Sagatun

Citation

Brynhildur Axelsdottir, Solvi Biedilae, Lillebeth Larun, Lena Viktoria Nordheim, Ase Sagatun. Exercise for depression in children and adolescents: a systematic review of randomized controlled trials. PROSPERO 2018 CRD42018101982 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018101982

Review question

What are the effects of exercise interventions in children and adolescents with depression?

Searches

We will search a wide range of bibliographic databases within medicine, psychology, healthcare and sports science, including 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.

We will not apply any limits on year, language or publication type.

We will search for grey literature in OpenGrey (www.opengrey.eu/). We will search for dissertations and theses in Dissertations and Theses (ProQuest). We will also search for conference abstracts in Web of Science, PsycINFO (Ovid), ERIC (EBSCO) and Proceedings (OCLC). In addition, we will search the trial registers ClinicalTrials.gov (www.ClinicalTrials.gov) and WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) for ongoing and unpublished trials.

We will contact experts in the field, authors of included studies and professional organizations and associations for information about ongoing or unpublished studies. We intend to screen the bibliographies of all included studies for further relevant studies.

Types of study to be included

Randomized controlled trials

Condition or domain being studied

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, 2017). Depression is one of the five leading causes of disability and is projected to become the second leading contributor to the global burden of disease by the year 2020 (GBD Disease and Injury Incidence and Prevalence Collaborators, 2017).

Depression in adolescence can cause problems at school, with friends, and in the family. It may have adverse effects on educational attainment and later employment status Severe depression can lead to suicide (World Health Organization, 2017).

The severity of depression is divided into following categories: mild, moderate or severe depression (NICE, 2005).

Participants/population

Children and adolescents (6-18 years) with depression

Intervention(s), exposure(s)

Exercise interventions, e.g., running, circuit training or weight lifting

Comparator(s)/control

Other treatments: Psychological therapies, pharmacological treatments, alone or in combination, treatment as usual or other alternative treatments.

No treatment: Waiting list or a non-intervention group

Context

Main outcome(s)

 Depression: The primary outcome is a measure of depression at the outcome assessment, either as a continuous measure or as a dichotomous outcome. Depression should be measured by self-report, health personnel report, parent report and/or teacher report with a standardized procedure. A variety of assessment tools are used to measure depression in children and adolescents. Examples of validated and commonly used tools are Beck Depression Inventory (BDI) and Children's Depression Inventory (CDI).
 Adverse events: reported in any way (e.g., using reporting systems such as Serious adverse reactions (SARs).

Timing and effect measures

We will include data from the end of treatment and if possible any long-term follow-up. We will attempt, if appropriate, to group the outcomes by follow-up.

We will start by identifying the data for the outcome measures from the included studies. We will present the results for each outcome and comparison. We will report 95% confidence intervals and p-values where possible. Dichotomous outcomes will be reported as relative risk and risk difference. Continuous outcomes will be reported as mean difference (MD), and standardized mean difference (SMD) since the outcomes might be measured using different instruments across the included studies

Additional outcome(s)

1. Psychological well-being: measured using any validated scale (e.g., KIDSCREEN and Child Health Questionnaire (CHQ).

2. Social functioning: measured using any validated scale (e.g., Child and Adolescents Social and Adaptive Functioning Scale (CASAFS).

3. Quality of life (QOL): measured using any validated scale (e.g., The Pediatric Quality of Life Inventory (PedsQL).

4. Acceptability measured as dropouts

Timing and effect measures

We will include data from the end of treatment and if possible any long-term follow-up. We will attempt, if appropriate, to group the outcomes by follow-up.

We will start by identifying the data for the outcome measures from the included studies. We will present the results for each outcome and comparison. We will report 95% confidence intervals and p-values where possible. Dichotomous outcomes will be reported as relative risk and risk difference. Continuous outcomes will be reported as mean difference (MD), and standardized mean difference (SMD) since the outcomes might be measured using different instruments across the included studies.

Data extraction (selection and coding)

Two authors (SB and BA) will independently screen the references. Any disagreements will be resolved by discussion. If needed, a third author will be asked to participate in a final decision.

Two authors (SB and BA) will independently extract data from the included studies. We will extract the following data from the included studies:

• Methods: study design, study location, study setting

• Participants: number, age, gender, severity of depression, comorbidity, inclusion and exclusion criteria, drop-outs

• Interventions: type of exercise, intensity, duration, frequency, number of sessions, setting, intervention provider, modes of delivery, control intervention(s). For extracting data about the interventions, we will use

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the template for intervention description and replication (TIDieR) checklist and guide (Hoffmann et al., 2014).

• Outcomes: primary and secondary outcomes at baseline, at the completion of the intervention and any follow-up measurements

• Notes: funding, conflict of interest

We will pilot test the data extraction form using one of the included studies, and if necessary, make adjustments to the form.

If any of the included studies are missing data, we will contact the study authors to obtain additional information.

Risk of bias (quality) assessment

Two authors (SB and BA) will independently assess the quality of the included studies using the Cochrane Collaboration Risk of Bias Tool by the following criteria:

- 1. Sequence generation
- 2. Allocation concealment
- 3. Blinding of participants and care providers
- 4. Blinding of outcome assessors
- 5. Incomplete outcome data
- 6. Selective outcome reporting
- 7. Other sources of bias

We will evaluate each criterion as either "high," "unclear" or "low" risk of bias.

Strategy for data synthesis

We will perform a meta-analysis to synthesize the results if appropriate.

If a meta-analysis is inappropriate because of the heterogeneity of the included studies, we will carry out a narrative synthesis where we present the results in text and tables. We will use CRD's framework for narrative synthesis (Centre for Reviews and Dissemination, 2009)

Analysis of subgroups or subsets

If suitable and we have the adequate number of studies, we will perform subgroup analyses for the primary outcomes. We will consider the following variables:

- Intensity of exercise.
- Type of exercise.

Contact details for further information

Brynhildur Axelsdottir ba@r-bup.no

Organisational affiliation of the review Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP Oslo) http://www.r-bup.no/no

Review team members and their organisational affiliations

Ms Brynhildur Axelsdottir. Centre for Child and Adolescent Mental Health, Oslo Norway (RBUP Oslo) Ms Solvi Biedilae. Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP
PROSPERO International prospective register of systematic reviews

Oslo)

Dr Lillebeth Larun. Norwegian Institute of Public Health, Division of Health Services Ms Lena Viktoria Nordheim. Centre for Evidence-Based Practice, Western Norway University of Applied Sciences Dr Ase Sagatum, Centre for Child and Adelescent Mental Health, Eastern and Southern Norway (PBLIP)

Dr Ase Sagatun. Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP Oslo)

Type and method of review Intervention, Meta-analysis, Systematic review

Anticipated or actual start date 02 April 2018

Anticipated completion date 01 May 2019

Funding sources/sponsors Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP Oslo)

Conflicts of interest

Language English

Country Norway

Stage of review Review Ongoing

Subject index terms status Subject indexing assigned by CRD

Subject index terms

Adolescent; Child; Depression; Depressive Disorder; Exercise; Humans; Randomized Controlled Trials as Topic

Date of registration in PROSPERO 20 July 2018

Date of publication of this version 20 July 2018

Details of any existing review of the same topic by the same authors

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). doi:10.1002/14651858.CD004691.pub2

Stage of review at time of this submission

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Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions 20 July 2018

PROSPERO

This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. The registrant confirms that the information supplied for this submission is accurate and complete. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

APPENDIX III

Aerobic exercise as treatment of depressive symptoms in early adolescents

T DieR

Aerobic exercise as treatment of depressive symptoms in early adolescents

Why:	Is it possible to effectively treat moderate depressive symptoms in early adolescents with a short-term aerobic exercise program in a school setting?
What (material):	N/A
What (procedures):	Treatment consisted of a walking-running program designed to increase the aerobic fitness of participants. The certified physical education instructor taught the students how to monitor their heart rate. During exercise treatment heart rate was monitored every five minutes in order to try to keep participants heart rates between 60-85% of maximum capacity. Students attempted to maintain a heart rate with a minimum of approximately 130 to 135 heart beats per minute.
Who provided:	The instructor was a certified physical education instructor at the junior high school.
How (mode of delivery; individual or group):	Group training.
Where:	In the school gym.
When and how much:	Participants in the exercise treatment group met on Monday, Wednesday and Friday during a six-week period for 20-minute sessions.
Tailoring:	N/A
Modification:	N/A
How well (planned):	Treatment integrity was monitored by the author trough random weekly visits to the treatment class.
How well (actual):	N/A

Effects of a running treatment program on depressed adolescents

T DieR

Effects of a running treatment program on depressed adolescents

Why:	To investigate the effects of a running treatment program on depressed adolescents.
What (material):	Each participant was given an general information about jogging in the heat (Appendix D in the Thesis) As well as the suggested schedule for the eight week running program (Appendix E in the Thesis). https://scholarlyrepository.miami.edu/dissertations/1432/
What (procedures):	The program included a walk-jog-run for thirty-five minutes. The participants gradually increased their pace so that their heart rate reached 75% of maximum cardiac output. They were encouraged to move in such a way that they were never gasping for air and were therefore able to converse.
Who provided:	instructors were highly trained and experienced in their respective fields.
How (mode of delivery; individual or group):	Group training.
Where:	On the physical education field of the high school.
When and how much:	Each group met for forty-five minute sessions, four times per week for a duration of nine weeks.
Tailoring:	Each individual ran at a pace and distance commensurate with fitness level.
Modification:	N/A
How well (planned):	N/A
How well (actual):	N/A

Preferred intensity exercise for adolescents receiving treatment for depression

T DieR

Preferred intensity exercise for adolescents receiving treatment for depression

Why:	To determine the effectiveness of a preferred intensity exercise intervention on the depressive symptoms of adolescents with depression
What (material):	N/A
What (procedures):	The circuit-training comprised of an interval pattern with eight separate exercise-stations. The stations consisted of strengthening and aerobic exercises: abdominal and back exercises from the supine and prone positions respectively; two medicine ball arm-based exercises from supine position; bouncing, static and dynamic balance exercises on a trampoline; body-weight squat exercise against the wall and stationary cycling. Following five minutes of stretching on major muscle groups in the upper and lower limbs, participants were encouraged to exercise for one minute then break for one minute, this was then repeated twice more.
Who provided:	A qualified exercise therapist supervised each session. Two additional staff members of the project exercised and interacted with participants in all sessions including the first author.
How (mode of delivery; individual or group):	Group-based (six to eight participants).
Where:	N/A
When and how much:	The intervention was a six week circuit-training consisting of 12 separate sessions which were run twice weekly. The total duration of each session was one hour (approximately 45 min of exercise and stretching). No pressure was applied to participants to attend the sessions.
Tailoring:	Preferred intensity was operationalised as follow: Participants could choose the order in which they undertook the different exercises as well as intensity in which they exercised on each station. They could choose to take rests when they wanted.
Modification:	N/A
How well (planned):	N/A
How well (actual):	N/A

T DieR

Intermittent walking in water on the severity of depression

Why:	To determine the effect of a six-week intermittent walking in the water on the rate of 24-hour urine MHPG sulfate and the severity of clinical depression in depressed girls.
What (material):	N/A
What (procedures):	A pool walking exercise program. 60-70% of maximum heart rate.
Who provided:	N/A
How (mode of delivery; individual or group):	N/A
Where:	The pool walking exercise was carried out in a pool with 15 meters width. The water height in the pool was considered as much as 70-80% of the cases height.
When and how much:	Pool walking exercise was implemented for 6 weeks and 3 sessions every week. The participants in the experimental group walked a total of 14.850 meters during 18 sessions. Generally the participants exercised two times daily during the first week, but for the next weeks they exercised three times daily.
Tailoring:	The experimental group were divided to some subgroups and in each subgroup, those who had similar VO2 max walked in the water with equal intensity and rhythm. After every set, the activity intensity was controlled with pulse rate.
Modification:	N/A
How well (planned):	N/A
How well (actual):	N/A

