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Exercise for the treatment of anxiety in children and adolescents (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 9. Art. No.: CD014426.
DOI: 10.1002/14651858.CD014426.

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[Intervention Protocol]

Exercise for the treatment of anxiety in children and adolescents

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Editorial group: Cochrane Common Mental Disorders Group.
Publication status and date: New, published in Issue 9, 2022.

Citation: Bailey AP, Castellano G, Aleman A. Exercise for the treatment of anxiety in children and adolescents (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 9. Art. No.: CD014426. DOI: 10.1002/14651858.CD014426.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

1. To estimate the treatment effect of exercise interventions for children and adolescents with anxiety disorders compared to control (e.g. no treatment, waitlist, attention placebo, naturalistic usual care), on remission, symptoms, safety and acceptability outcomes.

2. To estimate the treatment effect of exercise interventions for children and adolescents with anxiety disorders compared to other existing anxiety treatments (e.g. medication, psychological therapy), on remission, symptoms, safety and acceptability outcomes.

3. To estimate the treatment effect of adding exercise interventions to existing anxiety treatments for children and adolescents with anxiety disorders compared to those existing treatments alone, on remission, symptoms, safety and acceptability outcomes.

BACKGROUND

Description of the condition

Anxiety disorders are a group of mental health conditions defined by excessive or persistent fear, anxiety or worry (apprehensive expectation), and related behavioural and cognitive disturbance. Defining the boundaries between normal behaviour and clinical anxiety can be challenging, particularly in childhood and adolescence as experiences of fear, worry and anxiety can be developmentally appropriate (Beesdo 2009). Anxiety can also be adaptive, for example supporting learning, directing resources for problem-solving, attention and alertness (Evans 2017). Differentiating clinical anxiety typically requires evaluating persistence and severity of symptoms, level of distress and degree of associated impairment (APA 2022; WHO 2021).

The *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition – Text Revision* (DSM-5-TR) of the American Psychiatric Association (APA 2022) and the *International Classification of Diseases 11th Revision* (ICD-11) of the World Health Organization (WHO) (WHO 2021) distinguish anxiety disorders into the following categories.

- Generalised anxiety disorder (persistent and excessive worry or anxiety generally, or about multiple specific situations of everyday life, e.g. family, health, school).
- Panic disorder (recurring unexpected panic attacks).
- Agoraphobia (marked or excessive fear or anxiety about multiple situations where escape may be difficult, e.g. public places, open areas, enclosed spaces, public transport).
- Specific phobias (marked fear or anxiety about a specific object or situation that is out of proportion to actual danger).
- Social anxiety disorder/social phobia (marked or intense fear or anxiety of social situations).
- Separation anxiety disorder (developmentally inappropriate or excessive fear or anxiety about separation from attachment figures).
- Selective mutism (consistent selectivity in speaking in specific social situations despite ability to do so in others).
- Anxiety disorder due to other medical condition.
- Substance/medication-induced anxiety disorder.
- Other specified/unspecified anxiety disorders.

Anxiety disorders are among the most commonly diagnosed mental health conditions in children and adolescents. One meta-analytic estimate from 41 studies across 27 countries suggests the worldwide prevalence of anxiety disorders at any given time in six- to 18-year-olds is 6.5% (95% confidence interval (CI) 4.7 to 9.1) (Polanczyk 2015). The rate appears to increase with age, for example population data from the UK suggest that in 2017, anxiety disorders affected 3.9% of children aged five to 10 years, 7.9% of adolescents aged 11 to 16 years and 13.1% of adolescents aged 17 to 19 years (Sadler 2017). Estimates of lifetime prevalence suggest 20% to 30% of adolescents will experience an anxiety disorder at some point in their lives (Merikangas 2010). Childhood/adolescence is a specific period of risk, with 50% of all anxiety/fear-related disorders estimated to have their onset before the age of 18 years (median 17 years, interquartile range (IQR) 9 to 25) (Solmi 2022). Emergence appears to differ by age with some disorders having their onset earlier in childhood (e.g. specific phobia/separation anxiety disorder: median 8 years, IQR 5 to 17) and adolescence (e.g. social phobia: median 13 years, IQR 9 to 17), and others in young adulthood (e.g. panic disorder: median 26 years, IQR 18 to 36; generalised anxiety disorder: median 32 years, IQR 20 to 42) (Solmi 2022).

Females appear to develop anxiety disorders at twice the rate of males (Craske 2003). While some studies suggest differences in rates tend to be small in childhood and increase through adolescence and young adulthood (Craske 2003), others suggest these differences are established in younger age groups (Essau 2018).

Anxiety disorders emerging during childhood and early adolescence will often persist into young adulthood (Copeland 2014; Essau 2018). They often occur alongside other conditions such as depression, substance misuse and suicidal behaviour (Essau 2018; Hill 2011), and place young people at increased risk of experiencing comorbidities later in life (Plana-Ripoll 2019). Anxiety disorders can interfere with daily activities such as school work and relationships during the child/adolescent period (Wang 2017), with negative impacts on social, educational/vocational and health functioning persisting into young adulthood (Copeland 2014).

Anxiety produces an important burden of disease in young people. In 2019, the percentage of years lived with disability (YLD) due to anxiety in five- to 19-year-olds globally was estimated to be 5.39% (95% CI 3.61 to 7.76) of the total YLDs attributed to all causes in the age group (GBD 2019).

Anxiety disorders are also commonly associated with poor physical health indicators including low levels of physical activity and sleep problems. Young people who are less physically active show higher rates of anxiety disorders (Ströhle 2007), and sedentary behaviour is prospectively associated with higher anxiety symptoms across adolescence (Kandola 2020). Young people seeking help for anxiety and depression may not meet public health guideline levels of physical activity (Parker 2016). In terms of sleep, anxiety is associated with a range of sleep problems in children and adolescents compared to non-anxious peers, including shortened sleep duration, lower sleep efficiency, longer wake-after-sleep onset, and longer sleep-onset-latency (Hysing 2022; Ojio 2016; Zhang 2017). While changes occur naturally in these sleep domains over childhood/adolescence, they may be disrupted to a larger degree in those with anxiety symptoms and disorders.

Risk factors for anxiety include both environmental and genetic factors, and their interactions. Heritability of anxiety disorders is estimated to be 30% to 40% (Hettema 2001). Children whose parents have a threshold anxiety disorder have an estimated two-fold increase in risk of experiencing anxiety themselves (Lawrence 2019). Some studies have found higher risks to the child when the parental anxiety disorder emerged before 20 years of age, or where it was particularly severe or occurred with multiple anxiety diagnoses, and if two parents were affected (Schreier 2008).

Other factors with predictive value include a child's temperament, with behavioural inhibition producing an estimated seven-fold increase in risk of experiencing an anxiety disorder (Clauss 2012). Parenting style and behaviour may also contribute to risk (Gorostiaga 2019; Romero-Acosta 2021), with factors such as parental control and over-involvement being associated with later child/adolescent anxiety (e.g. Hudson 2012; Hudson

2019), however not universally (e.g. Sahithya 2021). A reciprocal relationship between parental style and behaviour, and child temperament is likely.

Antenatal and perinatal factors may increase the risk of experiencing a number of mental health conditions in childhood and adolescence. However, the strength of associations between these factors and anxiety disorders is limited compared to other psychiatric disorders (Ståhlberg 2020). Nonetheless, preterm birth and maternal somatic illnesses may increase the risk for anxiety disorders in offspring (Ståhlberg 2020). Adverse childhood experiences, such as sexual and physical abuse, divorce or loss of parents, are associated with most mental disorders, including anxiety (Björkenstam 2017).

In contrast, protective factors may include parental monitoring of child's behaviours, positive peer and adult role models, as well as acceptance and support by peers (Wüstner 2019).