APPENDIX IV

List of ongoing trials

Principal investigator	Name of trial	Trial identifier	Institution	Status/date of last update posted
De Volder, Anne G.	Move and Feel Good : Effects of Intensive Physical Training on Brain Plasticity, Cognition and Psychological Well-being. (Move&FG)	NCT02970825	Université catholique de Louvain Brussels, Belgium	Recruiting/ May 14, 2018
https://clinicaltrials.gov/ct2/show/NCT02970825?titles=Move+and+Feel+Good&rank=1 Study Type : Interventional (Clinical Trial) Estimated Enrollment : 100 participants Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment Official Title: Move and Feel Good : Effects of Intensive Physical Training on Brain Plasticity, Cognition and Psychological Well-being. "Effets de l'entraînement Physique Intensif Sur la plasticité cérébrale, la Cognition et le Bien être Psychologique". Study Start Date : September 2016 Estimated Primary Completion Date : November 2018 Estimated Study Completion Date : December 2019				

Principal investigator	Name of trial	Trial identifier	Institution	Status/date of last update posted
Oberste, M.	Effects of a 6-week, whole- body vibration strength-	DRKS00011772 German Clinical	Medical Center Kinder- und	Recruiting ongoing/?
	training on depression symptoms, endocrinological	Trials Register	Jugendpsychiatrie der Uniklink	
	and neurobiological parameters in adolescent		Köln	
	inpatients experiencing a major depressive episode			
	(the "Balancing Vibrations Study"): study protocol for a			

	randomized placebo- controlled trial			
https://trialsjourn https://www.drk	nal.biomedcentral.com/articles/ s.de/drks_web/navigate.do?navi	10.1186/s13063-01 igationId=trial.HTM	<u>8-2747-8</u> /IL&TRIAL_ID=DR	KS00011772
https://www.drks.de/drks_web/navigate.do?/navigationId=trial.HTML&TRIAL_ID=DRKS00011772 DRKS-ID: DRKS00011772 Date of Registration in DRKS: 2017/03/20 (Anticipated or Actual) Date of First Enrollment: 2017/05/22 Target Sample Size: 82				

Principal investigator	Name of trial	Trial identifier	Institution	Status/date of last update posted
Lin, Kangguang	A Study of Aerobic Exercise for Adolescents with Subthreshold Mood Syndromes	NCT03300778	Guangzhou Brain Hospital Guangzhou, Guangdong	Completed/August 23, 2018
Study Type : Actual Enrolln Allocation: Intervention M Masking: Primary Purpo Official Title: Subthreshold I Actual Study S Actual Primary Actual Study C	Interventional (Clinical Tr nent : 224 participants Randomized odel: Parallel Assignmen Double (Investigator, Outc se: Treatment A Randomised Controlled Depressive and/or Hypoman Start Date : October 10, Completion Date : Janu Completion Date : Janu	t omes Assessor) Trial of Aerobic I nic Syndrome and 2017 ary 5, 2018 ary 12, 2018	Exercise for Ad	dolescents With cal Adolescents

Principal investigator	Name of trial	Trial identifier	Institution	Status/date of last update posted
Dopp, R. R.	Exercise as Treatment	NCT00964054	National	Completed/March
	for Adolescents with		Institute of	14, 2013
	Depressive Disorders		Mental	
			Health	
			(NIMH)	
			USA	

Study Type : Interventional (Clinical Trial)
Actual Enrollment : 9 participants
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double (Investigator, Outcomes Assessor)
Primary Purpose: Treatment
Official Title: Adapting Exercise Treatment for Depression to Adolescents: A Pilot Study
Study Start Date : September 2012
Actual Primary Completion Date : January 2013
Actual Study Completion Date : February 2013

APPENDIX V

List of excluded trials with reason for exclusion

References	Notes
5-HTTLPR and MTHFR 677C>T polymorphisms and response to yoga-based lifestyle intervention in major depressive disorder: A randomized active-controlled trial. 2018. 60. 4. 410-426	Exclusion reason: Adult population
Cutting edge. 2007. Journal of the Royal Society for the Promotion of Health. 127. 6. 251-252	Exclusion reason: Wrong study design
Exercise doesn't protect against adolescent depression. 2014. Brown University Child & Adolescent Psychopharmacology Update. 16. 12. 1-3	Exclusion reason: Wrong study design
PORÓWNANIE ZACHOWAN ANOREKTYCZNYCH GIMNAZJALISTEK ZE SZKÓŕ SPORTOWYCH I NIESPORTOWYCH. 2009. Polish Journal of Sports Medicine / Medycyna Sportowa. 25. 6. 368-376	Exclusion reason: Wrong study design
Abdollahi, A. LeBouthillier, D. M. Najafi, M. Asmundson, G. J. G. Hosseinian, S. Shahidi, S. Carlbring, P. Kalhori, A. Sadeghi, H. Jalili, M. Effect of exercise augmentation of cognitive behavioural therapy for the treatment of suicidal ideation and depression. 2017. Journal of Affective Disorders. 219. 58-63	Exclusion reason: Adult population
Abenza, Lucia Olmedilla, Aurelio Ortega, Enrique Ato, Manuel Garcia-Mas, Alejandro. Analysis of the relationship between mood states and adherence behavior in injured athletes. 2010. Anales de Psicologia. 26. 1. 159-168	Exclusion reason: Wrong study design
Alharthi, Rajwa Saddik, Abdulmotaleb El. Exerlearn bike: An exergaming system for children's educational and physical well-being. 2012. 128	Exclusion reason: Wrong patient population
Annesi, J. J. Improvements in self-concept associated with reductions in negative mood in preadolescents enrolled in an after-school physical activity program. 2005. Psychological Reports. 97. 2. 400-404	Exclusion reason: Prevention
Annest, J. J. Correlations of depression and total mood disturbance with physical activity and self-concept in preadolescents enrolled in an after- school exercise program. 2005. Psychological Reports. 96. 3. 891-898	Exclusion reason: Wrong study design
Anonymous. 2013 SYR Accepted Poster Abstracts. 2013. International journal of yoga therapy. 23 Suppl. 32-53	Exclusion reason: Prevention
Ardic, Aysun Erdogan, Semra. The effectiveness of the COPE healthy lifestyles TEEN program: A school-based intervention in middle school adolescents with 12-month follow-up. 2017. Journal of Advanced Nursing. 73. 6. 1377-1389	Exclusion reason: Prevention
Atousa, G. D. Uzunboylu, H. Cavus, N. The effect of ten weeks individual and group training on the level of depression in female students of Islamic Azad University Ahvaz branch. 2009. 1. 1. 2637-2641	Exclusion reason: Adult population
Balchin, R. Linde, J. Blackhurst, D. Rauch, H. L. Schonbachler, G. Sweating away depression? The impact of intensive exercise on depression. 2016. Journal of Affective Disorders. 200. 218-21	Exclusion reason: Adult population

Balkin, Richard S. Tietjen-Smith, Tara Caldwell, Charmaine Shen, Yu-Pei.	Exclusion reason:
Ine Utilization of Exercise to Decrease Depressive Symptoms in Young	Adult population
Adult Women. 2007. ADULISPAN Journal. 6. 1. 30-35	
	Adult nonulation
NA OLIALIDADE VIDA NO TRATAMENTO DA DEDRESSÃE ALONGAMENTO	Addit population
$FAUCA \delta \delta fo E \delta sica am Bavista A 3 1-15$	
Barbasa Eilba V. C. Lones Ada S. Lima A. B. de Souza E. A. Gubert Edo, A.	Evolution reason:
Silva K S Vieira N E Trompieri Filbo N de Arquio T S de Bruin P E	Drevention
Mota Fortaleca sua Saude" Working Group Rationale and methods of	
a cluster-randomized controlled trial to promote active and healthy	
lifestyles among Brazilian students: the "Fortaleca sua Saude" program.	
2015. BMC Public Health, 15, 1212	
Barnow. Sven Bernheim. Dorothee Schroder. Carmen Lauffer. Heinz	Exclusion reason:
Fusch, Christoph Freyberger, Harald- I. Obesity in Childhood and	Prevention
Adolescence: First Results of a Multimodal Intervention Study in	
Mecklenburg-Vorpommern. 2003. PPmP: Psychotherapie Psychosomatik	
Medizinische Psychologie. 53. 1. 7-14	
Bar-Or, Oded Rowland, Thomas W. Emotional and Mental Disorders.	Exclusion reason:
2004	Wrong study design
Bartholomew, Jb Morrison, D Ciccolo, Jt. Effects of acute exercise on	Exclusion reason:
mood and well-being in patients with major depressive disorder. 2005.	Adult population
Medicine and Science in Sports and Exercise. 37. 12. 2032-2037	
Bass, M. A. Enochs, W. K. DiBrezzo, R. Comparison of two exercise	Exclusion reason:
programs on general well-being of college students. 2002. Psychological	Adult population
Reports. 91. 3. 1195-1201	
Battaglia, C. di Cagno, A. Fiorilli, G. Giombini, A. Borrione, P. Baralla, F.	Exclusion reason:
Marchetti, M. Pigozzi, F. Participation in a 9-month selected physical	Adult population
exercise programme enhances psychological well-being in a prison	
population. 2015. Criminal Behaviour and Mental Health. 25. 5. 343-354	
Beets, M. W. Mitchell, E. Effects of yoga on stress, depression, and health-	Exclusion reason:
related quality of life in a nonclinical, bi-ethnic sample of adolescents: a	Prevention
pilot study. 2010. Hispanic Health Care International. 8. 1. 47-53	
Beffert, Jerry Wayne. Aerobic exercise as treatment of depressive	Exclusion reason:
symptoms in early adolescents. 1993 9404228. 166	Duplicate
Beltran, M Brown-Einiliali, A Heid, A Ryce, P Otonedu, Me Hoover, D	Exclusion reason:
Ensor, K Beicher, Hitle. Yoga-based psychotherapy groups for boys	wrong study design
Health and Medicine 22, 1, 20-46	
Renavides S Caballero I. Ashtanga yoga for children and adolescents for	Evolution reason:
weight management and nsychological well being: An uncontrolled open	Wrong study design
nilot study 2009 Complementary Theranies in Clinical Practice 15.2	wrong study design
110-14.	
Benhaberou-Brun, Dalila, [The benefits of physical activity], 2012.	Exclusion reason:
Perspective Infirmiere. 9. 4. 22-25	Wrong study design
Berger, B. G. Exercice physique et reduction du stress. / Physical exercise	Exclusion reason:
and stress reduction. 1987. Science & Motricite. 3. 25-29	Prevention
Berger, B. G. Owen, D. R. Mood alteration in yoga and swimming: aerobic	Exclusion reason:
exercise not necessary. 1989. Unpublished Paper. [1-23]	Adult population
Berger, B. G. Owen, D. R. Stress reduction and mood enhancement in four	Exclusion reason:
exercise modes: swimming, body conditioning, Hatha yoga, and fencing. /	Wrong study design