Description of the intervention

While psychological and pharmacological interventions are mainstays of treatment for anxiety and depressive disorders in children and adolescents (James 2020; Walkup 2008; Wang 2017), alternative and adjunct treatment options are available, including exercise. A small number of randomised controlled trials have investigated the efficacy of exercise for adolescents experiencing clinical levels of depression (e.g. Bailey 2018; Carter 2021; Hughes 2013; Philippot 2022), while for adults, the available trial base is comparatively larger (e.g. Cooney 2013; Dunn 2005; Hallgren 2015). Exercise treatments for populations with clinical anxiety have received less attention with a limited number of trials in younger and other adults experiencing clinical anxiety (Aylett 2018; Henriksson 2022; Herring 2012; Ramos-Sanchez 2021). These trials generally show low-certainty evidence for improved symptoms or rates of remission, when exercise is compared to control conditions, including no-treatment/waitlist, attention placebo, treatment as usual (TAU) or lower intensity exercise (e.g. stretching). Most trials use aerobic-based exercises, while fewer have implemented resistance exercises (e.g. Henriksson 2022; Herring 2012). Existing systematic reviews focusing on physical activity and exercise interventions for anxiety in child/adolescent populations have included trials almost exclusively in healthy, non-clinical children and adolescents (Carter 2021; Larun 2006).

Treatment guidelines generally reflect this evidence, for example, the UK-based National Institute for Health and Care Excellence suggests a role for exercise in addressing mild depression, and adjunct to psychological therapy and medication for moderate-to-severe depression (NICE 2019). The recommendation is to consider a "structured and supervised exercise programme of typically up to 3 sessions per week of moderate duration (45 minutes to 1 hour) for between 10 and 12 weeks" (NICE 2019). However, exercise is not explicitly included within guidelines as an indicated treatment for anxiety disorders (e.g. NICE 2013). Its role in the clinical care of young people with anxiety appears restricted to general lifestyle advice (e.g. nutrition, sleep hygiene, exercise), which may be delivered as psychoeducation/self-help in early phases of assessment and treatment. This likely reflects the lack of available evidence in this population.

We begin a description of exercise interventions by defining terms. Physical activity is an umbrella term defined as any bodily movement produced by the skeletal muscles that results in energy expenditure above rest (Caspersen 1985). Exercise, as defined for this review, is a subcategory of physical activity and is planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness (Caspersen 1985; Liguori 2020). Health-related components of physical fitness may include cardiorespiratory endurance, muscle strength and endurance, body composition (e.g. bone, muscle, adipose tissue) and flexibility (e.g. range of motion). Skill-related components of physical fitness may include balance, agility, co-ordination, power, reaction time and speed (Liguori 2020).

Four common modalities of exercise are aerobic, resistance, flexibility and neuromotor exercise. Aerobic exercise typically aims to improve or maintain cardiorespiratory fitness by involving large muscle groups in dynamic, rhythmic activities resulting in substantial increases in heart rate, breathing rate and energy expenditure. Examples include jogging/running, cycling and swimming. Resistance exercise is designed to improve or maintain muscular strength or endurance (or both) typically by engaging muscle groups in concentric and eccentric actions under resistance (load) across a number of repetitions or sets of repetitions. Examples include lifting weights, using resistance bands, calisthenics or bodyweight exercises (e.g. push-ups, sit-ups, squats). Flexibility exercise typically aims to maintain or improve the range of motion of a joint and can be achieved by stretching exercises (e.g. ballistic, dynamic, active or passive stretching) and some forms of yoga. Neuromotor exercises target a broad range of motor skills such as balance, agility, co-ordination and proprioception. In practice many exercise regimens are multifaceted, incorporating elements from across the exercise categories. For example, tai chi, yoga, and pilates incorporate varying elements of neuromotor, resistance and flexibility exercises.

Exercise prescription can be described in terms of 'dose' according to the FITT (Frequency, Intensity, Time, and Type of training) principle. Frequency may describe the number of sessions per week, Intensity describes the 'effort' required or energy demand of activity (e.g. light, moderate, vigorous intensity), Time or duration may be described as minutes per session, and Type describes the exercise modality (e.g. treadmill running = aerobic). This can be extended with the additions of volume (e.g. 150 minutes per week or an energy expenditure target) and progression (e.g. intensity/duration increases or remains stable).

Intensity is a central feature of exercise prescription, and in general describes the energy demand of the exercise, or alternatively the perception of effort required. Exercise intensity can be estimated as relative intensity (e.g. percent of maximum heart rate, HR_{max}; % of heart rate reserve, HRR; % maximal oxygen uptake, VO_{2max}), absolute intensity (e.g. metabolic equivalents, METs), subjectively (e.g. Borg Rating of Perceived Exertion, RPE) (Norton 2010). Intensity of resistance exercise can be estimated relative to a maximal single repetition of the exercise (e.g. percent of one-repetition maximal, 1-RM) (Garber 2011). Thresholds have been constructed to support intensity prescription (Garber 2011; Norton 2010), for example:

- *light intensity* is equivalent to 1.6 to less than 3 METs; RPE 8 to 10; 40% to less than 55% HR_{max}; 20% to less than 40% HRR; 20% to less than 40% VO_{2max}; 30% to less than 50% 1-RM;

- *moderate intensity* is equivalent to 3 to less than 6 METs; RPE 11 to 13; 55% to less than 70% HR_{max}; 40% to less than 60% HRR; 40% to less than 60% VO_{2max}; 50% to less than 70% 1-RM;
- *vigorous intensity* is equivalent to 6 METs or greater; RPE 14 or greater; 70% HR_{max} or greater; 60% HRR or greater; 60% VO_{2max} or greater; 70% 1-RM or greater.

A youth compendium has been produced including activities and exercises and their associated youth metabolic equivalents (METy), which are appropriately adjusted for age, sex and body mass (Butte 2018). These can be used to estimate energy expenditure resulting from an exercise intervention. However, like all estimates of intensity, these are group level estimates and do not reflect individual difference in body composition, basal metabolic rate, cardiorespiratory fitness, mechanical efficiency and other factors that influence individual energy expenditure (Butte 2018).

Patient and practitioner decisions regarding appropriate exercise prescription will likely benefit from an understanding of which intervention elements (e.g. intensity, modality) are associated with important clinical effects or increased efficacy. A limited number of head-to-head trials of exercise for clinical anxiety have attempted this. Four trials in adults showed the potential for greater anxiety symptom reduction in moderate- to vigorous-intensity exercise versus light-intensity exercise (standardised mean difference (SMD) 0.38, 95% CI 0.08 to 0.68) (Aylett 2018). One small trial in young women with generalised anxiety disorder suggested the potential for higher remission rates in resistance-based (60%) versus aerobic-based (40%) exercise; however, there was no evidence of a difference for anxiety symptom severity (Herring 2011; Herring 2012).

Other trials have attempted to match exercise dose or volume to the levels recommended in public health guidelines (e.g. Dunn 2005 for adult depression), in part because of the physical health benefits associated with guideline concordant activity levels. However, both the general population and those with mental ill-health conditions typically do not meet these guideline levels of activity (Guthold 2020). The WHO physical activity guidelines for children and adolescents aged five to 17 years recommends engaging in at least a mean of 60 minutes per day of moderate-to-vigorous intensity, mostly aerobic, physical activity (which includes exercise) across the week (Chaput 2020). Vigorous-intensity aerobic activities and those that strengthen muscle and bone (e.g. resistance-based activities) should be incorporated at least three days per week on average (Chaput 2020). Randomised trials in clinical samples of adolescents have implemented exercise interventions with volumes substantially below these public health guideline levels, finding improved depression symptoms (e.g. Philippot 2022). These lower volumes are common across trials with adolescents, young adults and other adults with mental ill-health conditions (Aylett 2018; Bailey 2018; Carter 2021; Cooney 2013); however, evidence for their use with children and adolescents with clinical anxiety remains scarce. The necessary ingredients to improve clinical anxiety remain unclear at this stage due to the heterogeneous nature of available exercise modalities, dose parameters, volumes implemented and the limited availability of trials.

In terms of safety, exercise may be associated with adverse events such as initial muscle pain or musculoskeletal injury, particularly when initiating new regimens at high intensities in inactive populations (Garber 2011). Rare serious adverse events may include sudden cardiac arrest or acute myocardial infarction; however, these are almost exclusively restricted to adults with significant risk factors (Franklin 2020). One systematic review of 375 exercise trials across health conditions found an increase in risk of experiencing a non-serious adverse event of 19% in exercise interventions compared to non-exercising controls (risk ratio (RR) 1.19, 95% CI 1.09 to 1.30) (Niemeijer 2020). However, there was no increased risk of serious adverse events associated with exercise. Of concern is that 398 of 773 eligible trials did not report non-serious adverse events. Previous reviews of exercise and physical activity interventions for anxiety and depression in child and adolescent populations have not reported adverse events (Bailey 2018; Carter 2021; Larun 2006), likely because trials have failed to report such data. Overall, there is insufficient safety data in this population.