Reduction du stress et amelioration de l ' humeur dans quatre types d ' exercice: natation, culture physique, hatha yoga, escrime. 1988. Research Quarterly for Exercise & Sport. 59. 2. 148-159	
Berger, Bg Owen, Dr. Mood alteration with swimmingswimmers really do 'feel better'. 1983. Psychosomatic Medicine. 45. 5. 425-433	Exclusion reason: Adult population
Berger, Bonnie G. Owen, David R. Man, Frantisek. A brief review of literature and examination of acute mood benefits of exercise in Czechoslovakian and United States swimmers. 1993. International Journal of Sport Psychology. 24. 2. 130-150	Exclusion reason: Adult population
Berger, Bonnie G. Owen, David R. Mood alteration with Yoga and swimming: Aerobic exercise may not be necessary. 1992. Perceptual and Motor Skills. 75. 3, Pt 2. 1331-1343	Exclusion reason: Adult population
Bershadsky, S Trumpfheller, L Kimble, Hb Pipaloff, D Yim, Is. The effect of prenatal Hatha yoga on affect, cortisol and depressive symptoms. 2014. Complementary Therapies in Clinical Practice. 20. 2. 106-13.	Exclusion reason: Adult population
Bhagirathi, Sameer E. Mehtaa, Deepak. THE EFFECT OF YOGA ON SELECTED PHYSIOLOGICAL VARIABLES OF SCHOOL GIRLS LIVING IN MOST POLLUTED AND LEAST POLLUTED AREAS OF BHOPAL CITY. 2011. International Journal of Sports Sciences & Fitness. 1. 2. 150-159	Exclusion reason: Prevention
Blumenthal, J. A. New frontiers in cardiovascular behavioral medicine: Comparative effectiveness of exercise and medication in treating depression. 2011. VOL 78 SUPP/1. S35-S43	Exclusion reason: Adult population
Boeger, Annette Dorfler, Tobias Schut-Ansteeg, Thomas. Project adventure with adolescents: Influence on psychopathology and self- esteem. 2006. Praxis der Kinderpsychologie und Kinderpsychiatrie. 55. 3. 181-197	Exclusion reason: Prevention
Bonhauser, Marco Fernandez, Gonzalo Puschel, Klaus Yanez, Fernando Montero, Joaquin Thompson, Beti Coronado, Gloria. Improving physical fitness and emotional well-being in adolescents of low socioeconomic status in Chile: Results of a school-based controlled trial. 2005. Health Promotion International. 20. 2. 113-122	Exclusion reason: Prevention
Boone, Erin M. Leadbeater, Bonnie J. Game On: Diminishing Risks for Depressive Symptoms in Early Adolescence Through Positive Involvement in Team Sports. 2006. Journal of Research on Adolescence. 16. 1. 79-90	Exclusion reason: Wrong study design
Boyll, Jeffery R. The effects of active exercise and passive electronic muscle stimulation on self-concept, anxiety, and depression. 1986. Dissertation Abstracts International. 47. 5-B. 2219	Exclusion reason: Adult population
Branco, Jerônimo Costa Jansen, Karen Oses, Jean Pierre de Mattos Souza, Luciano Dias da Silva Alves, Giovanna Del Grande Lara, Diogo Rizzato da Silva, Ricardo Azevedo. Practice of leisure-time physical activities and episodes of mood alteration amongst men and women. 2014. 169.165- 169	Exclusion reason: Adult population
Brault, M. Fingerhut, R. Zelikovsky, N. Veltri, E. HEALTH LOCUS OF CONTROL, EXERCISE AND DEPRESSION IN COLLEGE STUDENTS. 2013. Annals of Behavioral Medicine. 45. S275-S275	Exclusion reason: Wrong study design
Brawner, Patricia S. Exercise as it relates to depression and locus-of- control. 1990. Dissertation Abstracts International. 50. 12-A, Pt 1. 3891	Exclusion reason: Adult population
Briggs, Jeralee M. Yoga as an ancillary treatment to acceptance and commitment therapy for depression. 2017. Dissertation Abstracts International: Section B: The Sciences and Engineering. 78. 4-B(E). No Pagination Specified	Exclusion reason: Adult population

Brollier, C. Hamrick, N. Jacobson, B. Aerobic exercise: A potential	Exclusion reason:
occupational therapy modality for adolescents with depression. 1993.	Wrong study design
Occupational Therapy in Mental Health. 12. 4. 19-29	
Brown, H. E. Whittle, F. Jong, S. T. Croxson, C. Sharp, S. J. Wilkinson, P.	Exclusion reason:
Wilson, E. C. F. van Sluijs, E. M. F. Vignoles, A. Corder, K. A cluster	Wrong outcomes
randomised controlled trial to evaluate the effectiveness and cost-	
effectiveness of the GoActive intervention to increase physical activity	
among adolescents aged 13-14 years. 2017. BMJ Open. 7. 9. 9	
Brown, Stella W. Welsh, M. Labbe, Elise E. Vitulli, William F. Kulkarni,	Exclusion reason:
Pandu. Aerobic exercise in the psychological treatment of adolescents.	Prevention
1992. Perceptual and Motor Skills. 74. 2, 555-560	
Brown Stella Watlington Welsh, M. Cay, Aerobic exercise in the	Exclusion reason:
psychological treatment of adolescents 1991 1344080 192	Dunlicate
Burrus Meredith lune THE EEECTS OF A BUNNING TREATMENT	Exclusion reason:
PROGRAM ON DEDRESSED ADOLESCENTS (AERORIC) 1984 8425890 190	Dunlicate
Proon John M. The effects of a cardiovascular fitness program on	Evolucion reaconu
depression, applied to the effects of a calculovascular fitness program of	Adult nonulation
uppression, anxiety, self-concept, and perceived physical niness in conege	Adult population
Wolflein, 1984. Dissertation Abstracts international. 45, 6-B. 1907	Fueles in a second
Cadenas-SAInchez, Civiora-Gonzaliez, Jivigueles, Jn Martan-Matilias, M	Exclusion reason:
GA ^s mez-vida, J Escolano-Margarit, MV Maldonado, J Enriquez, Gm Pastor-	Prevention
Villaescusa, B Teresa, C Navarrete, S Lozano, Rm Dios, Beas-JimA©nez J	
EstA©vez-LA°pez, F Mena-Molina, A Heras, MJ ChillA°n, P Campoy, C	
MuA±oz-HernAindez, V MartAnez-A• vila, Wd Merchan, Me Perales, Jc Gil,	
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Carmack, Cindy Lynn. Aerobic fitness and leisure physical activity as moderators of the stress-illness relation. 1996. Dissertation Abstracts International: Section B: The Sciences and Engineering. 57. 2-B. 1432	Exclusion reason: Wrong study design
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Duman, Marilyn. Aerobic exercise and mood disturbance in college women. 1993. Dissertation Abstracts International. 53. 7-B. 3770	Exclusion reason: Adult population
Dunn, A. L. Trivedi, M. H. O Neal, H. A. Physical activity dose-response effects on outcomes of depression and anxiety. 2003. VOL 33 NO 6 SUPPL. S587-S597	Exclusion reason: Wrong study design
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Felver, Joshua C. Butzer, Bethany Olson, Katherine J. Smith, Iona M.	Exclusion reason:
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Feuerstein, Lee William. The relationship of aerobic exercise and task	Exclusion reason:
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Finocchiaro, Melanie S. Schmitz, Catherine L. Exercise: A holistic approach	Exclusion reason:
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Forzani, Christina Ann. The experiences of adolescent females who	Exclusion reason:
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Frank, J. L. Kohler, K. Peal, A. Bose, B. Effectiveness of a School-Based Yoga	Exclusion reason:
Program on Adolescent Mental Health and School Performance: Findings	Prevention
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Frank, Jennifer L. Bose, Bidyut Schrobenhauser-Clonan, Alex. Effectiveness	Exclusion reason:
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Goldheid, G. S. Kenny, G. P. Alberga, A. S. Prud homme, D. Hadjiyannakis,	Exclusion reason:
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Psychology 36 4 357-365	
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M Ibanez P Koch F Martinez-Nicolas A Muntaner-Mas A Rommel A	Prevention
Rommelse N de Ruiter, S. Ebner-Priemer, U. W. Kieser, M. Ortega, E. B.	
Thome Buitelaar K Kuntsi Ramos-Ouiroga A Reif A Freitag (
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I Marsiglia E E The COPE healthy lifestyles TEEN randomized controlled	Prevention
trial with culturally diverse high school adolescents. Reseline	
characteristics and methods 2013 Contemporary Clinical Trials 36 1 41-	
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Shaihi Gabriel Improving physical activity mental health outcomes and	Adult nonulation
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NONPROFIL PROGRAM BENEFILS MENTAL REALTH FOR CHILDREN OF	Exclusion reason:
WOUNDED SERVICE MEMBERS. 2012. Exceptional Parent. 42. 3. 54-54	wrong study design
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Depression and Anyioty A Comparison to Transdiagnostic Cognitive	Adult nonulation
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Parker, A. G. Hetrick, S. E. Jorm, A. F. Yung, A. R. McGorry, P. D.	Exclusion reason:
Mackinnon, A. Moller, B. Purcell, R. The effectiveness of simple	Wrong intervention
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health problems in young people: A factorial randomised controlled trial.	
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Parker, Alexandra G. Hetrick, Sarah E. Jorm, Anthony F. Mackinnon,	Exclusion reason:
Andrew J. McGorry, Patrick D. Yung, Alison R. Scanlan, Faye Stephens,	Prevention
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Rashidi, M. Rashidy-Pour, A. Ghorbani, R. Diyant, H. Shanvarahian, M. The	Exclusion reason:
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anxiety in students. [Persian]. 2017. Roomesn. 19. 2. 555-540	
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Medical School. 30. 212.	Fuelester and an
Re, Pamela McConnell, John W. Reidinger, Gioria Schweit, Ronnie	Exclusion reason:
Hendron, Angela. Effects of Yoga on Patients in an Adolescent Mental	wrong study design
Realth Hospital and the Relationship Between Those Effects and the	
Patients Sensory-Processing Patierns. 2014. Journal of Child & Addiescent	
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Fitness Journal. 11. 3. 72-72	Adult population
Reigal Garrido, Rafael E. MÕ Rquez Casero, MarÕ A Victoria Videra	Exclusion reason:
GarcÕ A, Antonio MartÕ N Tamayo, Ignacio Ruiz De Mier, RocÕ O	Prevention
JuÕ Rez. Efecte agut de l'activitat fisicoesportiva i l'expressió corporal	
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African American girls: Stanford GEMS. 2010. Archives of Pediatrics &	
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Roth, David L. An experimental comparison of the cardiovascular and self-	Exclusion reason:
reported health effects of aerobic exercise and progressive relaxation.	Adult population
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life events. 1987. Psychosomatic Medicine. 49. 4. 355-365	
Rueter, M. A. Effects of running on individuals who are clinically	Exclusion reason:
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Alternative & Complementary Medicine. 20. 5. A55-A55	Adult population
Sarubin, N. Nothdurfter, C. Schule, C. Lieb, M. Uhr, M. Born, C.	Exclusion reason:
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Smith, Jay Andrew. Effects of yoga on stress among college students in a	Exclusion reason:
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St-Hilaire, Annie Marcotte, Diane. L'influence de la pratique d'un sport	Exclusion reason:
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Sturm, J. Ploderl, M. Fartacek, C. Kralovec, K. Neunnauserer, D.	Exclusion reason:
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Intervention in Depressive Mood of College Students, 2008, Journal of	Adult nonulation
Beijing Sport University 31 11 1534-1536	Addit population
Taylor Mark Gillies Robyn M. Ashman, Adrian F. Cognitive training	Exclusion reason:
conflict resolution and exercise: Effects on young adolescents' wellbeing	Wrong study design
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Tsiantoula, E. Tsiadoula, L. Patsiaouras, A. Kokaridas, D. Physical activity & depression. 2012. 4. 3. 83-90	Exclusion reason: Wrong study design
Tsumura, Hideki Shimada, Hironori. Effects of walking exercise on cognitive appraisal depressive mood, and attentional resources in self-focused attention. 2014. Japanese Journal of Health Psychology. 27. 2. 124-130	Exclusion reason: Wrong study design
Vancini, R. L. Rayes, A. B. R. Lira, C. A. B. Sarro, K. J. Andrade, M. S. Pilates and aerobic training improve levels of depression, anxiety and quality of life in overweight and obese individuals. 2017. Arquivos de Neuro- Psiquiatria. 75. 12. 850-857	Exclusion reason: Adult population
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Velazquez, Theresa. Health issues and the benefits of DanceSport. 2012. Dissertation Abstracts International Section A: Humanities and Social Sciences. 73. 4-A. 1297	Exclusion reason: Wrong study design
Wagener, T. L. Fedele, D. A. Mignogna, M. R. Hester, C. N. Gillaspy, S. R. Psychological effects of dance-based group exergaming in obese adolescents. 2012. Pediatric Obesity. 7. 5. e68-e74	Exclusion reason: Prevention
Wang, Chunyun. Improving health among elementary school children: A comparison of aerobic and mind-body exercise. 2013. Dissertation Abstracts International Section A: Humanities and Social Sciences. 74. 3-A(E). No Pagination Specified	Exclusion reason: Wrong outcomes
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Bloch, W. Zimmer, P. Graf, C. Schonau, E. Lehmkuhl, G. Bender, S. Fricke,	Wrong comparator
O. Whole body vibration added to treatment as usual is effective in	
adolescents with depression: a partly randomized, three-armed clinical	
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Wunram, Heidrun Lioba Hamacher, Stefanie Hellmich, Martin Volk, Maxi	Exclusion reason:
Janicke, Franziska Reinhard, Franziska Bloch, Wilhelm Zimmer, Philipp	Wrong comparator
Graf, Christine Schonau, Eckhard Lehmkuhl, Gerd Bender, Stephan Fricke,	
Oliver. Whole body vibration added to treatment as usual is effective in	
adolescents with depression: A partly randomized, three-armed clinical	
trial in inpatients. 2017. European Child & Adolescent Psychiatry. No	
Pagination Specified	
Zahn, William L. The effects of Tai Chi Chuan on mindfulness, mood, and	Exclusion reason:
quality of life in adolescent girls. 2009. Dissertation Abstracts	Prevention
International: Section B: The Sciences and Engineering. 69. 8-B. 5065	
Zhang, J. Qin, S. Zhou, Y. Meng, L. Su, H. Zhao, S. A randomized controlled	Exclusion reason:
trial of mindfulness-based Tai Chi Chuan for subthreshold depression	Adult population
adolescents. 2018. 14. 2313-2321	
Zhu, F. S. Yan, J. Effects of basketball exercise of low and moderate	Exclusion reason:
intensity on mental health of male college students. [Chinese]. 2006.	Adult population
Chinese Journal of Clinical Rehabilitation. 10. 20. 35-37	
Zhu, X. D. Li, Q. Y. Zhang, H. The Influence of Aerobics and Group Games	Exclusion reason:
for Male Teenager Compulsory Isolation Addicts' Mental Health	Prevention
Promotion. 2015. 48. 18-23	
Zwan, Je Vente, W Huizink, Ac Bögels, Sm Bruin, Ei. Physical activity,	Exclusion reason:
mindfulness meditation, or heart rate variability biofeedback for stress	Adult population
reduction: a randomized controlled trial. 2015. Applied Psychophysiology	
and Biofeedback. 40. 4. 257-268	