How the intervention might work

Despite the increasing evidence for the positive effects of exercise on mental health symptoms across populations, relatively little has been established in humans about the underlying mechanisms.

Several theories based on sparse data have suggested that adaptations in gamma-aminobutyric acid (GABA) levels, noradrenaline and serotonin-based neurotransmitter systems, among others, may explain the anxiolytic effects of exercise (Herring 2018). Exercise is hypothesised to regulate brain-derived neurotrophic factor and promote neuronal cell growth in brain areas implicated in mental ill-health (e.g. hippocampus) (Firth 2018; Ströhle 2010), it may influence oxidative stress and inflammatory pathways (Moylan 2013), or the endocannabinoid system, which is linked to pain relief and anxiolytic effects (Meyer 2019). However, none have been substantiated or confirmed as appropriate mechanism models for child and adolescent anxiety.

Studies have reported that aerobic exercise is related to decreased sympathetic system reactivity and increase parasympathetic system activity (Herzig-Anderson 2013; Matei 2022). The cross-stressor adaptation theory suggests that repeated exposure to physiological stress (e.g. exercise) may sensitise the system to subsequent stressors of a different type (e.g. speaking in public) (Sothmann 1996). Single session exercise studies suggest dampened cortisol reactivity, faster return to baseline and lower overall levels of cortisol in response to a social stressor directly following an exercise bout (Caplin 2021). However, longer-term exercise interventions show mixed results regarding the cross-stressor adaptation theory (Arvidson 2020; Klaperski 2014).

Exposure is a central element of cognitive behavioural therapy (CBT) interventions targeting child/adolescent anxiety disorders (Peris 2017; Reynolds 2012). Exercise elicits many of the same physical sensations associated with anxiety (e.g. elevated heart and respiration rate, perspiration). Through repeated exposure to fear-associated sensations, fear reduction may occur via habituation or extinction learning, potentially producing cognitive changes regarding physical sensations associated anxiety (reappraisals).

Additional benefits of exercise beyond the physiological level include social adaptation, improved self-esteem and body image, and improvement of quality of life (Ashdown-Franks 2020; Stubbs 2018; Wu 2017). Exercise improves psychological competencies such as self-control, autonomy and self-efficacy, which are some of the competencies that are targeted in psychotherapy for the treatment of anxiety (Bell 2019; Whitelaw 2010). These may

be achieved through opportunities for meaningful mastery and achievement experiences (Bandura 1977).

Effects adjacent to the exercise may play a role. For example, exercise may afford opportunities for social interaction and receipt of support, which in the context of anxiety where social withdrawal is common, may be considered a form of social behaviour change. Similarly, behavioural activation is a common treatment component for youth depression (Hetrick 2015), and given the high rates of anxiety–depression comorbidity, exercise may be a vehicle for those with anxiety to engage in adaptive activities, monitor mood and reinforce positive experiences associated with exercise (Veale 2008). The distraction or 'time out' hypothesis suggests bouts of exercise may disrupt the ruminative thought patterns maintaining depression and anxiety.

Few theories have been sufficiently developed to progress our understanding of the potential anxiolytic effects of exercise, and to-date none have been examined in trials with child/adolescent anxiety.

Why it is important to do this review

Anxiety disorders are the most common mental health disorder in childhood and adolescence (Higa-McMillan 2016). While first-line treatments such as CBT are effective for children and adolescents experiencing anxiety disorders, clinical trials suggest about 50% of those receiving CBT may not reach remission (James 2020). Antidepressants are considered another treatment option in some specific circumstances. A limited number of trials suggest combination antidepressant and psychological therapies has potential (e.g. Walkup 2008; Wang 2017). However, the adverse effect profiles of antidepressant medications are well known (Strawn 2015; Wang 2017), and any potential adverse events from psychological therapies remain underinvestigated. Even when modestly effective treatments are disseminated, availability is not universal, and seeking help for mental ill-health can be stigmatising. These factors may contribute to treatment dropout, or avoidance of help-seeking all together (Lake 2017). This suggests the need to investigate additional, non-stigmatising treatments that are safe and effective to supplement existing treatment modalities. Exercise is considered a favourable treatment modality by young people (Jorm 2007).

Two systematic reviews and one scoping review have approached this topic and improved our understanding of the effect of exercise on anxiety in mostly healthy, non-clinical young people and children (Carter 2021; Larun 2006; Pascoe 2020). Currently, there is no systematic synthesis of evidence focusing solely on threshold anxiety disorders in children and adolescents aged five to 19 years.

Low-certainty evidence is available on the efficacy of exercise in the treatment of anxiety in young adults and other adults, but evidence in children and adolescent is lacking. There is a need to understand if exercise is an efficacious and safe alternative treatment modality in this population when delivered alone, or in conjunction with existing treatments. Its comparison to other established interventions will support determination of where exercise fits within current treatment options. Additionally, there is limited understanding of the impact of intensity, frequency, duration and type of exercise on treatment effects in children and adolescents. There is also little evidence on the efficacy of exercise on the treatment of different types of anxiety. These potential moderating factors require investigation to support patient and practitioner decisions regarding appropriate use of exercise in practice. Given the high prevalence and burden associated with anxiety disorders as well as the gaps in knowledge that currently exist, we consider this review could contribute to improving our understanding of therapeutic alternatives for anxiety.

OBJECTIVES

1. To estimate the treatment effect of exercise interventions for children and adolescents with anxiety disorders compared to control (e.g. no treatment, waitlist, attention placebo, naturalistic usual care), on remission, symptoms, safety and acceptability outcomes.

2. To estimate the treatment effect of exercise interventions for children and adolescents with anxiety disorders compared to other existing anxiety treatments (e.g. medication, psychological therapy), on remission, symptoms, safety and acceptability outcomes.

3. To estimate the treatment effect of adding exercise interventions to existing anxiety treatments for children and adolescents with anxiety disorders compared to those existing treatments alone, on remission, symptoms, safety and acceptability outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) including parallel arms, such as cross-over, cluster or individually randomised trials.

Types of participants

We will include trials of children and adolescents aged five to 19 years old, with an anxiety disorder.

We will include trials using standardised diagnostic criteria to define participants with an anxiety disorder as identified in the DSM-5-TR or ICD-11 (APA 2022; WHO 2021) including previous versions (e.g. *Diagnostic and Statistical Manual of Mental Disorders Third Edition*, *Third Edition Revised*, *Fourth Edition*, *Fourth Edition Text Revision* and *Fifth Edition*; *International Classification of Diseases 9th Revision and 10th Revision*), or similar nosological manuals (e.g. *Chinese Classification of Mental Disorders*; Dai 2014).

According to the DSM and ICD we will include the following diagnoses: separation anxiety disorder (6B05), selective mutism (6B06), specific phobia (6B03), social anxiety disorder (or social phobia) (6B04), agoraphobia (6B02), generalised anxiety disorder (6B00), panic disorder (6B01) and other specified or unspecified anxiety disorders (6B0Y, 6B0X) (APA 2022; WHO 2021).

We will exclude post-traumatic stress disorder (6B40) and obsessive-compulsive disorder (6B20) given the separation of these disorders from the anxiety domain in DSM-5. For those studies published before 2014, if the authors stated that participants were specifically recruited with a primary diagnosis of PTSD or OCD, the studies will not be included in this review.

We will include trials where participants are permitted to have any comorbid physical (e.g. obesity) or psychiatric conditions (e.g.

depression, autism). We will also include true dual diagnosis trials where participants are recruited specifically because they have two diagnoses (e.g. anxiety disorder and diabetes). In both instances, the anxiety disorder should be the primary condition of focus for intervention.

Studies including both adults and children/adolescents will be excluded unless we can: extract data for child/adolescent participants separately or obtain them from trial authors, and confirm that randomisation was preserved.

We will include all types of settings (school, sport institutions, home, clinics or others).

Types of interventions

Experimental intervention

Experimental interventions will include any exercise intervention delivered to children or adolescents with anxiety disorders. Interventions must meet the exercise definition according to Caspersen 1985 and the American College of Sports Medicine (Liguori 2020), see Description of the intervention. The exercise must be planned, structured and use repetitive movements of the body to improve or maintain one or more components of physical fitness. These components may be health-related (cardiorespiratory endurance, muscular strength or endurance, body composition, flexibility) or skill-related (balance, co-ordination, agility, power, speed, reaction time) (Caspersen 1985; Liguori 2020). These components of physical fitness are typically targeted with four main exercise modalities: aerobic, resistance, flexibility and neuromotor exercises (see Description of the intervention for examples).