APPENDIX VI

Risk of bias assessments of included trials

Beffert 1993 Overall <mark>high risk of bias</mark>

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk 🗨	"Students who scored a 75 or higher on the second screening were then randomly assigned to either an aerobic exercise treatment group or a waitlist control group". (p. 84).
Allocation concealment (selection bias)	Unclear risk 🗨	No description found in text
Blinding of participants and personnel (performance bias)	Hiah risk 🗨	Owing to the nature of the intervention, it was not possible to conceal allocation to the intervention from participants or personnel.
Blinding of outcome assessment (detection bias)	Hiah risk 🗨	Self-report outcome measurement tool (RADS)
Incomplete outcome data (attrition bias)	Unclear risk 🗨	Precise numbers for drop-out was not reported
Selective reporting (reporting bias)	Unclear risk 🗨	No published protocol for the study available.
Other bias	Unclear risk 🗨	Unclear (wait-list control).

Burrus 1984 Overall <mark>high risk of bias</mark>

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk 🗨	"The students were assigned by a stratified [sic] random sampling procedure to a program of jogging, exercise, or Red Cross First Aid and Personal Safety." (p. 54). "Assignment to treatment groups was to be random. However, due to the variance found in levels of depression and levels of cardiovascular fitness, both variables were stratified and then statistically analyzed to ensure that the groups could be considered equivalent." (p. 53).
Allocation concealment (selection bias)	Unclear risk 🗨	No description found in text
Blinding of participants and personnel (performance bias)	Hiah risk 🗨	Owing to the nature of the intervention, it was not possible to conceal allocation to the intervention from participants or personnel.
Blinding of outcome assessment (detection bias)	Hiah risk 🗨	Self-report outcome measurement tool (DACL)
Incomplete outcome data (attrition bias)	Unclear risk 🗨	"during the second week of the study, one female withdrew from the running group due to medical reasons" (p. 48). "There was an attrition of only one student who, for medical reasons, dropped out of school" (p. 58).
Selective reporting (reporting bias)	Unclear risk 🗨	No published protocol for the study available.
Other bias	Unclear risk 🗨	Unclear

Carter 2015 Overall unclear risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk 🗨	The random allocation sequence was computer generated by the trial statistician using permuted block randomisation with varying block size.
Allocation concealment (selection bias)	Low risk 🗨	In order to ensure allocation concealment sequentially numbered opaque sealed envelopes were used. Individuals were randomised to groups by a researcher not connected to the study team.
Blinding of participants and personnel (performance bias)	Hiah risk 🖵	Owing to the nature of the intervention, it was not possible to conceal allocation to the intervention from participants or personnel.
Blinding of outcome assessment (detection bias)	Unclear risk 🗨	Self-rated outcome measurement tool (CDI- 2) Outcome assessors, including the data input administrator, were blind to treatment group at both follow up time points. The analysis was conducted on a data set in which group allocation was unlabelled.
Incomplete outcome data (attrition bias)	Unclear risk 🗨	In total, 87 young people were recruited and randomized across the two arms of trial; intervention (<i>n</i> =44), control (<i>n</i> =43). At post intervention the total loss to follow up was 25 %, with more participants dropping out in the control arm than the intervention.» «At six months, the total loss to follow up was 51% with a higher dropout rate in the control compared to the intervention arm.» « 8 participants (18.1 %) attended no exercise sessions. The reason for non- engagement of these 8 participants was mostly unknown as the majority were non- contactable. Only 3 participants gave

		reasons for non-engagement; exam pressure, high levels of anxiety and feeling too low in mood.
Selective reporting (reporting bias)	Low risk 🗨	Protocol is available, ClinicalTrials.gov Identifier: NCT01474837. All of the study's pre-specified outcomes have been reported in the pre-specified way.
Other bias	Low risk 🗨	Trial appears to be free of other problems that could put it at high risk of bias.

Roshan 2011 Overall <mark>high risk of bias</mark>

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk 🗨	"They were divided randomly into experimental group (12 cases) or control group (12 cases)."
Allocation concealment (selection bias)	Unclear risk 🗨	No description found in text
Blinding of participants and personnel (performance bias)	Hiah risk 🗨	Owing to the nature of the intervention, it was not possible to conceal allocation to the intervention from participants or personnel.
Blinding of outcome assessment (detection bias)	Unclear risk 🗨	Clinician-rated outcome measurement tool (HAM-D)
Incomplete outcome data (attrition bias)	Unclear risk 🗨	No description found in text
Selective reporting (reporting bias)	Unclear risk 🗨	Retrospective registration of study protocol (2011-08-30).
Other bias	Unclear risk 🗨	Unclear (wait-list control)

Exercise for Depression in Children and Adolescents: A Systematic Review and Meta-analysis

Article manuscript

Master's students: Sølvi Biedilæ and Brynhildur Axelsdóttir Master's program: Master in Evidence-Based Practice in Health Sciences Faculty: Faculty of Health and Social Sciences Institution: Western Norway University of Applied Sciences Journal for submission of the article manuscript: PLoS One Total number of words: 4710

Exercise for Depression in Children and Adolescents: A Systematic Review and Meta-analysis

Brynhildur Axelsdottir, Sølvi Biedilæ. Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP).

Abstract

The objective of this systematic review was to examine the effects of exercise interventions as treatment of depression in children and adolescents compared to other treatments or no treatment. A study protocol was registered in PROSPERO (CRD42018101982). The bibliographic databases 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 inception to December 2018 for randomized controlled trials. Databases for grey literature, dissertations, and trials registers were also searched. The search strategy was developed using a wide range of search terms, both index terms, and text words, for depression, children and adolescents, exercise and study design and adapted to each database. Two authors independently screened references, extracted data and assessed the quality of the included trials with the Cochrane Risk of Bias tool. The certainty of the evidence was assessed using the Grading of Recommendations Assessments, Development, and Evaluation (GRADE) approach. Four trials (n=143) were included. A meta-analysis with a random effect model was performed, and a moderate effect in favour of exercise on depression severity post-intervention was identified (SMD = -0.59, 95% CI = -1.11, to -0.07, p=0.03). However, the trials were assessed as having an unclear or high risk of bias, and the overall certainty of the evidence for this outcome was graded as low. The severity of depression at six months follow-up was reported in one trial. The overall certainty of the evidence for this outcome was graded as very low. None of the trials commented on the presence or absence of adverse events. Exercise appears to be a promising intervention for children and adolescents with depression, but large, highquality trials with a longer follow-up time are needed.
Introduction

Depression is a mental disorder, characterized by persistent sadness and a loss of interest in and ability to carry out daily activities [1]. Depression is a major public health problem and one of the most common psychiatric disorders in children and adolescents. [2, 3]. Worldwide, depression is the leading cause of years lost due to disability (YLDs) in females aged 15-24 years, and the third leading cause in adolescent males [4]. The one-year prevalence of depression in adolescents was estimated to be 5.6% in a systematic review, and for children under thirteen-year-old, the one-year prevalence was 2.8% [5]. Depression is more common in girls [5, 6].

Depression in childhood and adolescence can disturb the social and familial connections and education, with life long effects on employment and social status [7, 8]. Severe depression can lead to suicide [9].

Established treatments for depression in children and adolescents are psychological therapies, and in severe cases, antidepressant medications [2, 10, 11]. These treatments, however, have modest effects, high relapse rates, are not acceptable or available to all patients, and antidepressant medications have adverse effects [12-16]. It is therefore important to investigate alternative or adjunct treatments. Exercise is one treatment that shows promising results in adults with depression [17].

Four reviews on the effects of physical activity or exercise on depressive symptoms in children, adolescents, and young people have been published in the past few years [18-21]. Additionally, a Cochrane review was published in 2006 [22]. These reviews all found a small to moderate effect of exercise on the reduction of depression.

None of these reviews have looked at adverse events. It is vital to investigate whether exercise can be harmful to this population. Quality of life is another important outcome that is not covered in the reviews. The four recent reviews all excluded and did not search for non-English language studies and studies not published in peer-reviewed journals [18-21]. This can lead to biased results [23]. Some of these reviews have included trials on participants both with and without depression (e.g., whole school classes or at-risk participants that did not have depression). The inclusion criteria for interventions are in some of the reviews, physical activity, in others exercise (without a definition) or both. Some of the reviews have also included trials where the comparison group received another type or intensity of exercise.

In this review only trials where the participants had depression were included, the intervention was exercise, and the control groups received a non-exercise treatment or no treatment. Adverse events and quality of life as outcomes were included. Trials published in all languages, all publication types, and non-published trials were searched for, and assessed for inclusion to reduce the risk of biased results.

The objective of this systematic review was to summarize studies on the effects of exercise interventions as treatment of depression in children and adolescents compared to other treatments or no treatment.