All exercise modalities will be eligible for inclusion, including single modality interventions (e.g. resistance exercise such as lifting weights), multimodal interventions (e.g. circuit training involving separate aerobic and resistance exercises) and cross-modal interventions where different modalities are recruited to perform the activity (e.g. yoga involving resistance, flexibility and neuromotor elements).

Interventions may use recreational activities (e.g. sports, dancing), providing they meet the exercise definition (see below for exclusions). However, activities of daily living will generally be ineligible as they are considered unstructured.

All exercise interventions will be eligible for inclusion regardless of the type (exercise modality), intensity (light, moderate, vigorous), frequency or duration of sessions.

We will include both individual and group-based exercise. Exercise sessions may take place in any environment and may be supervised (e.g. by an exercise professional) or unsupervised, with face-to-face or remote delivery via telehealth delivery. We will include interventions that use additional technology support (e.g. wearable activity trackers, mobile apps, instructional videos, Wii fit, virtual reality). They may be prescribed in terms of modality or dose, or rely on individual patient preference/ability, or a combination.

We will exclude trials where: the intervention does not involve repetitive movements of the body; the intervention is unstructured and dose principles (i.e. frequency, duration and intensity) cannot theoretically be applied to the activity; or the theoretical improvement/maintenance of at least one component of physical fitness cannot be assumed to result from the activity. However, we will not require trials to report the exercise dose or the physical fitness component(s) targeted by their intervention, nor whether either is actually achieved, to be eligible for inclusion. While transparent reporting of interventions is critical (e.g. Hoffmann 2014; Moher 2010; Slade 2016), these elements remain poorly reported in trials of physical activity and exercise in the youth mental health field (Pascoe 2021a).

We will exclude interventions solely using recommendations or psychological methods to increase exercise behaviour (e.g. counselling/motivational enhancement).

We will exclude trials measuring outcomes immediately before and after a single exercise session, and trials that provided less than a week of exercise. While these very brief interventions may reduce state anxiety and anxiety sensitivity in healthy young people (Pascoe 2021b), it is unlikely that threshold anxiety disorders will be responsive over such a short intervention period. We will exclude trials where exercise is delivered as part of a broader package (e.g. including lifestyle, psychological therapy, medication components), unless the comparison arm equally receives these components.

Comparator interventions

Main comparisons include:

- objective 1: exercise versus control:
  - exercise versus no treatment and waitlist;
  - exercise versus attention or activity placebo;
  - exercise versus naturalistic usual care;
- objective 2: exercise versus other anxiety treatments:
  - exercise versus other anxiety treatments (psychological, psychosocial or pharmacological anxiety treatments, including standardised TAU);
- objective 3: exercise adjunct to other treatments:
  - exercise plus standardised TAU versus standardised TAU;
  - exercise plus other anxiety treatments vs other anxiety treatments.

Comparators under objective 1 include waitlist, no treatment, attention or activity placebo, and naturalistic usual care. We define attention or activity placebo as any non-specific intervention that is not an established and accepted active anxiety intervention. Generally, these placebo controls will attempt to control for the components of an exercise intervention such as treatment exposure within a trial, session attendance, expectations and social interaction. Naturalistic usual care refers to any care available outside the trial (e.g. within the community) that a participant may or may not access of their own accord. This may include varying elements at varying degrees of intensity which may or may not be guideline concordant (Freedland 2011). These comparators were selected to establish whether exercise interventions in their own right have some effect on anxiety.

Comparators under objectives 2 and 3 include any existing psychological, psychosocial or pharmacological intervention or standardised TAU targeting anxiety, at any dose or with any characteristic. Standardised TAU is defined where there is some level of standardisation of the TAU model and components

as part of the trial (e.g. protocol, manual or clinical guideline implemented), ensuring all participants receive the same standard TAU. This may include but is not limited to, medication, case management, psychological therapy or their combination. An example may include where the trial is conducted within a clinical service or inpatient setting where standardised treatment protocols are implemented according to clinical guidelines, sometimes referred to as 'standard of care' (Freedland 2011). This is distinct from naturalistic usual care for anxiety as defined above. We chose these comparators to determine how exercise treatments compare to other established anxiety treatments including 'standard of care', and further, if there is additional benefit when exercise is added to these existing treatment modalities.

Naturalistic usual care for anxiety within the community (obtained outside the trial) may be present for both arms in all comparisons.

Types of outcome measures

Primary outcomes

- Anxiety disorder remission rate (dichotomous): defined as the absence of anxiety disorder diagnosis, made by reliable and valid structured or semi-structured interviews for DSM or ICD child/adolescent anxiety disorders (e.g. Anxiety Disorder Interview Schedule for Children – Child and Parent, ADIS-C/P; Silverman 1996). We chose this as the most robust method to establish the resolution of the anxiety disorder.
- Anxiety symptom severity (continuous): measured as clinician-, other observer-, or self-report anxiety symptoms using a standardised, validated and reliable continuous scale (e.g. Screen for Child Anxiety Related Emotional Disorders, SCARED; Birmaher 1999; or Pediatric Anxiety Rating Scale, PARS; Riddle 2002). We will use clinician-rated measures in the first instance; when these are not available, we will use self-, parent- or teacher-report measures. We will prioritise broad anxiety symptom measures (e.g. Spence Children's Anxiety Scale, SCAS; Spence 1997) over disorder-specific measures (e.g. Social Phobia and Anxiety Inventory for Children, SPAI-C; Beidel 1995) where both are available. We will prioritise broad measures to limit potential heterogeneity due to measurement of different anxiety domains.
- Overall adverse events (dichotomous): defined as the number of participants reporting at least one adverse event (e.g. pain, fatigue, negative psychological events or others), from randomisation to postintervention regardless of the cause of the event.

Secondary outcomes

- Dropout as a proxy for intervention acceptability (dichotomous): defined as the number of participants who left their assigned arms early for any reason. Where dropout is not fully reported, we will use missing data from randomisation to the postintervention time point to estimate rate of dropout.
- Quality of life (continuous): measured by validated scales such as the Child Health and Illness Profile (Starfield 1993) or Child Health Questionnaire (CHQ) (Landgraf 2014), or any other validated scales (Ravens-Sieberer 2014).

Reporting of primary or secondary outcomes within trials is not a required inclusion criteria. Eligible trials that did not measure or report these outcomes will be included within results tables and narrative synthesis.

Hierarchy of outcomes

Where a trial measures the same outcome domain in multiple ways (e.g. anxiety symptoms measured on two different scales), we will prioritise the outcome measure most commonly reported across trials contributing to meta-analysis.

Timing of outcome assessment

The primary endpoint for the review will be postintervention (i.e. immediately following the intervention period). We will also consider the following secondary endpoints.

- Short-term follow-up (time frame: six months postintervention).
- Long-term follow-up (time frame: greater than six months postintervention).

If a trial reports more than one follow-up point within the same time frame, we will use data from the longest follow-up. Primary and secondary outcomes will be considered at each time point, where appropriate.

Search methods for identification of studies

Electronic searches

An information specialist with the Cochrane Common Mental Disorders Group (CCMD) will run searches on the following databases using relevant keywords, subject headings (controlled vocabularies) and search syntax, appropriate to each resource:

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL) (current issue);
- Ovid MEDLINE (1946 onwards) (Appendix 2);
- Ovid Embase (1974 onwards);
- Ovid PsycINFO (1806 onwards);
- EBSCOhost ERIC (Educational Resources Information Center) (all available years).

There will be no restriction on date, language or publication status applied to the searches.

We will search the international trials registries (including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/)) to identify additional ongoing and unpublished studies.

Searching other resources

Grey literature

We will search the grey literature for dissertations and theses:

- Electronic Theses Online Service (EThOS) – British Library (ethos.bl.uk/Home.do);
- DART – Europe e-theses Portal (www.dart-europe.eu/basic-search.php);
- Networked Digital Library of Theses and Dissertations (NDLTD) (search.ndltd.org/);

- PQDT Open – open access dissertations and theses (pqdtopen.proquest.com/search.html);
- ProQuest Dissertations & Theses Global (search.proquest.com/pqdtglobal/dissertations/).

We will also search Open Grey (System for information on Grey Literature), to identify research produced by organisations outside the traditional academic publishing and distribution channels.

Reference lists

We will check the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (e.g. unpublished or in-press citations).

Correspondence

We will contact study authors and subject experts for information on unpublished or ongoing studies, or to request additional data.

Data collection and analysis

Selection of studies

Two review authors (from CG, AA, CV, IM) will independently perform selection of studies, with differences resolved through discussion with a third review author. We will screen titles and abstracts for inclusion, and retrieve and screen the full-text of any potentially eligible studies.

We will use the trial as the unit of interest for this review, collating multiple reports stemming from the same trial and removing any duplicate reports. We will report a PRISMA flow diagram of the complete search and selection process (Page 2021), and record excluded studies in the 'Characteristics of excluded studies' table with reasons for exclusion.

Data extraction and management

At least two review authors will independently perform data extraction. We will use a data extraction form specially designed for this review, following a piloting process. We will resolve disagreements by discussion and, if necessary, by a third-party arbitration. We will enter extracted data into the Covidence toolkit (Covidence).

We will extract the following study characteristics and present them in the characteristics of included studies table.

- Methods: study design, total duration of study, number of study centres and location, study setting and its characteristics, and date of study.
- Participants: number randomised, number lost to follow-up or withdrawn/dropped out and their reasons, number analysed, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria, comorbid conditions.
- Interventions: details of the intervention including type/content; exercise intensity; the number, frequency and duration of exercise sessions; and length of intervention period; adherence assessed by attendance at exercise interventions (e.g. as mean percentage of sessions attended), and the number of participants who did not complete the interventions; any concomitant treatments and their details, and any excluded treatments. We will use the Consensus on Exercise Reporting Template to assess characteristics of the intervention (Slade 2016). This is an adaptation of the TIDieR (Template for Intervention Description and Replication) template designed specifically for exercise trials (Hoffmann 2014).
- Comparators: details of the comparators, including type/content, dose and duration, any concomitant treatments and their details, and any excluded treatments.
- Outcomes: primary and secondary outcomes, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

If outcome data are not reported in a usable way, we will attempt the following: contact trial authors, calculate missing information from the reported data (if possible), attempt extraction of graphically presented data using available tools (e.g. WebPlotDigitizer), or state as missing if unattainable.

We will extract continuous outcome data as mean postintervention score, standard deviation (SD) and number of participants per group included in the trial analysis. Where postintervention scores are not reported or obtainable, we will extract mean change from baseline to postintervention scores (i.e. change scores). For dichotomous or event-like outcome data, we will extract number of events (i.e. participants with event) and number of total participants randomised per group, and those available at post-treatment or included in trial analysis. We will note whether data are generated using intention-to-treat (ITT) principles, including any imputation or analysis method used, or an available-case analysis (ACA) noting the number of participants not included within such analysis.

Three review authors (CG, AA, CV) will transfer data into Review Manager Web and another review author (TJ) will double-check data entries (RevMan Web 2022).

Assessment of risk of bias in included studies

Two review authors will independently use the Cochrane RoB 2 tool to assess the risk of bias for the primary outcomes (Sterne 2019). A third review author will resolve disagreements in ratings between authors. We will assess the risk of bias according to the following domains.

- Bias in the randomisation process.
- Bias due to deviations from the intended intervention (assignment to treatment).
- Bias due to missing data.
- Bias in the measurement of the outcome.
- Bias in the selection of the reported result.

We will judge each potential source of bias as 'high risk', 'low risk' or 'some concerns' and will provide a supporting quotation from the study report together with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where necessary, we will contact the trial authors for further information. Where information on risk of bias relates to unpublished data or correspondence with a trial author, we will note this in the risk of bias table. We will present risk of bias data graphically and in the text.

We will consider a study to be at high risk of bias overall if at least one domain is rated 'high risk'. We will consider a study to have some concerns regarding bias if at least one domain is rated 'some concerns' and all others 'low risk'; however, we may consider a study to be at high risk of bias if multiple domains are rated 'some concerns'. We will consider that a study has low risk of bias if all domains are rated 'low risk'.

We will use risk of bias assessment as part of the judgement regarding the certainty of the evidence for each outcome according to the GRADE recommendations (Schünemann 2013).

We anticipate that exercise interventions will not be blinded and, therefore, bias in the measurement of the outcome could be high by default for child/adolescent-reported outcomes. For the outcomes assessed by the clinician or other observer (parent/teacher), potential for bias may not be high if adequate assessor blinding is implemented.

Measures of treatment effect

Dichotomous data

We will calculate the RR with 95% CI for dichotomous and event-like outcomes for each comparison. For the primary analysis, we will calculate individual trial effect estimates for dichotomous outcomes according to ITT principles, using the number of participants with an event (numerator) from total participants randomised (denominator) (see Dealing with missing data for further details).

For remission and adverse events, we will present an ACA alongside the primary analysis, using those participants available or analysed at post-treatment as denominator, rather than those randomised.

To aid interpretation of dichotomous data, we will calculate a summary percentage of participants who remitted, experienced at least one adverse event and who dropped out for both exercise and comparator arms. We will present summary of findings tables for illustrative comparative risks for intervention and comparator groups (per 1000 population). We will use the assumed comparator risk (pooled from comparator groups of included trials, expressed per 1000 population) and the relative effect measure (RR) to derive the corresponding intervention risk per 1000 population (Schünemann 2022a).

Continuous data

We will analyse continuous outcomes by calculating mean differences (MD) and 95% CIs between exercise and comparator groups, where trials use the same outcome measure. If it is possible to combine results that use different scales, we will calculate SMDs with 95% CIs. For the primary analysis, we will calculate individual trial effect estimates using means and SDs from participants available at post-treatment or included in trial analyses. We will give preference to data generated via ITT principles over ACA/observed-case analysis where multiple analyses are reported.

We will prioritise mean postintervention scores for MD or SMD calculations. Where a trial reports only mean change from baseline to postintervention scores (i.e. change scores), we will combine these with post-treatment scores for MD calculations. Where studies use different scales, indicating an SMD calculation, we will attempt to transform change scores to post-treatment scores using the reported mean baseline score. Where this is not possible, we will combine change scores with trials reporting postintervention scores. While the combination is theoretically problematic for SMD calculations, in practice there appears to be negligible impact on pooled effect estimates (da Costa 2013). In this case, we will attempt to standardise SMDs using available post-treatment SDs or via baseline SD imputation. We will investigate any impact in sensitivity analysis (Schünemann 2022b).

To aid interpretation of SMDs, a back translation to a commonly used scale will be provided after analysis. If possible, we will prioritise the scale most commonly reported within included trials. In this case, we will calculate the SD as a weighted mean across intervention groups from trials using that scale (Furukawa 2006). Otherwise, we will interpret SMDs using commonly defined cut points for standardised effect sizes where 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988). We will use these effect measure interpretations in summary of findings tables (Schünemann 2022b).

Unit of analysis issues

The unit of analysis will be the participants in RCTs. In case of cluster-RCTs, we will use the generalised estimating equation (GEE) to directly estimate the required effect measure of analysis that adequately takes into account the design by group (Higgins 2022a). When the authors have not conducted a GEE analysis, we will use an approximate approach by inflating the standard errors (Higgins 2022a). In the case of cross-over trials, we will only use data from the first phase prior to crossing over, where data are available. This is due to the risk of carry-over effects from one phase to the next and the possibility of 'period effects' in mental health conditions (Higgins 2022a).

Multi-arm trials can pose unit of analysis problems when conducting pairwise meta-analysis due to inclusion of non-independent effect estimates. For such trials, we will define pairwise comparisons of exercise interventions and comparators relevant to the objectives of the review to avoid double-counting trial participants. For trials with multiple eligible exercise arms within a comparison (e.g. aerobic exercise versus resistance exercise versus waitlist), we will divide the comparator group sample size by the number of exercise arms to enable pairwise comparisons. For trials with multiple eligible comparator arms within a comparison (e.g. exercise versus not treatment versus activity placebo, or exercise versus CBT versus medication), we will divide the exercise intervention group sample size by the number of comparator arms to allow pairwise comparisons. For continuous outcomes, means and SDs will remain unchanged when group size is split. For dichotomous outcomes, events will be split evenly between newly created groups. It is acknowledged that this approach only partially overcomes the unit of analysis error as multiple effects from the same trial within a comparison remain correlated and between-trial heterogeneity may be artificially reduced (Higgins 2022a). We prioritise here preserving useful trial data matching the comparisons relevant to our review objectives while supporting approximate investigations of heterogeneity (i.e. subgroup analysis) due to the inclusion of different exercise intervention modalities and different comparator conditions within trials, both of which may influence effect sizes (Aylett 2018; Gold 2017). We will investigate the effect of this decision with sensitivity analysis.