Methods

The Cochrane Collaboration methodology for conducting systematic reviews was followed [24]. The reporting is according to the PRISMA guidelines [25]. The PRISMA checklist is available in Supplementary S1. The protocol for the systematic review is registered in PROSPERO [26]. CRD42018101982

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018101982

Selection criteria

In this systematic review only randomized controlled trials (RCTs), both parallel, cluster or individual RCTs, or the first phase of cross-over trials, were included.

The participants in the included trials must be children and adolescents between 6 and 18 years with depression. Trials, where the author defined the participants as having depression (by any method of diagnosis and with any severity of depression), were included.

Trials that include children and adolescents with psychotic or borderline conditions, autism, physical handicaps, eating disorders and/or chronic or serious somatic diseases were excluded.

Trials where the exercise intervention falls within the American College of Sports Medicine definition of exercise: "planned, structured and repetitive bodily movement done to improve and/or maintain one or more components of physical fitness" were included [27]. All types of exercise were included, both aerobic, anaerobic, resistance, flexibility, and mixed fitness training. Group-based or individual exercise and supervised or unsupervised programs were

included. The programs can be prescribed (fixed) intensity or preferred intensity (i.e., the participants choose the intensity themselves). Trials, where exercise is one component of a combination treatment, were excluded since it is not possible to separate the effect of exercise. Trials with a single exercise session and trials which provide less than a week of exercise were excluded since it is unlikely to have any lasting effects on depression. All settings were included, e.g., schools, primary care settings, hospitals, including inpatients, and the trials could be carried out in both high-, middle- and low-income countries.

The control group may receive an intervention other than exercise, e.g., psychological therapies, pharmacological treatments alone or in combination, treatment as usual or other alternative treatments, or they may receive no treatment, e.g., waiting list or a non-intervention group.

Outcomes were chosen based on the standard set of outcomes recommended by the ICHOM Depression and Anxiety Working Group [28].

The primary outcomes were:

- Depression: Any measure of depression, reported either as a continuous or dichotomous outcome. Depression should be measured by self-report, health personnel report, parent report and teacher report
- Adverse events (any unwanted effects of the intervention)

The secondary outcomes were:

- Psychological well-being
- Social functioning
- Quality of life
- Acceptability measured as dropouts

Data from the end of treatment and if possible any long-term follow-up were included.

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 inception to December 2018. 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 searched for ongoing and unpublished trials

The search strategy was developed using a wide range of search terms, both index terms, and text words, for depression, children and adolescents, exercise and study design. Search terms were combined using boolean operators. No limits were applied on year, language or publication type. The search strategy was peer-reviewed using the PRESS checklist [29] and adapted to each database. Full search strategies are available in Supplementary S2.

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

Data collection and analysis

Selection of studies

The titles and abstracts of the identified references were independently screened by two authors (SB and BA) using Covidence Systematic Review Software [30]. Any references that one or both screeners included were ordered in full text and screened independently. Disagreements were resolved by discussion and if needed a third reviewer was consulted to reach a final decision.

Data extraction and management

Data from the included studies were extracted independently by two authors (SB and BA). Participant characteristics, setting, intervention characteristics, measurement tools, effect estimates, measures of uncertainty and study design were extracted. For the description of the interventions, the web-based TIDieR template (Template for Intervention Description and Replication) was used [31].

Assessment of risk of bias in included studies

The quality of the included studies was assessed using the Cochrane Collaboration Risk of Bias Tool [32, chapter 8.5.1] by two authors (SB and BA) independently. 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.

Data analysis

The effect sizes for depression post-intervention were pooled in a meta-analysis using RevMan [33]. A random-effects model was used since heterogeneity across the included studies was expected [23]. Statistical heterogeneity was assessed using the I^2 statistic. Heterogeneity is considered moderate if I^2 exceeds 50% and high if over 75% [34].

Depression was measured with different measurement tools across the included studies. To be able to pool the results standardized mean differences (SMD) was calculated using Hedges (adjusted) *g*. in RevMan [35]. The effect size was considered to be small if SMD was between 0.2 and 0.5, medium if between 0.5 and 0.8, and large if larger than 0.8 [36]. Outcomes were reported with 95% confidence intervals (CI). The other outcomes were not possible to pool in a meta-analysis, and are therefore described narratively.

Subgroup analysis and Sensitivity analysis

Subgroup analyses for the variables of type and intensity of exercise were planned, but it was not possible due to a limited number of included trials. Sensitivity analysis for the primary outcomes by removing studies that were at high or unclear risk of bias was planned. This was not possible because none of the included trials were classified as low risk of bias.

Assessment of publication bias

There were not a sufficient number of included studies (10 or more) to check for publication bias by visually examining funnel plots for asymmetry [23, chapter 10.4].

Certainty of the evidence (GRADE)

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the certainty of the evidence [37]. The risk of bias assessments were incorporated, and additional appraisal of directness, consistency, precision, and risk of reporting bias was performed for the primary outcome, depression at post-intervention and follow-up. A "Summary of findings"-table was created using the GradePro software [38, chapter 12.2.1, 39].

Results

The literature searches retrieved 15869 through database searching and 212 records through other sources. After removing duplicate records, 11007 remained for screening. 10698 records were excluded based on title and abstract. 309 full-text articles were assessed and 301 excluded. Four ongoing trials were identified [40-43]. Details of the study selection process and reasons for exclusion are in the PRISMA flow diagram (figure 1).



PRISMA 2009 Flow Diagram



Included studies

Four trials were included (*n*=143) [44-47]. All trials were published in English. Two were articles in peer-reviewed journals [45, 46], while two were doctoral dissertations [44, 47]. One trial was conducted in Nottingham, UK at community centres [46]. Two trials were conducted in the USA, one in a Miami, Florida high school [47], and the other in a junior high school in Cheyenne, Wyoming [44]. The fourth trial was conducted in Iran, at a swimming pool with all female high school students [45]. The characteristics of the included trials are summarized in table 1. More details of the included trials are described in Supplementary S3.

Intervention (exercise component)								
Study, year	Participants	Country, Setting	Туре	Dose	Control	Outcome Measures (depression)	Baseline severity of depression Mean (SD)	Results (lower score is better) SMD (CI)
Carter <i>et al.</i> 2015	n=64 14-17 years M=15.4 years 78% females	UK Community centres	Circuit-training (aerobic and strengthening exercises)	45 min 2 times/wk 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 <i>et al.</i> 2011	n=24 15-18 years M=16.9 years 100% females	Iran High school	Pool-walking program	3 times/wk 6 weeks	No exercise, no anti- depressant 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)	20 min 3 times/wk 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=29 15-18 years M=N/A 60% females	USA High school	Walk-jog-run (aerobic running program)	45 min 4 times/wk 9 weeks	Anaerobic treatment, Red Cross First Aid and Personal Safety Class	DACL Self-report	I: 19.14 (3.73) C: 19.33 (3.71)	-0.27 (-1.00, 0.46)

*All trials are RCTs (Randomised Controlled Trials)

*All interventions were group-based and supervised.

Note: CDI-2= Children's Depression Inventory; Ham-D= Hamilton Rating Scale for Depression; RADS= Reynolds Adolescent Depression Scale; DACL= Depression Adjective Checklist.

Participants

Sample sizes in the included trials ranged from 24 to 64 participants. Age ranges were twelve to 15 years, mean not reported [44]; 15 to 18 years, mean not reported [47]; 14 to 17 years, mean 15.4 [46], and 15 to 18 years, mean 16.91 [45]. All trials had a majority of female participants.

Participants were recruited from Child and Adolescent Mental Health Services in one trial [46]. In the other three trials, all students in entire high school grades were screened for depression, and students who scored above the criterion level were invited to participate in the trial [44, 45, 47].

Interventions and comparisons

The four included trials evaluated different types of exercise. All interventions were groupbased training. Intervention periods ranged from 6-9 weeks, with 2-4 sessions per week. Total sessions ranged from 12-36 sessions, and the duration varied from 20-45 minutes in three trials. One trial did not report the duration of the sessions [45].

In Carter et al. [46] six weeks of interval circuit-training was compared to treatment as usual. Treatment as usual in this trial consisted of various psychological therapies and in some cases pharmacotherapy. The circuit-training had eight different exercise-stations, which consisted of both strengthening and aerobic exercises. Participants could choose the order in which they undertook the different exercises, as well as intensity. They could also choose to take rests when they wanted.

Roshan et al. [45] compared six weeks of interval pool walking to no treatment. The water height in the pool reached 70-80% of the participant's height, and the intensity was about 60-70% of maximum heart rate. The twelve participants in the experimental group walked a total of 14.850 meters during the 18 sessions.

Beffert [44] compared a six-week walking-running program to waitlist. The walking-running program was designed to increase the aerobic fitness of the participants. The intensity was about 60-85% of maximum heart rate.

In Burrus [47] a nine-week running program was compared to a first aid and personal safety course. The running program consisted of walk-jog-run for thirty-five minutes. The participants gradually increased their pace until their heart rate reached 75% of maximum

cardiac output. In this trial, there was also a second control group that received anaerobic exercise. The results from this control group were not included in the data analysis because studies comparing two types of exercise are not eligible in this systematic review.

Three trials had a certified physical education instructor or exercise therapist who supervised each session [44, 46, 47]. One trial did not report if the trainers were either certified or experienced in their respective fields [45]. For further details of the interventions see TIDieR tables in Appendix II.

Primary outcomes

The severity of depression was measured using a different measurement tool in each of the included trials. Beffert [44] used the Reynolds Adolescent Depression Scale (RADS) [48]. Burrus [47] used the Depression Adjective Checklist (DACL) [49]. Carter et al. [46] used Children's Depression Inventory 2 (CDI-2) [50]. Hamilton Rating Scale for Depression (Ham-D) was used in Roshan et al. [45]. All trials reported the severity of depression as continuous outcomes. None of the included trials commented on the presence or absence of adverse events.

Secondary outcomes

Quality of life was evaluated in one trial [46], using EQ-5D, a standardized measure of healthrelated quality of life [51].

Psychological well-being and social functioning as outcomes were not evaluated in any of the included trials.

Timing of outcome measures

All trials reported outcome measured at the end of the intervention period. Follow-up data beyond the end of treatment is reported in only one trial (6-month follow-up) [46].

Risk of bias in included studies

All included trials were assessed as having a high or unclear risk of bias. The random sequence generation and allocation concealment were adequate in only one trial [46] and unclear in the other three trials. Blinding of participants and personnel in exercise trials is not possible to achieve; we, therefore, rated all the four trials as high risk of bias for that domain. Blinding of outcome assessment, selective reporting, and other bias are satisfactory reported in only one trial [46] and unclear in the other three trials. Incomplete outcome data or attrition was rated as unclear risk of bias in all the four trials. See Risk of bias graph in figure 2 and 3.

Figure 2. Risk of bias graph



Figure 3. Risk of bias graph



Effects of interventions

Depression (post-intervention)

For the primary outcome, change in depression post-intervention, the results of four trials (n=143) were pooled in a meta-analysis, and found a moderate effect in favour of exercise (SMD = -0.59, 95% CI = -1.11, to -0.07, p=0.03). See forest plot in figure 4.

The heterogeneity across the four trials was moderate ($I^{2=52\%}$). The heterogeneity may be explained by different control interventions and measurement tools. However, it was decided to undertake a meta-analysis as the participants, treatments and clinical questions were similar enough to pool in a meta-analysis.

Figure 4. Forest plot of comparison: exercise versus control, outcome: change in depression post-intervention.



Depression (follow-up)

Effects at six-month follow-up was reported in one trial (n=42, 22 were lost to follow-up from post-intervention) [46]. The trial found a moderate effect in favour of exercise (SMD = -0.59, 95% CI = -1.22, to 0.04, p=0.07).

Quality of Life

Quality of life at post-intervention was reported in one trial (n=64) [46]. There were no statistically significant differences (SMD=0.27, 95% CI = -0.35, to 0.89, p=0.39).

Drop-out

It was not possible to pool data on this outcome. No drop-out was reported in one trial [45]. Precise numbers for drop-out was not reported in Beffert [44]. In Burrus [47] one participant withdrew from the intervention group due to medical reasons. In Carter et al. [46] "At post-intervention the total loss to follow up was 25%, with more participants dropping out in the control arm than the intervention". "At six months, the total loss to follow up was 51% with a higher dropout rate in the control compared to the intervention arm".

Certainty of the evidence (GRADE)

The outcome, change in depression post-intervention, was downgraded two levels, one for risk of bias, and one for imprecision. The overall certainty of the evidence for this outcome was graded as low.

The outcome, change in depression at six months follow-up, was downgraded three levels, one for risk of bias and two for imprecision. The overall certainty of the evidence for this outcome was graded as very low. Further details of the grading are in the summary of findings table (table 2).

Outcomes	Anticipated absolute effects [*] (95% CI)		Relative effect (95%	№ of participants (studies)	Certainty of the evidence (CRADE)
	Risk with control	Risk with Exercise	CI)		
Change in depression post-intervention		SMD 0.59 lower (1.11 lower to 0.07 lower)		143 (4 RCTs)	$ \begin{array}{c} \bigoplus \bigoplus \bigoplus \bigoplus \\ LOW^{12} \end{array} $
Change in depression follow-up (6 months)		SMD 0.59 lower (1.22 lower to 0.04 higher)		42 (1 RCT)	
GRADE Working Group grades of evidence.					

Table 2. Summary of findings table.

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.

Footnotes

¹ Lack of blinding probably increased effect sizes. Sequence generation was considered unclear in 3 studies.

² 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.

³ The confidence interval encompasses benefit and harm

Discussion

The purpose of this review was to systematically assess the effects of exercise interventions on children and adolescents with depression. Four trials were included, and pooling the trials found a moderate effect in favour of exercise on depression severity post-intervention. However, the trials were assessed as having an unclear or high risk of bias. The overall certainty of the evidence for this outcome was graded as low. This means that our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect. The severity of depression at six months follow-up was reported in one trial. The overall certainty of the evidence for this outcome was graded as very low. This means that we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

Strength and limitations

A strength of this review is the use of standardized methods recommended by Cochrane and PRISMA. A comprehensive and systematic literature search was performed to identify relevant trials. In addition to published journal articles, a wide search for unpublished and ongoing trials was performed. There is however always the risk of missing trials. Systematic and transparent methods were used in the screening of references, data extraction, risk of bias assessment and evaluating the certainty of the evidence. These steps were performed by two authors independently. A limitation in this review is that it was not possible to perform a

publication bias assessment due to a low number of included trials. There is a possibility that studies with negative effects are not published.

The included trials had few participants, wide confidence intervals and low statistical power. The exercise interventions were all group-based and supervised. Therefore, we were unable to conclude about the effects of non-supervised individual exercise. Mechanisms other than the physiological or biological aspects of exercise may have accounted for the reduction in depression. The participants had social support, met new people, perhaps made some new friends, and the intervention can also be a diversion from negative thoughts and feelings. The skills of the supervisors, both professional, interpersonal, and the ability to motivate the participants might also have influenced the results.

It was not possible to make conclusions about what type of exercise has the largest benefits (e.g., aerobic, anaerobic, or team sports), or whether the intensity has any impact on the results. Intensity means how hard they exercise in each session. The duration of the exercise interventions varied from 6-9 weeks, whether the effect is different if the intervention duration is shorter or longer is not known.

None of the included trials had participants under 12 years old, and no conclusions about the effect of exercise in younger children with depression can be made.

Only one of the included trials compared an exercise intervention to established treatments [46]. It is important to find out how a new treatment compares with established treatments, and not compared to placebo. Not offering the participants in the comparison groups an established treatment can be considered unethical [52].

A limitation is that several important outcomes are not evaluated in the included trials. The severity of the depression at post-intervention was the only outcome reported in all trials. None of the trials commented on the presence or absence of adverse events. Safety should be a major focus in the evaluation of interventions. Better recording and reporting are needed to make conclusions about whether exercise can be harmful for this population. Quality of life was only measured in one of the trials, and no conclusions can be drawn. Social functioning or psychological well-being were not measured in any of the trials. Only one of the included studies measured long term effects [46]. This is unfortunate since depression is often a chronic or recurring illness, and investigating whether treatments have long-lasting effects is important [53].

Comparison with other systematic reviews

The other reviews on this subject have included more trials than this systematic review, but two dissertations included in this review are not included in any of the other recent reviews [44, 47]. This is due to different inclusion criteria. Despite these differences, the result in this review, a moderate effect in favour of exercise on depression post-intervention, is consistent with the results in the previous reviews.

Implications for practice

Based on the results of this systematic review exercise may reduce depression severity in adolescents with depression. However, the trials have a high risk of bias, a limited number of participants and the overall certainty of the evidence is low or very low. Exercise appears to be a promising intervention, but further trials are needed.

Implications for future research

Large, high-quality trials with children and adolescents with depression are needed. Adequate numbers of participants should be recruited to detect a difference between the groups. The trials need to reduce the risk of bias. The trials need a longer follow-up time to assess long-term effectiveness. The comparison groups should be offered either treatment as usual or other recommended treatments for depression (e.g., cognitive behaviour therapy). Studies, where exercise is an add-on to other treatments are also needed since that is perhaps the most realistic in real-life situations. A wider range of outcomes should be measured in future trials, and the choice of outcome should be based on agreed standardized sets of outcomes (Core Outcome Sets). Complete reporting of adverse events is vital.

Declarations of interest and funding

The authors have no known conflicts of interest to declare. The authors received no specific funding for this work, but the work on this thesis has been done as a part of our work at the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP). The Centre has not influenced objectives, research question, methods or conclusions.

Acknowledgments

We wish to thank Astrid Dahlgren and Åse Sagatun for feedback on the article manuscript. Information specialists Marte Ødegaard and Mari Elvsåshagen peer-reviewed the Medline search strategy with the PRESS checklist. Researchers Simon-Peter Neumer and Parvin Kiamanesh helped with reading articles in German and Persian, and statistician Tore Wentzel-Larsen helped to assess the randomization in one of the trials.

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PRISMA 2009 Checklist

ALLA STREET

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title		Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	N	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	e	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	പ	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	9	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	2	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	80	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary S2
Study selection	6	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	9
Data items	÷	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Supplementary S1

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PRISMA 2009 Checklist

SIJE STREET

Synthesis of results	4	Describe the methods of handling data and combining results of studies, if done, including measures of 7 consistency (e.g., I ²) for each meta-analysis.	
		Page 1 of 2	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

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Supplementary S2

Search strategies

Date for search: 23rd of March 2018 Date for update search December 18th 2018 Date for search insources for grey literature and ongoing trials 5th of February 2019

Searh strategies developed by: Sølvi Biedilæ and Brynhildur Axelsdóttir

Peer-reviewed with PRESS Checklist (McGowan et al 2016) by two librarians: Marte Ødegaard and Mari Elvsåshagen.

Total number of results in bibliographic databases from all searches with duplicates: **15.869** Total number of results in sources for grey literature and ongoing trials in manual screening: **212** Total number of results in bibliographic databases from all searches without duplicates: **11.007**

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to March 14 2018> (Ovid SP)

Date: 23.03.2018 Results: 2043 Date: 18.12.2018 Results: 486

#	Searches
1	Depression/
2	depressive disorder/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/
3	(depress* or dysthymi* or melanchol* or dysphori* or sadness or low mood*).ti,ab.
4	(seasonal adj3 (affect* or mood*) adj3 disord*).ti,ab.
5	or/1-4
6	Adolescent/ or exp Child/ or Minors/ or exp Puberty/ or exp Pediatrics/ or exp Schools/
7	(child* or kid or kids or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or boy or boys or boyhood* or girl* or underag* or under-ag* or pediatr* or paediatr* or pediatr*).ti,ab,hw,kf,jw.
8	(young* adj (person* or people* or individual* or male* or female* or man or mans or men* or woman* or women*)).ti,ab.
9	or/6-8

10	exp Exercise/ or exp Exercise Therapy/ or Exercise Movement Techniques/ or exp Sports/ or "Physical Education and Training"/ or Tai ji/ or Yoga/ or Physical Exertion/ or exp Physical Endurance/ or exp Physical Fitness/ or Dancing/ or "Play and playthings"/ or games, recreational/
11	(exercis* or exertion* or (physical* adj3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or fitness or sport* or gymnastic* or athletic* or workout* or work out* or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or tread-mill* or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or yoga or tai ji or tai chi or thai chi or taiji or taichi or thaichi or taijiquan or ai chi or pilates or dance* or dancing* or ((weight* or power*) adj3 lift*) or weightlift* or powerlift* or musc* strength* or ((weight* or resistance or strength* or circuit*) adj3 train*) or cardiopulmonary conditioning* or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*).ti,ab.
12	or/10-11
13	5 and 9 and 12
14	randomized controlled trial.pt.
15	controlled clinical trial.pt.
16	randomized.ab.
17	placebo.ab.
18	drug therapy.fs.
19	randomly.ab.
20	trial.ab.
21	groups.ab.
22	or/14-21
23	exp animals/ not humans.sh.
24	22 not 23
25	13 and 24

Database: PsycINFO <1806 to March Week 3 2018> (Ovid SP)

Date: 23.03.2018 Results: 3207 Date: 18.12.2018 Results: 145

#	Searches
1	"depression (emotion)"/ or major depression/ or dysthymic disorder/ or endogenous depression/ or reactive depression/ or recurrent depression/ or treatment resistant depression/ or atypical depression/ or seasonal affective disorder/ or sadness/
2	(depress* or dysthymi* or melanchol* or dysphori* or sadness or low mood*).ti,ab.
3	(seasonal adj3 (affect* or mood*) adj3 disord*).ti,ab.
4	or/1-3
5	(adolescence 13 17 yrs or school age 6 12 yrs).ag.
6	puberty/ or pediatrics/ or schools/ or elementary schools/ or high schools/ or junior high schools/ or middle schools/
7	(child* or kid or kids or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or boy or boys or boyhood* or girl* or underag* or under-ag* or pediatr* or paediatr* or peadiatr*).ti,ab,id,hw,jx.
8	(young* adj (person* or people* or individual* or male* or female* or man or mans or men* or woman* or women*)).ti,ab.
9	or/5-8
10	exp Exercise/ or exp Sports/ or physical education/ or physical endurance/ or Physical Fitness/ or Dance/ or childrens recreational games/ or jumping/ or running/ or walking/ or physical strength/ or recreation/ or athletic participation/ or athletic performance/ or athletic training/ or physical activity/
11	(exercis* or exertion* or (physical* adj3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or fitness or sport* or gymnastic* or athletic* or workout* or work out* or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or tread-mill* or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or yoga or tai ji or tai chi or thai chi or taiji or taichi or thaichi or taijiquan or ai chi or pilates or dance* or dancing* or ((weight* or power*) adj3 lift*) or weightlift* or powerlift* or musc* strength* or ((weight* or resistance or strength* or circuit*) adj3 train*) or cardiopulmonary conditioning* or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*).ti,ab.
12	or/10-11

13	4 and 9 and 12
14	exp treatment effectiveness evaluation/ or clinical trials/ or followup studies/ or exp program evaluation/ or empirical methods/ or exp experimental methods/ or experimental design/ or between groups design/ or repeated measures/ or exp treatment outcomes/ or placebo/
15	(clinical trial or empirical study or followup study or quantitative study or treatment outcome).md.
16	(random* or trial* or control or (control* adj3 (study or studies)) or crossover* or cross-over* or allocat* or assign* or factorial* or volunteer* or (quasi adj experimental) or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group*)) or placebo*).ti,ab.
17	or/14-16
18	13 and 17