Dealing with missing data

In the first instance, we will contact trial authors for missing group-level statistics (e.g. SDs, means) and individual participant data (e.g. diagnostic status of participants not included in post-treatment analysis). We will also request any unreported reasons for dropout/withdrawal or missingness, and any further information on how missing data were handled when conducting data analyses. All correspondence with trial authors will be documented and reported, including the source and any analyses the obtained data contributes to.

Missing statistics

For trials with missing SD, where it cannot be obtained from authors or calculated from other reported statistics (e.g. CIs, t values, P values, as per Higgins 2022b), we will impute a pool SD based on other trials included in the analysis following the method described in Furukawa 2006. For trials reporting only medians and IQRs, we will estimate means and SDs and impute them following the method described in Wan 2014 and Higgins 2022b.

Missing participant outcome data

Continuous data

We will use ITT data when available. Where missing participant data (MPD) is evident, we will prioritise data generated from mixed-effects models or by multiple imputation, followed by last-observation-carried forward and finally ACA/observed-case analysis where multiple approaches are reported. If the number of participants analysed is not reported, we will use the number randomised. We will not impute missing individual participant data (i.e. means) for the primary analysis.

We will investigate whether the primary analysis is robust to missing data by conducting sensitivity analyses, following the guidance reported in Guyatt 2017, Ebrahim 2013, and Ebrahim 2014. For participants with missing data, we will impute their missing values with mean values (and the median SD of comparator arms) from other included trials, combining them with reported data. We plan to use five sources of data from other included trials for this imputation: A. 'best' intervention arm mean score; B. 'best' comparator arm mean score; C. comparator arm mean score of the same trial; D. 'worst' intervention arm mean score and E. 'worst' comparator arm mean score. These sources will be used in four imputation strategies, progressively increasing in stringency to challenge the primary analysis: 1. source C for missing data in both arms; 2. source D for missing intervention arm data, and source B for missing comparator arm data; 3. source E for missing intervention arm data, and source B for comparator arm missing data; 4. source E for missing intervention arm data and source A for missing comparator arm data.

Dichotomous data

We will use ITT data when available. For remission, we will assume that participants with missing data continued to experience an anxiety disorder diagnosis. We will calculate remission rates using the number randomised as denominator, leaving the numerator unchanged. For overall adverse events, we will calculate the rate using the number randomised as denominator and the number of participants experiencing at least one adverse event from randomisation to follow-up as numerator. We will assume participants with missing data did not experience an adverse event, unless one is recorded prior to loss-to-follow-up (e.g. dropout due to lack of efficacy/worsening symptoms/adverse event).

We will present primary analyses alongside ACAs using only data from those participants available/analysed at follow-up (i.e. ignoring missing data), using the 'missing at random' assumption (Mavridis 2014).

We will investigate whether the primary analysis is robust to missing data in a series of sensitivity analyses following the approach in Akl 2013 and Guyatt 2017. We will impute missing event rates by adjusting the relative incidence (RI) among those with MPD compared to those available at follow-up (FU) in the same arm ($RI_{MDP/FU}$), and recalculate pooled effects (Akl 2013).

Where the primary result suggests harm with exercise, we will impute an $RI_{MDP/FU}$ = 1 in comparator participants with missing data, and a $RI_{MDP/FU}$ less than 1 in intervention participants with missing data, using progressively more extreme $RI_{MDP/FU}$ for the intervention arm in each sensitivity analysis (e.g. 0.8, 0.5, 0.2). Alternatively, we may impute $RI_{MDP/FU}$ = 1 for intervention participants and a $RI_{MDP/FU}$ greater than 1 for comparator participants, using progressively more extreme $RI_{MDP/FU}$ for the comparator arm for each sensitivity analysis (e.g. 1.5, 2, 3, 5).

Where the primary result suggests benefit with exercise, we will impute $RI_{MDP/FU}$ = 1 for comparator participants and $RI_{MDP/FU}$ less than 1 for intervention participants (e.g. 0.8, 0.5, 0.2).

Where the result includes both harm and benefit, we will impute $RI_{MDP/FU}$ = 1 for comparator participants and $RI_{MDP/FU}$ greater than 1 for intervention participants (e.g. 1.5, 2, 3, 5).

Assessment of heterogeneity

We will assess statistical heterogeneity by carrying out the Chi^2 test of homogeneity (Cochran 1954), calculating the I^2 statistic (Higgins 2003), and conducting a visual inspection of forest plots (i.e. overlap of CIs for individual trials).

We will use the Chi^2 test to assess whether observed differences between trial results are compatible with chance. We estimate retrieving a limited number of eligible trials with small sample sizes and, therefore, the Chi^2 test may have low power to detect heterogeneity. We will use a P value of 0.10 to define statistical significance. A statistically significant result (or a large Chi^2 statistic relative to degrees of freedom, or both) may suggest important heterogeneity.

The I^2 statistic represents the percentage of total variability in effect estimates that may be due to between-trial heterogeneity. Where there is heterogeneity, we will report it and conduct planned subgroup analyses investigating potential causes. We will use the following approximate guide to interpret the magnitude of heterogeneity (Deeks 2001):

- 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.

The importance of the observed value of the I^2 statistic depends on magnitude and direction of effects.

We will discuss the different types of heterogeneity (methodological, clinical and statistical) narratively. If we consider studies to be too clinically heterogeneous, we will not perform meta-analysis.

Assessment of reporting biases

We will attempt to limit the effect of reporting bias by using comprehensive searches (including trials registers, unpublished literature), without language limits. We will also attempt to retrieve trial protocols and contact trial authors for missing trial reports or missing results, or both.

We will assess potential reporting bias using a number of methods: we will construct funnel plots (effect estimates plotted against the standard error of the effect estimate) for visual inspection and conduct a formal test for asymmetry (i.e. small-study effects) using the Egger test (Egger 1997; Page 2022). These will only be conducted for analyses where a minimum of 10 trials contribute data (Sterne 2011). We will use contour-enhanced funnel plots placing contour lines at P = 0.1, 0.05 and 0.01 in an attempt to differentiate non-reporting bias from other factors. Where asymmetry is suspected, we will explore reasons, for example: non-reporting bias at the trial or result level, poor methodological quality in smaller trials, heterogeneity, artefactual (e.g. effect sizes being correlated with their standard errors) and chance (Egger 1997). We will consider the interventions and circumstances in which they are implemented (including adherence) in different trials to help identify true heterogeneity as a cause of funnel plot asymmetry. We may contact authors for more information.

We will carry out sensitivity analysis in cases where small-study effects are suspected to distort the results of meta-analyses. For example, comparing fixed-effect and random-effects estimates (Sterne 2011).

Data synthesis

Where trials cannot be combined in meta-analysis due to the degree of between-trial heterogeneity or lack of available data, we will synthesise results narratively. Otherwise, and where there are sufficient trials available per outcome, we will perform meta-analysis using Review Manager Web (RevMan Web 2022).

We will use the inverse-variance method to pool continuous data (MDs or SMDs). For dichotomous data (RR), we will use the Mantel-Haenszel method.

We plan to use the random-effects model as it is assumed that trials are estimating intervention effects following a distribution across trials, rather than a common intervention effect (DerSimonian 1986). We will contrast this assumption using the fixed-effect model in sensitivity analysis.

Subgroup analysis and investigation of heterogeneity

We will conduct observational subgroup analyses regarding potential sources of heterogeneity such as intervention, comparator and sample characteristics. These will be run for our co-primary outcomes (anxiety disorder remission rate, anxiety symptom severity, overall adverse events) where sufficient trials are available to do so.

Intervention characteristics

Components of exercise interventions may represent important moderators of treatment effects. For example, in adults with anxiety, head-to-head trials show a potential for greater symptom reduction in higher- versus lower-intensity exercise (Aylett 2018). In addition to intensity, a range of exercise modalities can be implemented (e.g. resistance-based, aerobic-based). A small trial in young adults with generalised anxiety disorder suggested higher rates of remission from resistance- versus aerobic-based exercise, although there was no evidence of difference in terms of symptoms (Herring 2011; Herring 2012). This information is critical for informing practitioners and patients about the most appropriate forms of exercise intervention prescription. Indeed, intervention setting is another potential moderating factor, with group-based activities reported to confer a range of social benefits compared to individual activities (Eime 2013). However, whether these settings produce differential effects for child/adolescent anxiety disorders remains unclear. Anxiety is commonly associated with social avoidance and, therefore, delivery setting needs careful consideration. We planned to conduct subgroup analyses by the following intervention characteristics:

- exercise intensity (moderate- to vigorous-intensity versus light-intensity exercise);
- exercise modality (predominantly aerobic-based versus predominantly resistance-based versus other);
- exercise setting (group programme versus individual programme).

Comparator characteristics

Meta-analytic findings suggest the type of comparator has a material impact on the magnitude of pooled effects (Gold 2017; Michopoulos 2021; Mohr 2014). Therefore, we planned the following comparator subgroupings for each objective:

- control type (no treatment/waitlist versus attention placebo versus naturalistic usual care);
- comparator intervention type (e.g. CBT versus medication versus standardised TAU);
- adjunct intervention type (e.g. CBT versus medication).

Sample characteristics

There is some evidence that different forms of anxiety may respond differently to the same efficacious treatment modality. For example CBT, a first-line treatment across anxiety disorders, may be less beneficial for both children and adults with social anxiety disorder compared to those with non-social types of anxiety disorders (Cuijpers 2016; Ginsburg 2011; Hudson 2015). Similarly, it is important to determine which anxiety disorders may be responsive to the current treatment under investigation. Therefore, we will conduct subgroup analysis by the following sample characteristic:

- type of anxiety disorder (e.g. separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, generalised anxiety disorder, panic disorder, agoraphobia, others specified/unspecified, or a mixture of different anxiety diagnoses).

We will calculate the test for interaction available in Review Manager Web (RevMan Web 2022).

Sensitivity analysis

If adequate data are available, we will perform sensitivity analyses to assess the robustness of results for our three primary outcomes (Cochran 1954). We will investigate the impact, if any, the following decisions may have on pooled estimates:

- inclusion of trials judged at high risk of bias. We will restrict sensitivity analyses to trials judged at low risk/some concerns;
- imputation of missing values. We will remove trials where we imputed missing statistics (e.g. SDs, means);
- use of random-effects model. We will run sensitivity analyses using the fixed-effect model;
- source of anxiety symptom rating. We will restrict sensitivity analysis to anxiety symptoms rated by a single source (1. clinician/researcher-rated, 2. parent-rated, and 3. self-report). There may be material differences in symptom ratings depending on the source of those ratings (Bowers 2020; Cole 2000; Wren 2004).
- combining broad anxiety symptom scales with disorder-specific scales. We will run sensitivity analyses excluding trials using only disorder-specific scales.
- assumptions for MPD. Sensitivity analyses as described in Dealing with missing data;
- inclusion of non-independent effect estimates within a comparison. We will use an alternative method for multi-arm trials where we will combine eligible exercise or comparator arms creating a single pairwise comparison.
- inclusion of skewed data. We will exclude trials reporting continuous outcomes where skewness is suspected (i.e. where the mean minus lowest possible scale score divided by SD is less than two).
- combining change and postintervention scores in SMD calculations. We will exclude trials using only change scores from the sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables to present the main findings from each of our three comparisons: 1. exercise versus control; 2. exercise versus other anxiety treatments; and 3. exercise adjunct to other anxiety treatments. For each main comparison, we will report the outcomes listed below at the post-treatment time point, where available, and will present standardised effect size estimates and 95% CIs.

- Anxiety disorder remission rate
- Anxiety symptom severity
- Overall adverse events
- Dropout
- Quality of life

Two review authors (AA, GC) will independently assess the certainty of the evidence using GRADE with disagreements resolved by discussion or involvement of a third review author (AB) (Schünemann 2013; Schünemann 2022a). For each outcome under each main comparison, we will consider the following domains: study limitations (risk of bias), inconsistency, imprecision, indirectness and publication bias. The GRADE approach specifies four levels of the certainty for a body of evidence for a given outcome: high, moderate, low and very low. Decisions to upgrade or downgrade level of certainty will be documented using footnotes.

We will use GRADEpro GDT to create the summary of findings tables, and will follow the methods for preparing the tables laid out in the *Cochrane Handbook for Systematic Reviews of Interventions* (GRADEpro GDT; Schünemann 2022a).

ACKNOWLEDGEMENTS

We thank the Iberoamerican Cochrane Center, Spain for providing guidance during protocol development, particularly the support from Marta Roque and Sera Tort.

Cochrane Common Mental Disorders (CCMD) supported the authors in the development of this protocol.

The following people conducted the editorial process for this article.

- Sign-off Editor (provided editorial guidance to authors, final editorial decision): Sarah Hetrick, University of Auckland.
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Hendon, Centre for Reviews and Dissemination, University of York.
- Information Specialist (provided editorial guidance to authors, edited the article, developed searches): Sarah Dawson, University of Bristol.
- Peer-reviewers (provided comments and recommended an editorial decision): Laiana A Quagliato, Federal University of Rio de Janeiro (content review); Claire McCartan, Queen's University Belfast (content review); Jane Simmonds, UCL Great Ormond Street Institute of Child Health, University College London (content review); Nji Mbaka Fon (consumer review); Kerry Dwan, Cochrane (methods review); Nuala Livingston, Cochrane (methods review); Lindsay Robertson, Centre for Reviews and Dissemination, University of York (methods review).

The authors and the CCMD Editorial Team are grateful to the peer reviewers for their time and comments. They would also like to thank Cochrane Copy Edit Support for the team's help.

Cochrane Group funding acknowledgement: the UK National Institute for Health and Care Research (NIHR) is the largest single funder of the CCMD Group.

Disclaimer: the views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the NIHR, National Health Service (NHS), the Department of Health and Social Care or the UK government.

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APPENDICES

Appendix 1. Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

Cochrane Common Mental Disorders (CCMD) maintains two archived clinical trials registers at its editorial base in York, UK: a references register and a studies-based register. The CCMDCTR-References Register contains over 40,000 reports of randomised controlled trials (RCTs) in depression, anxiety and neurosis. Approximately 50% of these references have been tagged to individual, coded trials. The coded trials are held in the CCMDCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary; (please contact the CCMD Information Specialists for further details). Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950 to 2016), Embase (1974 to 2016) and PsycINFO (1967 to 2016); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trial registers via the World Health Organization's trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCMD's generic search strategies (used to identify RCTs) can be found on the Group's website (cmd.cochrane.org/specialised-register), with an example of the core MEDLINE search (used to inform the register) listed below. The Group's Specialised Register fell out of date in the summer of 2016, with the Editorial Group's move from Bristol to York. It is currently archived but includes relevant reports of RCTs to June 2016.

Core search strategy used to inform the Cochrane Common Mental Disorders Group's Specialised Register: Ovid MEDLINE

A weekly search alert based on condition + RCT filter only
1. *[MeSH Headings]:* eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body

dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/
2. *[Title/ Author Keywords]:* (eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.
3. *[RCT filter]:* (controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)
4. (1 and 2 and 3)
Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record. Similar weekly search alerts were also conducted on OVID Embase and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

****

The CCMDCTR will be searched for this review using the following terms:

CCMDCTR-Studies (all available years)
#1 (agoraphobia or anxi* or mutism or phobia or phobias or panic or "school refusal") and STUDY:CRSTYPE and INSEGMENT
#2 exercise and STUDY:CRSTYPE and INSEGMENT
#3 (child* or adolescent*) and STUDY:CRSTYPE and INSEGMENT
#4 (#1 and #2 and #3)