Database: Embase <1974 to 2018 March 22> (Ovid SP) Date: 23.03.2018 Results: 1401 Date: 18.12.2018 Results: 180

#	Searches
1	depression/ or adolescent depression/ or agitated depression/ or atypical depression/ or chronic depression/ or dysphoria/ or dysthymia/ or endogenous depression/ or major depression/ or melancholia/ or minor depression/ or organic depression/ or reactive depression/ or recurrent brief depression/ or seasonal affective disorder/ or treatment resistant depression/ or sadness/
2	(depress* or dysthymi* or melanchol* or dysphori* or sadness or low mood*).ti,ab.
3	(seasonal adj3 (affect* or mood*) adj3 disord*).ti,ab.
4	or/1-3
5	child/ or exp adolescent/ or exp adolescence/ or childhood/ or exp puberty/ or pediatrics/ or child psychiatry/ or school/ or high school/ or middle school/ or primary school/ or elementary student/ or high school student/ or middle school student/ or school child/
6	(child* or kid or kids* or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or boy or boys* or boyfriend* or boyhood* or girl* or under 18* or under eighteen* or underag* or under-ag* or pediatr* or paediatr* or pediatr*).ti,ab,kw,hw,jx.
7	(young* adj (person* or people* or individual* or male* or female* or man or mans or men* or woman* or women*)).ti,ab.
8	or/5-7
9	exp Exercise/ or exp Sport/ or Training/ or Dancing/ or exp Physical activity/ or Physical education/ or Endurance/ or Fitness/ or Play/ or Recreational game/
10	(exercis* or exertion* or (physical* adj3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or fitness or sport* or gymnastic* or athletic* or workout* or work out* or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or tread-mill* or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or yoga or tai ji or tai chi or thai chi or taiji or taichi or thaichi or taijiquan or ai chi or pilates or dance* or dancing* or ((weight* or power*) adj3 lift*) or weightlift* or powerlift* or musc* strength* or ((weight* or resistance or strength* or circuit*) adj3 train*) or cardiopulmonary conditioning* or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*).ti,ab.
11	or/9-10
12	randomized controlled trial/ or crossover procedure/ or double blind procedure/ or single blind procedure/

13	(crossover* or cross over* or placebo* or allocat* or random*).ti,ab.
14	(doubl* adj blind*).ti,ab.
15	trial*.ti.
16	or/12-15
17	4 and 8 and 11 and 16

Database: AMED (Allied and Complementary Medicine) <1985 to March 2018> (Ovid SP) Date: 23.03.2018 Results: 98 Date: 18.12.2018 Results 8

#	Searches
1	depression/ or depressive disorder/
2	(depress* or dysthymi* or melanchol* or dysphori* or sadness or low mood*).ti,ab.
3	(seasonal adj3 (affect* or mood*) adj3 disord*).ti,ab.
4	or/1-3
5	exp Adolescent/ or Child/ or Child Hospitalized/ or Puberty/ or Pediatrics/ or Schools/
6	(child* or kid or kids or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or boy or boys or boyhood* or girl* or underag* or pediatr* or paediatr* or pediatr*).ti,ab,hw,et,jx.
7	(young* adj (person* or people* or individual* or male* or female* or man or mans or men* or woman* or women*)).ti,ab.
8	or/5-7
9	exp Exercise/ or exp Exercise Therapy/ or exp Sports/ or exp physical education/ or yoga/ or exp exertion/ or Physical Fitness/ or Dancing/ or "play and playthings"/
10	(exercis* or exertion* or (physical* adj3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or fitness or sport* or gymnastic* or athletic* or workout* or work out* or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or tread-mill* or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or yoga or tai ji or tai chi or thai chi or taiji or taichi or thaichi or taijiquan or ai chi or pilates or dance* or dancing* or ((weight* or power*) adj3 lift*) or weightlift* or powerlift* or musc* strength* or ((weight* or resistance or strength* or circuit*) adj3 train*) or cardiopulmonary conditioning* or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*).ti,ab.
11	or/9-10
12	4 and 8 and 11

Database: Cochrane Library Central Database

Date: 23.03.2018 Results: 1031 Date: 18.12.2018 Results: 330

- ID Search Hits
- #1 MeSH descriptor: [Depression] this term only
- #2 MeSH descriptor: [Depressive Disorder] this term only
- #3 MeSH descriptor: [Depressive Disorder, Major] this term only
- #4 MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
- #5 MeSH descriptor: [Dysthymic Disorder] this term only
- #6 MeSH descriptor: [Seasonal Affective Disorder] this term only
- #7 (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*"):ti,ab,kw
- #8 ("seasonal" near/3 (affect* or mood*) near/3 disord*):ti,ab,kw
- #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
- #10 MeSH descriptor: [Adolescent] this term only
- #11 MeSH descriptor: [Child] explode all trees
- #12 MeSH descriptor: [Minors] this term only
- #13 MeSH descriptor: [Puberty] explode all trees
- #14 MeSH descriptor: [Pediatrics] explode all trees
- #15 MeSH descriptor: [Schools] explode all trees
- #16 (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr*):ti,ab,kw 215839
- #17 (young* near/1 (person* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*)):ti,ab,kw
- #18 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
- #19 MeSH descriptor: [Exercise] explode all trees
- #20 MeSH descriptor: [Exercise Therapy] explode all trees
- #21 MeSH descriptor: [Exercise Movement Techniques] this term only
- #22 MeSH descriptor: [Sports] explode all trees
- #23 MeSH descriptor: [Physical Education and Training] this term only
- #24 MeSH descriptor: [Tai Ji] this term only
- #25 MeSH descriptor: [Yoga] this term only
- #26 MeSH descriptor: [Physical Exertion] this term only

- #27 MeSH descriptor: [Physical Endurance] explode all trees
- #28 MeSH descriptor: [Physical Fitness] explode all trees
- #29 MeSH descriptor: [Dancing] this term only
- #30 MeSH descriptor: [Play and Playthings] this term only
- #31 MeSH descriptor: [Games, Recreational] this term only
- #32 (exercis* or exertion* or (physical* near/3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "thaichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or ((weight* or power*) near/3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or circuit*) near/3 train*) or "cardiopulmonary conditioning*" or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*):ti,ab,kw
- #33 #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or
- #32
- #34 #9 and #18 and #33 in Trials
Database: Web of Science (Core Collection)

Date: 23.03.2018 Results: 2152 Date: 18.12.2018 Results: 243

# 6	#5 AND #4 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 5	TS=(random* or trial* or "control" or (control* NEAR/3 ("study" or "studies")) or crossover* or "cross-over*" or allocat* or assign* or factorial* or volunteer* or ("quasi" NEAR/1 "experimental") or ((waitlist* or "wait* list*" or "treatment as usual" or "TAU") NEAR/3 ("control" or group*)) or placebo*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI
	Timespan=All years
#4	#3 AND #2 AND #1
	Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 3	TS=(exercis* or exertion* or (physical* NEAR/3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "treadmill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "thaichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or ((weight* or power*) NEAR/3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or climbing* or bouldering* or hiking* or swim* or row* or skate* or skating* or bouldering* or hiking* or badminton* or stretching*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 2	TS=(child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr* or (young* NEAR/1 (person* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))) Indexes=SCI- EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
# 1	TS=(depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*" or ("seasonal" NEAR/3 (affect* or mood*) NEAR/3 disord*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

Database: SportDiscus (EBSCO)

Date: 23.03.2018 Results: 773 Date: 18.12.2018 Results: 38

#	Query
S1	TI (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*" or ("seasonal" N3 (affect* or mood*) N3 disord*)) OR AB (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*" or ("seasonal" N3 (affect* or mood*) N3 disord*)) OR SU (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*" or ("seasonal" N3 (affect* or mood*) N3 disord*))
S2	TI (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or pediatr* or (young* N1 (person* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))) OR AB (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr* or powers* or juvenil* or adoles* or youth* or youngster* or teen* or midteen* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))) OR SU (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or prepube* or pubescen* or school* or highschool* or girl* or underag* or "under-ag*" or pediatr* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))) OR SU (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr* or peadiatr* or geople* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*)))
S3	TI (exercis* or exertion* or (physical* N3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "tai ji" or "taiji" or "taiji" or "taiji" or "taiji" or "taijitor" or taijitor or taijitor or taijitor or taijitor or taijitor or taijitor" or to endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or "yoga" or "tai ji" or "tai chi" or "taijii or "tai chi" or "taijiquan" or "ai chi" or "taiji or "tai chi"

"tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "taichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or ((weight* or power*) N3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or circuit*) N3 train*) or "cardiopulmonary conditioning*" or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*)

S4 S1 AND S2 AND S3

12

Database: CINAHL (Ebsco)

Date: 23.03.2018 Results: 1574 Date: 18.12.2018 Results: 993

#	Query
S1	(MH "Depression") OR (MH "Depression, Reactive") OR (MH "Dysthymic Disorder") OR (MH "Seasonal Affective Disorder")
S2	TI (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*")
S3	AB (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*")
S4	TI ("seasonal" N3 (affect* or mood*) N3 disord*)
S5	AB ("seasonal" N3 (affect* or mood*) N3 disord*)
S6	S1 OR S2 OR S3 OR S4 OR S5
S7	(MH "Adolescence+") OR (MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Institutionalized") OR (MH "Minors (Legal)")
S8	(MH "Puberty")
S9	(MH "Pediatrics")
S10	(MH "Schools") OR (MH "Schools, Elementary") OR (MH "Schools, Middle")OR (MH "Schools, Secondary")
S11	TI (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr*)
S12	AB (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr*)
S13	TI (young* N1 (person* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))

S14	AB (young* N1 (person* or people* or individual* or male* or female* or "man" or "mans" or men* or woman* or women*))
S15	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16	(MH "Exercise+") OR (MH "Aerobic Exercises+")
S17	(MH "Sports+")
S18	(MH "Physical Education and Training+")
S19	(MH "Physical Endurance") OR (MH "Exertion")
S20	(MH "Physical Fitness")
S21	(MH "Physical Activity")
S22	(MH "Yoga") OR (MH "Tai Chi")
S23	(MH "Dancing+") OR (MH "Exergames") OR (MH "Play and Playthings")
S24	TI (exercis* or exertion* or (physical* N3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "thaichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or ((weight* or power*) N3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or circuit*) N3 train*) or "cardiopulmonary conditioning*" or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or cricket* or rugby* or tennis* or badminton* or stretching*)
S25	AB (exercis* or exertion* or (physical* N3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "thaichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or

	((weight* or power*) N3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or circuit*) N3 train*) or "cardiopulmonary conditioning*" or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*)
S26	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S27	S6 AND S15 AND S26

Database: ERIC (Ebsco)

Date: 23.03.2018 Results: 715 Date: 18.12.2018 Results: 30

#	Query
S1	DE "Depression (Psychology)"
S2	TX (depress* or dysthymi* or melanchol* or dysphori* or "sadness" or "low mood*")
S3	TX ("seasonal" N3 (affect* or mood*) N3 disord*)
S4	S1 OR S2 OR S3
S5	DE "Adolescents" OR DE "Early Adolescents" OR DE "Late Adolescents"
S 6	DE "Children" OR DE "African American Children" OR DE "Hospitalized Children" OR DE "Minority Group Children" OR DE "Preadolescents" OR DE "Young Children"
S7	DE "Youth" OR DE "Disadvantaged Youth" OR DE "Out of School Youth" OR DE "Rural Youth" OR DE "Urban Youth"
S 8	DE "Puberty"
S9	DE "Pediatrics"
S10	DE "Schools" OR DE "Elementary Schools" OR DE "Middle Schools" OR DE "Secondary Schools" OR DE "Elementary School Students" OR DE "Middle School Students" OR DE "Secondary School Students" OR DE "High School Students"
S11	TX (child* or "kid" or "kids" or minors* or juvenil* or adoles* or youth* or youngster* or teen* or preteen* or midteen* or pubert* or prepube* or pubescen* or school* or highschool* or student* or "boy" or "boys" or boyhood* or girl* or underag* or "under-ag*" or pediatr* or paediatr* or peadiatr*)
S12	TX (young* N1 (person* or people* or individual* or male* or female* or "man" or "mans" or "men*" or woman* or women*))
S13	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14	DE "Exercise"

S15	DE "Athletics" OR DE "Aquatic Sports" OR DE "Extramural Athletics" OR DE "Intramural Athletics" OR DE "Racquet Sports" OR DE "Team Sports" OR DE "Track and Field" OR DE "Womens Athletics"
S16	DE "Physical Activities" OR DE "Dance"
S17	DE "Physical Fitness" OR DE "Health Related Fitness" OR DE "Physical Recreation Programs" OR DE "Physical Education"
S18	DE "Play"
S19	TX exercis* or exertion* or (physical* N3 (train* or education* or fit* or effort* or activ* or endur* or strength* or condition*)) or "fitness" or sport* or gymnastic* or athletic* or workout* or "work out*" or cycling* or cycle* or bicycl* or bike* or biking* or walk* or run* or jog* or treadmill* or "tread-mill*" or jumping* or hopping* or plyometric* or aerobic* or anaerobic* or calisthenic* or isometric* or "yoga" or "tai ji" or "tai chi" or "thai chi" or "taiji" or "taichi" or "thaichi" or "taijiquan" or "ai chi" or "pilates" or dance* or dancing* or ((weight* or power*) N3 lift*) or weightlift* or powerlift* or "musc* strength*" or ((weight* or "resistance" or strength* or circuit*) N3 train*) or "cardiopulmonary conditioning*" or exergam* or climbing* or bouldering* or hiking* or hike* or swim* or row* or skate* or skating* or football* or soccer* or volleyball* or basketball* or baseball* or handball* or cricket* or rugby* or tennis* or badminton* or stretching*)
S20	S14 OR S15 OR S16 OR S17 OR S18 OR S19
S21	S4 AND S13 AND S20

Database: PEDro Physiotherapy Evidence Database

Date: 23.03.2018 Results: 80 Date: 18.12.2018 Results: 11

depress* and child* - in clinical trial depress* and adoles* - in clinical trial

Search strategies in sources for grey literature and ongoing trials in bibliographic databases

Database: Papers First (OCLC) Date: 05.02.2019 Results: 43

PapersFirst results for: kw: depress* n10 exercise* Records found: 22

PapersFirst results for: kw: depress* n10 physical w activity Records found: 21

Database: ProQuest Dissertations & Theses A&I

Date: 05.02.2019 Results: 283

noft(depress*) AND noft(exercise* or "physical activity") AND noft(child* or adolescen* or youth or teen*)

283 results

Search strategies in sources for grey literature and ongoing trials screened manually

Database: OpenGrey Date: 05.02.2019 Results: 50

http://www.opengrey.eu/search/request?q=depress*+AND+exercise (35 hits)

http://www.opengrey.eu/search/request?q=depress*+AND+%22physical+activity%22 (15 hits)

Database: ClinicalTrials.gov Date: 05.02.2019 Results: 72

23 Studies found for: (depression or depressive or depressed) | exercise | Child

https://clinicaltrials.gov/ct2/results/details?term=%28depression+or+depressive+or+depressed%29&in tr=exercise&age=0

49 Studies found for: (depression or depressive or depressed) | physical activity | Child

<u>https://clinicaltrials.gov/ct2/results?term=%28depression+or+depressive+or+depressed%29&intr=phy</u> <u>sical+activity&age=0</u>

Database: WHO International Clinical Trials Registry Platform

Date: 05.02.2019 Results: 90

Both searches are limited to children

57 records for 57 trials found for: depress* AND exercise

33 records for 33 trials found for: depress* AND physical activity

http://apps.who.int/trialsearch/default.aspx

Supplementary S3

Detailed characteristics of included studies

Beffert 1993

Methods	Randomized controlled trial (RCT).
Participants	N=26 randomized Number analyzed: completed first stage of study n=26 Drop-out: No reporting of drop-out Age: 12-15 years old. Gender:83% female Recruitment: All seventh and eight-grade students in a public junior
	high school were screened twice using the RADS. Baseline of severity of depression: I: 122.53 (6.03) C: 124.91 (6.92) Inclusion criteria:
	 High school students who ranged in age from 12-15 years. Scoring 75 or above on RADS on both screenings
	Exclusion criteria:
	1. Severe level of depression. Students who scored four or more of the six critical items on the RADS were viewed as possibly being too seriously depressed to be included
	2. Currently receiving antidepressant medication or any other treatment for depression
	3. Restricted from participating in aerobic exercise
	4. Not received written parental permission to participate
	Location: Cheyenne, Wyoming USA

Interventions	 Aerobic exercise (walking-running program) Heart rate between 60- 85% of maximum capacity. The instructor was a certified physical education instructor. Group-based training. 6 weeks 3 sessions per week 18 sessions in total Duration of each session was 20 minutes Setting: Medium-sized urban junior high school Waitlist
Outcomes	 The severity of depressive symptoms as measured by the Reynolds Adolescent Depression Scale (RADS), measured at end of treatment: 6 weeks Cardiovascular fitness measured using the time required for them to complete a 1.5-mile walk-run (female students) or 2-mile run (male students).
Notes	PhD dissertation Funding: Greg Hannah research fund Conflict of interest: N/A Trial registration: N/A Intention to treat analysis: N/A Sample size calculation: N/A

Burrus 1984

Methods	Randomized controlled trial (RCT). Stratified
Participants	N=46 randomized Number analyzed: 45 (29 included in meta-analysis) (Red Cross group N=15 was not included in the analyses of the systematic review). Drop-out: 1 Age: 15-18 years old Gender: 60% female

	Recruitment: Recruitment: 700 senior high school students (grades 10, 11, 12) were screened twice for depression using the Depression Adjective Checklist (DACL), Form A.
	Baseline of severity of depression: I: 19.14 (3.73) C: 19.33 (3.71)
	Inclusion criteria: 1. Scored at or above the 93 rd percentile on two administrations at an interval of from one to six months on the DACL.
	Exclusion criteria:
	1. Not resided in the United States during the previous 5 years
	2. In psychotherapeutic treatment
	3. Exempt from physical education for medical reasons
	4. Involved in a running or regular exercise program
	Location: Miami, Florida USA
Interventions	1. Aerobic running program (high physiological activity). The program included a walk-jog-run. Heart rate at a maximum 75%. All instructors were highly trained and experienced in their respective fields. Groupbased training.
	 9 weeks 4 sessions per week 36 sessions in total Duration of each session was 45 minutes (35 spent on exercise)
	Setting: High school
	2. Anaerobic treatment (medium physiological activity). 15 minutes weight training program using universal equipment, bar bells and exercise bars, and 20 minutes of anaerobic team activities including volleyball, softball, archery and melon ball.
	 9 weeks 4 sessions per week 36 sessions in total Duration of each session was 45 minutes (35 spent on exercise)
	3. Red Cross treatment (low physiological activity). Learned first aid and personal safety in a classroom.
	• 9 weeks

	 4 sessions per week 36 sessions in total Duration of each session was 45 minutes
Outcomes	 The severity of depressive symptoms as measured by the Depression Adjective Checklist (DACL), measured at end of treatment: 9 weeks Weight Blood pressure Cardiovascular fitness measured using the One Minute Step Test
Notes	PhD dissertation Funding: N/A Conflicts of interest: N/A Trial registration: N/A Intention to treat analysis: N/A Sample size calculation: N/A

Carter 2015

Methods	Pragmatic Randomized Controlled Trial (RCT) (parallel design)
Participants	 N=87 randomized Number analyzed: at six-week N=64, at six months N=42 Drop-out: At post-intervention the total loss to follow up was 25%, with more participants dropping out in the control arm than the intervention Age: mean 15.4 (SD 1.0) (intervention group), 15.4 (SD 0.9) (control group). Gender: 78% female Recruitment: referred by general practitioners (GPs), Child and Adolescent Mental Health Services (CAMHS) and school nurses. Baseline severity of depression: I: 29.1 (9.4) C: 28.2 (6.8) Inclusion criteria: 1. Adolescents aged 14-17 years

	2. Receiving treatment from a health or social care professional for depression
	3. Scoring above 14 on the Children's Depression Inventory-2 (CDI-2).
	Exclusion criteria:
	1. Presence of a medical condition that would make exercise participation unsafe
	Location: East Midlands area, England
Interventions	1. Circuit-training at preferred intensity alongside treatment as usual. The circuit training comprised of an interval pattern with eight separate exercise-stations. Preferred intensity. The stations consisted of strengthening and aerobic exercises. A qualified exercise therapist supervised each session. Group-based training.
	 6 weeks 2 sessions per week 12 sessions in total Duration of each session was one hour (approximately 45 min of exercise and stretching).
	Setting: Community centres
	2. Treatment as usual
Outcomes	Primary outcome:
	1. The severity (change) of depressive symptoms as measured by the Children's Depression Inventory 2 (CDI-2). Measured at the end of treatment: 9 weeks
	Secondary outcomes:
	1. Health-related quality of life as measured by the EuroQol group EQ- 5D-5 L and EQ-VAS
	2. Leisure time physical activity as measured by the Leisure Time Exercise Questionnaire (LTEQ).
	Participants were assessed at baseline, six week (post-intervention) and six-month follow-up.

Funding: National Institute of Mental Health, Research for Patient
Benefit Programme
Conflicts of interest: None reported
Trial registration: ClinicalTrials.gov NCT01474837
Intention to treat analysis: Yes
Sample size calculation: A medium effect size of 0.50 using Cohen's d
parameters was anticipated. To detect such a difference between
two groups at a two tailed 0.05 significance level using 80 % power, 64
participants were required in each arm. After adjusting for 20 %
anticipated attrition rates, the required sample size was inflated to 158.
They were unable to recruit to the required sample size.

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Methods	Randomized controlled trial (RCT).
Participants	N=24 randomized Number analyzed: 24 Drop-out: no reporting of drop-out.
	Age: mean 16.91 (SD 1.03) (intervention group), 16.83 (SD 0.82) (control group). Gender: 100% female.
	Recruitment: 152 female high school students were assessed for presence of major depressive disorder. Baseline severity of depression: I: 30.15 (7.62) C: 29.58 (7.25
	Inclusion criteria:
	1. Age range 15-18 years
	2. Presence of major depressive disorder (MDD) according to DSM-IV- TR criteria
	3. Scoring \geq 18 on the Hamilton Rating Scale for Depression (Ham-D)
	Exclusion criteria:
	1. Other simultaneous psychiatric disorders such as anxiety disorders, psychotic disorders, substance abuse or dependency, personality disorders, and bipolar mood disorder in depressive phase

	Location: Iran
Interventions	 A pool walking exercise program. 60-70% of maximum heart rate. Group-based training. Provider of intervention N/A 6 weeks 3 sessions per week. 18 sessions in total Duration of each session N/A Setting: high school
	2. No exercise and no anti-depressant treatment
Outcomes	 Severity of depression as measured by the Hamilton Rating Scale for Depression (Ham-D), measured at the end of treatment: 6 weeks MHPG Urine Sulfate Maximum Oxygen Uptake (VO2 Max) Participants were assessed at baseline and after six weeks (post- intervention).
Notes	Journal article Funding: University of Mazandaran, Iran. (listed in clinical trials registration). Conflicts of interests: N/A Trial registration: Retrospective registration (2011-08-30). IRCT201104251457N8 <u>https://www.irct.ir/trial/726</u> Intention to treat analysis: N/A Sample size calculation: N/A