CCMDCTR-References (all available years)
[*Condition*]
#1 ((infant* or child* or adolesc* or pediatric* or paediatric* or teen* or young* or youth or student* or school* or preschool*) adj2 anxi*) AND INSEGMENT
#2 (agoraphobi or anxiety or (depress* adj2 anxi*) or GAD or mute* or mutism or panic or phobi* or (school adj2 refus*) or (social adj2 anxi*)) AND INSEGMENT
#3 (ADIS-C* or ADIS-P* or DISCAP or SCARED or SCAS or RCADS or RCMAS or MASC or CBCL or STAI-C or SPAI-C or SAS-A) AND INSEGMENT
#4 (#2 or #3)
[*Intervention*]
#5 (aerobics or sport* or exercis* or (physical* adj (activ* or condition* or effort* or exertion or education or game* or fitness or mobility or train*)) or "keep* fit" or "fitness training" or ((recreation or activity) adj5 therap*) or bike or bikes or biking or bicycl* or ((recreational or distance) adj cycling) or walks or walking or hiking or climbing or tramping or mountaineer* or pedomet* or fitbit* or "fit bit*" or "wii fit*" or ((fitness or activit*) adj track*) or (steps adj2 (count* or track* or monitor*)) or running or jogging or skipping or sprinting or "park run*" or treadmill* or ((aqua* or water) adj (activit* or fit*)) or swimming or sailing or boating or yachting or canoeing or kayaking or surfing or sailboard* or "sail board*" or skiing* or snowboarding or "snow boarding" or iceskat* or "ice skat*" or skating or skateboard* or "skate board*" or calisthenics or dance or dancing or ballet or salsa or zumba or jumping or hopping or gymnas* or "team game*" or football* or rugby or cricket or rounders or baseball or netball or volleyball or tennis or squash or badminton or golf*) AND INSEGMENT
#6 (“muscle strengthening” or (muscular adj5 (strength or resistance)) or ((weight or weights) adj5 lifting) or weightlifting or “power lifting” or “weight train*” or pilates or stretching or plyometric* or “cardiopulmonary conditioning” or “motion therap*” or “neuromuscular facilitation*” or “movement therap*” or “isometric training” or “lifting effort*” or gardening or ((leisure or recreation*) adj activ*))) AND INSEGMENT
#7 (qigong or "qi gong" or "chi kung" or taichi or "tai chi" or taiji or taijiquan or shadowboxing or "shadow boxing" or yoga or yogic or pilates or kinesiology or ((breathing or respiration) adj5 therap*) or relaxation or ((moderate* or graded) adj2 activit*)) AND INSEGMENT
#8 ((fitness or leisure or wellness) adj (cent* or facility or facilities)) AND INSEGMENT
#9 (#5 or #6 or #7 or #8)
[Age Group]
#10 (infant* or child* or adolesc* or paediatr* or pediatr*):emt,mh,kw,ky,so AND INSEGMENT
#11 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pre-adolesc* or pubert* or pubescen* or prepube* or pre-pube* or teen* or (young adj (adult* or survivor* or offender* or minorit*)) or youth* or student* or school* or preschool* or nurser* or kindergarten):ti,emt,mh,kw,ky AND INSEGMENT

#12 (#10 or #11)
#13 (#1 and #9) OR (#4 and #9 and #12)

****

Appendix 2. Database search strategies: MEDLINE

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 onwards>
Search strategy:

[RCT Filter]
1 controlled clinical trial.pt.
2 randomized controlled trial.pt.
3 (randomi#ed or randomi#ation or randomi#ing).ti,ab,kf.
4 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,kf.
5 (placebo or ((attention or active) adj control*)).ti,ab,kf.
6 trial.ab,ti,kf.
7 ((control* or group* or compar*) adj5 (((care or treatment*) adj2 (usual or standard or routine)) or TAU or CAU)).ab.
8 ((control* or group* or compar*) adj5 (waitlist* or wait* list* or waiting or WLC)).ab.
9 or/1-8
[*Condition*]
10 ANXIETY DISORDERS/
11 *ANXIETY/ or ANXIETY/di, pc, px, th or anxiety.ti.
12 AGORAPHOBIA/ or PANIC DISORDER/ or ANXIETY, SEPARATION/
13 PHOBIC DISORDERS/ or PHOBIA, SOCIAL/
14 (agoraphobi* or generali#ed anxiety or GAD or separation anxiety or (social* adj2 (anxi* or fear*)) or phobi* or mute? or mutism or school refusal).ti,ab,kf.
15 anxiety.ab. /freq=3
16 panic.mp.
17 or/10-16
[Age Group]
18 ADOLESCENT/ or CHILD/ or CHILD, PRESCHOOL/
19 (infant? or child* or adolesc* or paediatr* or pediatr* or young adults).hw,jn.
20 (infant* or child* or boy* or girl* or kids or juvenil* or minors or paediatric* or pediatric* or adolesc* or preadolesc* or pre-adolesc* or pubert* or pubescen* or prepube* or pre-pube* or teen* or (young adj (adults or survivor* or offender* or minorit*)) or youth* or student* or school? or preschool* or nurser* or kindergarten).ti,kf.
21 (infant? or child* or adolesc* or paediatr* or pediatr*).ab. /freq=3
22 or/18-21
23 (17 and 22)
24 ((infant? or child* or adolesc* or p?ediatric* or teen* or young* or youth or student? or school? or preschool*) adj2 anxi*).ti,ab,kf.
25 anxiety.mp. and (child development disorders, pervasive/px or autism spectrum disorder/px or autistic disorder/px)
26 (anxiety adj5 (autism or autistic)).ti,ab,kf.
27 (ADIS-C* or ADIS-P* or DISCAP or SCARED or SCAS or RCADS or RCMAS or MASC or CBCL or STAI-C or SPAI-C or SAS-A).ab.
28 or/24-27
29 (9 and (23 or 28))
[Intervention]
30 exp Exercise/
31 Exercise Therapy/
32 Physical Exertion/
33 Physical Fitness/
34 Leisure Activities/
35 exp Recreation/
36 exp Sports/
37 (exercise or games or sport? or sporting or ((leisure or recreation*) adj activ*) or ((recreation or activity) adj3 therap*)).ti,ab,kf.
38 (running or jogging or jumping or hopping or plyometric* or skipping or sprinting or park run? or treadmill? or tread mill?).ti,ab,kf.
39 (climbing or hiking or tramping or mountaineer*).ti,ab,kf,hw.
40 (skiing? or snowboarding or snow boarding or iceskat* or ice skat* or skating or skateboard* or skate board*).ti,ab,kf,hw.
41 bicycling.sh. or (bike? or biking or bicycl* or ((recreational or distance) adj cycling)).ti,ab,kf.
42 (water sports or ((aqua* or water) adj (activit* or fit*)) or swimming or sailing or boating or yachting or canoeing or kayaking or surfing or sailboard* or sail board*).ti,ab,kf,hw.

43 (team game? or football* or rugby or cricket or rounders or baseball or netball or volleyball or tennis or squash or badminton or golf*).ti,ab,kf,hw.
44 (physical* adj (activ* or condition* or effort* or exertion or education or game* or fitness or mobility or train*)).ti,ab,kf.
45 ((weight? adj1 (lift* or train*)) or weightlifting or power lifting or lifting effort* or ((strength or resistance) adj training) or calisthenics).ti,ab,kf.
46 (muscle strengthening or (muscular adj3 (strength or resistance)) or cardiopulmonary conditioning or motion therap* or neuromuscular facilitation* or movement therap* or isometric training).ti,ab,kf.
47 exercise movement techniques/ or breathing exercises/ or qigong/ or dance therapy/ or tai ji/ or yoga/ or kinesiology/
48 (qigong or qi gong or chi kung or Tai Chi or Taiji or Tai Chi Chuan or Taichi Quan or Taijiquan or Shadowboxing or Shadow Boxing or Tai Chi Chih or T'ai Chi Chuan or yoga or yogic or pilates or kinesiology).ti,ab,kf,ot.
49 ((moderate* or graded) adj2 activit*).ti,ab,kf.
50 (aerobics or keep* fit or fitness training or wii fit*).ti,ab,kf.
51 (walking or walks or pedomet* or fitbit? or fit bit? or ((fitness or activit*) adj track*) or (steps adj2 (count* or track* or monitor*))).ti,ab,kf.
52 (ballet or dance or dancing or salsa or zumba).ti,ab,kf.
53 (gardening or horticultur* or allotment* or ((nature or animal) adj2 therap*)).ti,ab,kf,hw.
54 Fitness Trackers/
55 "Physical Education and Training"/
56 fitness centers/
57 (gym* or ((fitness or leisure or wellness) adj (cent* or facility or facilities))).ti,ab,kf.
58 or/30-57
59 (29 and 58)
****

CONTRIBUTIONS OF AUTHORS

APB: contributed to the background and protocol design and methodology.

GC: contributed to the background and protocol design and methodology.

AA: contributed to the background and protocol design and methodology.

DECLARATIONS OF INTEREST

APB: none.

AA: none.

GC: none.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided