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[Intervention Protocol]

Physical exercise training to increase cardiorespiratory fitness in people with spinal cord injury

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ABSTRACT

Objectives

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

This review aims to determine the effects (benefits and harms) of physical exercise training for increasing cardiorespiratory fitness compared with control (i.e. no intervention or placebo intervention) in people with spinal cord injury.

BACKGROUND

This is the protocol for a review, and there is no abstract. This review aims to determine the effects (benefits and harms) of physical exercise training to improve cardiorespiratory fitness compared with control (i.e. no intervention or placebo intervention) in people with spinal cord injuries. Trials with usual care will be included, but only if the usual care is provided for both groups.

Description of the condition

Spinal cord injury (SCI) is a neurological condition that results from damage to the spinal cord. It is often due to trauma from motor vehicle accidents, falls, or violence (James 2019; Kumar 2018). However, some SCIs are due to medical conditions and disease processes, such as spinal artery aneurysms and spinal tuberculosis.

Damage to the spinal cord leads to loss of motor, sensory, and autonomic function in the body below the injury level (Kirshblum 2011). This leads to paralysis or weakness, loss of sensation, and disruption of the bladder, bowel, sexual, and other autonomic bodily functions. It also adversely affects mobility and other fundamental tasks of daily living. The extent of neurological loss and its implications are highly variable, and depend not only on the level of the injury but also on the extent of the damage to the spinal cord (Kirshblum 2011). Injuries in the cervical levels of the spinal cord (neck) result in tetraplegia, with all four limbs and the trunk potentially affected. Whereas, injuries in the thoracic, lumbar, or sacral levels (back) of the spinal cord result in paraplegia, affecting the lower limbs and sometimes the trunk.

Spinal cord injuries are classified according to the International Standards for Neurological Classification of SCI (Kirshblum 2020). The classification relies on a systematic neurological examination of all dermatomes (areas of skin on the body with specific nerve connections to a particular level of the spinal cord) and myotomes (a group of muscles whose activity is driven by a single spinal nerve root). The examination results are used to define a right and left sensory level, a right and left motor level, and one neurological level. They are also used to classify an SCI as complete or incomplete, according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS).

An SCI reduces a person's cardiorespiratory fitness (CRF (Janssen 2002)). Cardiorespiratory fitness refers to the capacity of the circulatory and respiratory systems to supply oxygenated blood to the working skeletal muscles during a bout of exercise, and for the muscles to use oxygen as a source of energy for movement (Ross 2016). Cardiorespiratory fitness is one of the three critical aspects of a person's physical fitness (the other two aspects are strength and flexibility (ACSM 2021; Garber 2011)).

Cardiorespiratory fitness is best quantified by the maximal volume of oxygen consumed per minute (VO_2max (ACSM 2021; Joyner 2008)). It is determined by measuring oxygen consumption whilst exercising at increasing workloads. The VO_2max is typically defined as the point where oxygen consumption plateaus, regardless of increases in workload. It reflects the body's maximal ability to use oxygen.

Maximal oxygen consumption is, in part, determined by cardiac output (Jones 2000; Joyner 2008). That is the body's ability to circulate oxygen to exercising muscles. Cardiac output is a direct function of heart rate and stroke volume (as per the Frank-Starling Law), and reflects the heart's capacity to pump blood. However, the amount of oxygen delivered to exercising muscles is also determined by the oxygen-carrying capacity of the blood, and in particular, by haemoglobin mass. The ability of the exercising muscles to extract oxygen is another factor that determines maximal oxygen consumption (Joyner 2008). The extraction of oxygen within the muscles depends on many factors, including muscle mass, local blood flow, circulating hormones, and a muscle's ability to use oxygen. For example, mitochondrial adaptations can increase a muscle's ability to use oxygen. Therefore, CRF relies on the interplay of many different organ systems within the body, including the motor, sensory, respiratory, circulatory, autonomic, hormonal, and skeletal-muscle organ systems. All can be disrupted by an SCI (Perrier 2017).

Often, it is not possible to measure VO_2max in people with SCI, particularly if they are only able to use their upper limbs to exercise. Often, their maximal exercise capacity is reached before there is a plateau in oxygen consumption. This point is referred to as VO_2peak, rather than VO_2max.

The level and severity of an SCI has implications for CRF (Janssen 2002; Krassioukov 2014). For example, a person with motor-complete tetraplegia and no supraspinal sympathetic control is more profoundly affected than a person with low neurological levels of paraplegia and no involvement of the sympathetic nervous system. Similarly, the physical exercise response of a person with extensive paralysis in the lower limbs and trunk is different to that of a person without it. There are many reasons why the level and severity of an SCI affects CRF. First, as the degree of paralysis increases, there is a reduction in the amount of muscle mass a person is able to activate voluntarily. This reduces their maximal oxygen uptake. This effect is particularly pronounced in those with tetraplegia, who can have total paralysis of the trunk and leg muscles and partial paralysis of the upper limbs. Second, those with a higher level of injury have increased loss of supraspinal control over the sympathetic nervous system (Fossey 2022). This adversely affects the body's capacity for vasoconstriction in response to exercise. Consequently, there is limited capacity to increase venous return, which restricts stroke volume, and hence, cardiac output. At submaximal exercise levels, cardiac output can be partly maintained by a compensatory increase in heart rate. However, this mechanism is limited, because the loss of supraspinal control of the sympathetic nervous system also affects maximal heart rate. Third, the level and severity of an SCI affects CRF because it also affects respiratory function (Theisen 2012). For example, those with C6 tetraplegia can have a 60% reduction in vital capacity (Haisma 2006). Without good respiratory function, the body is limited in its ability to oxygenate the blood. Together, these factors contribute to the lower maximal exercise capacity of a person with tetraplegia than of a person with paraplegia. Similarly, they explain the lower maximal exercise capacity of a person with high paraplegia than of a person with low paraplegia. Consequently, what is considered poor or excellent CRF is different for those with tetraplegia than for those with paraplegia (Janssen 2002; Simmons 2014). An SCI also impairs a person's ability to thermoregulate with exercise (Grossmann 2021). Like most of these factors, the impairment is more profound with higher neurological levels of injury (Grossmann 2021; Handrakis 2017). Together, all these factors contribute to the lower maximal exercise capacity of a person with tetraplegia than of a person with paraplegia.

People with tetraplegia are considered to have excellent CRF if their VO_2peak exceeds 15.2 mL/kg/minute, while people with paraplegia are only considered to have excellent CRF if their VO_2peak exceeds 22.4 mL/kg/minute. Similarly, the definition of poor CRF for a person with tetraplegia is a VO_2peak of 5.3 mL/kg/minute or less, while a person with paraplegia is considered to have a poor CRF with a VO_2peak of 12 mL/kg/minuteor less (Simmons 2014). However, these values should be interpreted with caution and only used as a guide, because they are retrospectively derived from 12 studies involving 169 participants, which may not be a good reflection of the population of people with SCI (Simmons 2014).

The poor CRF in people with SCI compared to their non-injured counterparts is also due, in part, to the direct effects of SCI on the body's response to exercise, and to the general deconditioning and immobility that results from paralysis and the individual's limited capacity to move (Soriano 2022; Theisen 2012). In addition, many social and environmental factors can make it difficult for people with SCI to exercise regularly (Vissers 2008; Hansen 2021). For example, people with SCI can have difficulties travelling to and from, and accessing gyms, exercise classes, exercise equipment, or sporting venues. They may also lack information or access to support staff with appropriate skills and knowledge (e.g. coaches or trainers with an understanding of SCI). These problems are more pronounced in low- and middle-income countries (Vermaak 2022).

As CRF increases, so does the physical work capacity, enabling a person with SCI to exercise maximally, or perform physical activities for an extended period of time within the constraints of their neurological loss (Bassett 2000; Yamagishi 2022). An increase in work capacity also enables a person with SCI to perform the same physical activity with less strain. For example, improvements in physical work capacity for a person with incomplete paraplegia may increase a person's ability to walk with aids and orthoses up a slight incline; and improvements in a person with tetraplegia's physical work capacity may increase a person's ability to push a wheelchair on a flat surface. Increases in CRF may also increase physical activity levels and feelings of well-being, reduce depression or anxiety, and improve sleep (Hicks 2003; Itodo 2022; Liu 2021; Selph 2021).

Description of the intervention

Physical exercise training is "planned, structured, repetitive, and purposive" physical activity performed over an extended period of time (as first described by Caspersen 1985). Specifically, physical exercise training to increase CRF involves general body movement or contractions of the larger muscles of the upper or lower limbs and typically involves dynamic/rhythmic contractions. It needs to be sufficiently strenuous to demand the body's ability to circulate and use oxygen (ACSM 2021; Garber 2011). The exercises within a training session can be performed continuously or in short bouts with rest periods ranging from a few seconds to a few hours (ACSM 2021). The movement involved in physical exercise training is typically driven by voluntary contractions of muscles, although muscle contractions can also be driven by electrical stimulation. Movement solely driven by robotic devices (such as continuous passive motion machines) or through the hands of another person (such as passive movements delivered by a therapist) is not considered physical exercise training for CRF and will not be included in this review.

For this review, we will only consider physical exercise training programmes conducted for at least two weeks, regardless of the number of sessions per week. We will not include trials that provide physical exercise training for less than two weeks, because this is most unlikely to be long enough to have a training effect (MacInnis 2017). This is consistent with similar decisions made by others conducting reviews on this topic (Farrow 2020; Hodgkiss 2023; Itodo 2022; Valentino 2022). We will not include exercise interventions that are primarily intended for purposes other than increasing CRF, regardless of the outcomes.

How the intervention might work

It is well-established that physical exercise training improves CRF in the non-disabled population if it challenges the body to use oxygen, and is performed regularly (Garber 2011; Piercy 2018). Such training results in adaptations to the neuromuscular, metabolic, cardiovascular, respiratory, and endocrine organ systems, which collectively improve the body's ability to increase the supply of oxygenated blood to the working muscles, and for the muscles to then extract and use the oxygen (Jones 2000).

Physical exercise training may increase CRF in people with SCI by stimulating physiological adaptations similar to those of people without disabilities (Liu 2021). However, many adaptations commonly seen in people without SCI can be absent or impaired in people with SCI, particularly those with tetraplegia, who have extensive paralysis and disruption of the autonomic nervous system (Lavis 2007).

The physiological changes responsible for CRF improvement are dependent on training parameters, such as the frequency, intensity, duration, total volume, and specificity (type) of the physical exercise training (Jones 2000; Pierce 1990; Wenger 1986). It is essential that training is progressed, to ensure physical exercise continues to challenge the body to use oxygen (Huang 2016). The American College of Sports Medicine (ACSM) recommends moderately intense physical exercise training to improve CRF for most non-disabled adults (which they refer to as "aerobic physical exercise" (Garber 2011)). They recommend that it be performed for at least 30 minutes a day, five days a week. Alternatively, if the exercise is more intensive, they recommend at least 20 minutes a day, three days a week. The recommendations for people with SCI are similar, although authors vary on the details (ACSM 2021; Martin Ginis 2018; Tweedy 2017; Van Der Schee 2017). For example, some recommend at least 20 minutes of moderately-vigorous intensity exercises twice a week (Martin Ginis 2018), whilst others recommend slightly more than this (ACSM 2021; Tweedy 2017). Importantly, the evidence base for these recommendations is not clear, with a recent overview of systematic reviews on the effectiveness of fitness (and strength) training concluding that the quality of all systematic reviews to date was ''critically low" (Eitivipart 2019).

Why it is important to do this review

It is important to know whether, and to what extent, physical exercise training is effective for increasing CRF, because of the importance of CRF for people with SCI. Notably, CRF is a key determinant of health, independence, and quality of life (Cragg 2013; Kuklina 2013). Good CRF enables people to carry out daily tasks without undue fatigue, with vigour and energy. This is particularly important for people with SCI, because some everyday

activities require physical exertion when done with extensive paralysis. For example, it is physically strenuous for a person who is wheelchair-dependent to propel a wheelchair up a slope. The ability to perform such everyday tasks affects participation and quality of life for those with SCI (Anneken 2010).

It is also important to know whether physical exercise training improves CRF, because of the increased risk of cardiovascular disease (CVD) and mortality for people with SCI (Kuklina 2013; Phillips 2015). There is a clear case for increasing CRF to address these issues in non-disabled people (Imboden 2018; Lee 2010; Yusuf 2004), for whom higher levels of CRF are associated with approximately five extra years of life compared to lower levels of CRF (Clausen 2018). There is some evidence to indicate the situation may be the same for those with SCI, although this is yet to be proven in robust studies (Hicks 2011; Itodo 2022). Therefore, physical exercise training that improves CRF in people with SCI may not only promote improvement in physical capacity, but may also have long-term health effects when performed regularly over many years.

Since 2019, at which time an overview of systematic reviews on the effectiveness of aerobic fitness (and muscle strength training) concluded that the quality of systematic reviews to date was "critically low" (Eitivipart 2019), there have been a number of additional systematic reviews (Chiou 2022; Hodgkiss 2023; Itodo 2022; Peters 2021; Richings 2023; Selph 2021; Valentino 2022). However, they differ from our systematic review in many ways. For example, none of these recent systematic reviews were restricted to just randomised controlled trials (RCTs, i.e. they included cohort, quasi-experimental, non-randomised trials, pre- and post-, or observational studies); two only conducted a narrative synthesis of the data, and were limited to people with SCI with specific characteristics (i.e. people using a wheelchair or people undergoing rehabilitation following recent onset of SCI (Richings 2023; Selph 2021)); three only included studies involving specific types of physical exercise training (i.e. only vigorous intensity training, arm-crank exercise, or perceptually regulated exercise (Chiou 2022; Peters 2021; Valentino 2022)); one included a trial that combined CRF training (aerobic training) with strength training (Itodo 2022); and one included seven RCTs that compared different physical exercise intensities (Hodgkiss 2023). In contrast, our review will be restricted to RCTs, and to RCTs that isolate the effects of physical exercise training (i.e. we will only include studies that compare physical exercise training with no intervention or placebo intervention; studies with co-interventions, such as usual care, will only be included if the co-intervention is provided to both groups).

Regardless of any possible duplication between this review and those of others, Cochrane reviews are essential on important topics, because they are internationally recognised as the gold standard of systematic reviews, and consequently, they are widely read and trusted by consumers, health professionals, and governments. For most, they are a readily accessible first point of call to find answers to important clinical questions (as posed in this review). Cochrane reviews enjoy this reputation because they are conducted, and regularly updated, according to rigorous methodology, with detailed and transparent reporting on decisions, all of which have been extensively and independently scrutinised (Useem 2015).

OBJECTIVES

This review aims to determine the effects (benefits and harms) of physical exercise training for increasing cardiorespiratory fitness compared with control (i.e. no intervention or placebo intervention) in people with spinal cord injury.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), regardless of language, including parallel within-participant randomised controlled trials, parallel between-participant randomised controlled trials, cross-over randomised controlled trials, cluster-randomised controlled trials, step-wedge randomised controlled trials, and adaptive design randomised controlled trials. These may include pilot studies.

We will exclude quasi-randomised trials, in which the method of allocation of participants to each treatment arm is not truly random (e.g. assignment by alternation, date of birth, or medical record number).

We will not exclude trials on the basis of other methodological considerations.

Types of participants

We will include trials in which 80% or more of the participants are adults (> 16 years) with a traumatic or non-traumatic spinal cord injury (SCI; any time post-onset of SCI), provided all participants have some neurological condition, regardless of age, severity, cause, onset, or underlying pathology.

We will not consider spinal cord disorders due to congenital or progressive conditions (e.g. spinal bifida or multiple sclerosis).

Types of interventions

Interventions

We will include trials that compare physical exercise training programs to improve cardiorespiratory fitness (CRF) with no intervention. We will include trials that provide usual care only if the usual care is offered to both groups. For this review, we define physical exercise training as a planned, structured, and repetitive physical exercise programme that includes specific recommendations for the type, intensity, frequency, and duration of the training. Physical exercise training must also be implemented with the aim of increasing CRF, and must be sufficiently strenuous to challenge the body's ability to circulate and use oxygen (Garber 2011). The training can be continuous or intermittent (such as high-intensity interval training), but it must involve rhythmic and constant general body movement; that is, the gross movement of any or all limbs. It does not include isolated muscle contractions, typically provided as part of strength training programs. In this review, we will include trials that conducted physical exercise training at least once a week for at least two weeks.

Physical exercise training may include, but is not limited to, any of the following modalities of physical exercise, with or without functional electrical stimulation (FES):

- arm ergometry/cycling/rowing;
- leg ergometry/cycling/rowing;
- wheelchair ergometry;
- wheelchair propulsion;
- overground gait training;
- treadmill gait training, with or without body weight support (BWS);
- robotic-assisted gait training ;
- activity gaming (e.g. Wii Fit games);
- sports training (e.g. swimming, boxing, rowing); and
- circuit training (provided the circuit training involves general body movement, and not solely isolated strength training exercises).

Physical exercise training may be provided as part of an inpatient, outpatient, or community programme, and may be supervised or unsupervised. However, we will not include interventions:

- that merely promote an active lifestyle, or increase physical activity without the delivery of a planned and structured physical exercise training programme; or
- in which the movement is solely driven by robotic devices, or through the hands of another person, in people with SCI and no motor function in the exercised limbs.

Comparisons

This review aims to compare physical exercise training to increase CRF versus control (i.e. no intervention or placebo intervention). Therefore, to isolate the effects of physical exercise training, we will include trials if they compare:

- physical exercise training versus no intervention; or
- physical exercise training versus placebo intervention (an intervention that could not conceivably affect CRF; for example, stretching exercises, or education on skincare).

Trials can also include usual care, provided both groups receive the same usual care. Usual care could consist of general physical rehabilitation, mobility training, strength training, stretching, or usual activity.

To reduce the complexity of the review, we will exclude trials that compare one type of physical exercise training versus another type of physical exercise training; or one intensity of physical exercise training versus another intensity of physical exercise training.

Types of outcome measures

We will consider outcome measures of impairment, activity limitations, and participation restrictions according to the International Classification of Functioning, Disability and Health (ICF (WHO 2001)). For the purpose of this review, we will only include trials that report a measure of CRF, as outlined below). This criterion is justified for two reasons. First, if a trial does not include a measure of CRF, the trial will not provide any data upon which to address the main aim of this review. Second, this criterion helps to wean out exercise programmes to improve the ability to move or walk, which are not specifically designed to improve CRF (Pierce 1990; Piercy 2018).

We will extract only one type of outcome measure from a trial to reflect each of the primary and secondary outcomes. If a trial contains more than one type of measure for any outcome, we will give preference to the most reliable and valid measure used in the retrieved trials. We will log all decisions transparently.

We will extract data on each outcome for two time points that correspond with the short-term (< 6 weeks) and long-term (6 weeks or more) effects. If outcomes are measured on more than one occasion within the first six weeks, we will prioritise outcomes measured sooner rather than later to reflect the short-term effects. For example, if outcomes are collected one week and four weeks after the end of the intervention, we will prioritise data collected at one week. If outcomes are measured on more than one occasion at or after six weeks, we will prioritise outcomes measured later rather than sooner to reflect the long-term effect. For example, if outcomes are collected six weeks and six months after the end of the intervention, we will prioritise data collected at six months.

Table 1 provides a summary of the inclusion and exclusion criteria for trials in this review.

Primary outcomes

Cardiorespiratory fitness: measured by physiological measures attained during any type of maximal or sub-maximal exercise test, such as maximal volume of oxygen consumed per minute (VO_2max), peak oxygen consumption/uptake (VO_2peak), and peak power output (ACSM 2021). We will also include results from sub-maximal exercise tests used to predict physiological measures of maximal exercise capacity, in the absence of results from maximal exercise tests.

Secondary outcomes

We will include measures of functional fitness and perceived exertion, as well as various measures of impairments, independence, quality of life, and any related adverse events. These include:

- **Functional fitness:** functional performance measures, such as the time taken to walk or push a wheelchair a set distance, for example, the 20-metre shuttle test (Stickland 2003), or the distance walked or pushed in tests such as the 2-, 6- or 12-minute walk tests (ATS 2002; Kosak 2005; Scivoletto 2011), the 6-minute arm test (Hol 2007), the wheelchair push test, or the sprint test (Cowan 2012; Marszałek 2019), and the number of steps climbed in the 2-minute step test (Bohannon 2019);
- **Perceived exercise exertion:** measures, such as the Borg Rating of Perceived Exertion Scale (Borg 1982), the Omnibus scale (Utter 2004), the Talk Test (Reed 2014), or the Counting Talk Test (Norman 2008);
- **Independence:** measures, such as the Spinal Cord Independence Measure (Fekete 2013; Itzkovich 2018), Quadriplegia Index of Function (Yavuz 1998), or the Functional Independence Measure (Keith 1987);
- **Quality of life (QoL):** measures, such as the Satisfaction with Life Scale (Post 2012), Medical Outcomes Short-Form Health Survey (Forchheimer 2004), World Health Organization Quality of Life-Brief version (Chiu 2006),or the Quality of Life Index-Spinal Cord Injury (May 2002). We will include any version of these outcome measurement tools.

- **Physical activity level:** measures, such as the Physical Activity Recall Assessment for People with SCI (PARA-SCI (Latimer 2006)), or the Physical Activity Scale for Individuals with a Physical Disability (Washburn 2002), and measures attained from accelerometers, ambulatory monitoring systems, or any mHealth device (Bussmann 2001; Postma 2005);
- **Fatigue:** measures, such as the Fatigue Severity Scale (Learmonth 2013), the Brief Fatigue Inventory Index (Whitehead 2009), or the Global Fatigue Index (Ashman 2008);
- **Sleep quality:** measures, such as the Insomnia Severity Index (Bastien 2001), the PROMIS-Sleep Disturbance (Purvis 2018), or the Pittsburgh Sleep Quality Index (Buysse 1989);
- **Depression and Anxiety:** measures, such as the Hospital Anxiety and Depression Scale (Snaith 2003), or the Patient Health Questionnaire Anxiety and Depression Scale (Herdman 2022);
- **Adverse events:** this will include outcomes such as death, hospitalisation, falls, cardiovascular events (e.g. stroke or myocardial infarction), heat exhaustion, dehydration, hyperthermia, autonomic dysreflexia, pain, musculoskeletal injury, or skin injury. Adverse events (AEs) will be broadly categorised and described according to whether they involved the musculoskeletal, cardiovascular, bowel/bladder, or other organ systems, and whether they were likely to be caused by the intervention. However, all adverse events will be grouped together for meta-analyses.

We will not include measures of cardiovascular disease (CVD), because trials must have been conducted over many years to determine the effect of physical exercise training on CVD. Such trials have not been conducted in people with SCI, and are most unlikely to be conducted in the near future. We will also not include surrogate markers of CVD (such as cholesterol levels and blood pressure), because they would add considerable complexity to the review, and have limited potential to yield useful findings. Furthermore, we believe that people with SCI would be less likely to value surrogate markers of CVD than other selected outcome measures.

Search methods for identification of studies

We will search for eligible trials by combining terms for the health condition (SCI), the intervention (physical exercise training), and primary outcome (CRF), and the method (RCTs and randomised cross-over trials). We will not include search terms to capture the secondary outcomes, because measurement of these outcomes is not an inclusion criterion for trials for this review. We will not apply any language or publication restrictions to any component of the search strategy.

The search strategy we will use for each database can be found in Appendix 1.

Electronic searches

We will identify reports of relevant trials through systematic searches on the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL, latest issue) in the Cochrane Library;
- MEDLINE Ovid (1946 to present);
- MEDLINE Ovid (In-Process & Other Non-Indexed Citations (latest issue);
- Embase Ovid (1974 to present);
- CINAHL Plus EBSCO (1937 to present);
- Physiotherapy Evidence Database (PEDro; pedro.org.au; latest issue).

We will identify ongoing or unpublished trials by searching these clinical trial registries:

- WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/clinical-trials-registry-platform);
- ISRCTN registry (www.isrctn.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu);
- Australian New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au/);
- Brazilian Registry of clinical trials (REBEC; ensaiosclinicos.gov.br).

Searching other resources

We will contact key researchers and guideline authors to request information about any unpublished or ongoing trials. In addition, we will conduct searches of the following resources, to identify further published, unpublished, and ongoing trials:

- Cited Reference Search on Web of Science (Thomson Reuters) Science Citation Index (SCI) and Social Science Citation Index (SSCI) to track relevant references;
- the reference lists of all retrieved trials that are included in the review, as well as relevant systematic reviews and meta-analyses identified during the searches.

Data collection and analysis

Selection of studies

We will screen the identified titles and abstracts using the prespecified inclusion criteria to identify potentially relevant trials, which we will then assess in full text to determine whether each trial meets the inclusion criteria. We will include trials that meet the inclusion criteria in the review. We will exclude trials that do not meet the inclusion criteria, and will record the reason for their exclusion. These steps will be performed independently by two review authors (JI and LAH). Disagreements will be resolved by discussion, or if required, by a third review author (JVG).

We will use a PRISMA flow diagram, described in the PRISMA statement, to report the number of unique records identified (Page 2021); the number of duplicate records identified; the number of records excluded by title and abstract and the reasons; the number of full-text records retrieved; the number of full-text records excluded and the reasons; the number of trials included in the review; and the number of trials contributing to the analysis.

Data extraction and management

We will extract data from the trials and record them on an Excel spreadsheet. We will test and adapt the spreadsheet before commencing the data extraction process. Two review authors (JI and LAH) will independently extract data from all trials for which neither is an author. For trials for which either of them is

an author, another review author or author pair (JC and/or EB) will independently extract relevant data. Disagreements will be resolved by discussion, or if required, by a fifth review author (JVG).

We will contact trial authors for missing, unclear, or contradictory data. Should data be acquired in this way, we will report relevant dates and content of correspondence. If the trial results are presented in more than one publication, we will use all the publications to extract the data. However, we will not duplicate the results in the analyses.

We will extract the following data.

- **Trial identification details:** trial authors, publication status (published, unpublished, or ongoing), year of publication, setting and country, and type of report (full text, abstract, conference proceeding, thesis)
- **Trial method:** type of trial (parallel within-participant randomised controlled trial, parallel between-participant randomised controlled trial, cross-over randomised controlled trial, cluster-randomised controlled trial, step-wedge randomised controlled trial, adaptive design randomised controlled trial), trial inclusion and exclusion criteria
- **Participants:** overall number of participants, and number of participants in each group, age, sex/gender, neurological level of SCI, American Spinal Injury Association (ASIA) Impairment Scale (AIS) classification of SCI, type of SCI (traumatic or non-traumatic), overall motor score and time since injury
- **Intervention details:** mode of training (i.e. the use of the upper and lower limbs, use of electrical stimulation, and the modalities of physical exercise as previously described in Types of interventions), where the intervention was administered (i.e. hospital, community, home), who delivered the intervention (i.e. healthcare professional, sports/exercise/gym coach), overall training period (weeks), and the number of sessions, frequency (i.e. sessions per day, sessions per week), intensity (i.e. work per unit time), session duration (i.e. time per session), total training volume (i.e. the duration of each training session multiplied by the total number of sessions), and progression of physical exercise training
- **Co-interventions:** information on any co-interventions provided to both the experimental and the control groups
- **Comparison:** information on what, if anything, the control group did or were asked to do as part of the trial
- **Outcomes:** all outcomes reported, with details about measurement time points, and which of the trial outcome measures were selected to reflect the primary and secondary outcomes of the review
- **Data to determine the effect sizes:** data on the trial outcomesselected to reflect the primary and secondary outcomes of the review(see Measures of treatment effect)
- **Adherence:** the number of exercise sessions completed as a proportion of the number of exercise sessions planned
- **Dropouts/withdrawals:** numbers (overall and in each group) and reasons for dropouts/withdrawals

Table 2 provides a template for the characteristics of included studies table.

Assessment of risk of bias in included studies

We will assess the risk of bias for the outcomes we plan to include in the summary of findings table. This includes: CRF, functional fitness, quality of life, depression/anxiety, and adverse events. We will quantify the effect of assignment to the intervention (the intention-to-treat (ITT) effect), not whether the intervention was completed. We will use the five domains of the Cochrane RoB 2 tool (Higgins 2023a; RoB 2). This includes an assessment of the risk of bias arising from:

- the randomisation process;
- deviations from intended interventions;
- missing outcome data;
- the measurement of the outcome; and
- the selection of the reported result.

We will also assess cluster-randomised controlled trials for the risk of bias arising from:

- identification or recruitment of individual participants within clusters (Higgins 2023b).

We will use the RoB 2 Excel tool to record our judgement of bias for each domain of the selected outcomes in each trial, using an algorithm that maps responses to the series of signalling questions to a proposed judgement. We will provide the Excel tool as a supplementary file in the review.

We will answer each signalling question in one of the following ways:

- yes;
- probably yes;
- probably no;
- no; and
- no information.

The responses of yes and probably yes have the same implications for risk of bias. Similarly, the responses no and probably no have the same implications. Based on the responses to signalling questions, we will rate each domain as low, high, or some concerns.

We will rate the overall risk of bias judgement for the selected outcomes in each trial as:

- low risk of bias: low risk of bias for all judged domains;
- some concerns: some concerns in at least one domain, but no high risk for any domain;
- high risk of bias: high risk in at least one domain; or some concerns for multiple domains.

Two review authors (JI and LAH) will independently perform all steps of the risk of bias judgement, except for trials in which they were involved, when another author (JC or EB, or both) will fulfil this role. Disagreements will be resolved by discussion, or if required, by a fifth review author (JVG). We will present the results in a risk of bias graph to illustrate the risk of bias judgements based on domains, and a risk of bias summary. In addition, we will present the results of the risk assessment in the characteristics of included studies table (see the table template in Table 2).

Assessment of bias in conducting the systematic review

We plan to conduct the review according to this published protocol, and will report any deviations in the differences between protocol and review section of the review.

Measures of treatment effect

We will express continuous data as:

- mean differences (MDs), if measured with the same measurement tool, with 95% confidence intervals (CI); and
- standardised MDs (SMDs), if measured with different measurement tools, with 95% CI.

If outcomes are only reported graphically, we will extract the means and standard deviations (SDs) from the graphs. If the trials only provide medians and interquartile ranges (IQRs), we will use the medians and the IQRs to estimate the means and SDs (Higgins 2023c; Wan 2014). We will not combine post-intervention scores using ANCOVA adjusted between-groups, or change scores in meta-analyses using SMDs (Deeks 2023).

We will express dichotomous data as risk ratios (RR) with 95% CI; and time-to-event data as hazard ratios (HR) with 95% CI.

We will use the calculator incorporated into RevMan 2024 to convert data when necessary (e.g. to convert standard error (SE) to SD). If authors provide per-protocol and ITT data, we will give preference to, and extract and analyse the ITT data.

When outcome scales measure the same outcome, but these scales work in opposite directions, we will express the effect in the same direction across trials included in the same forest plot (with or without meta-analyses). For example, a forest plot with one trial in which a higher score reflects a better outcome and another trial in which a lower score reflects a better outcome will be expressed so that both trials indicate that a higher score reflects a better outcome. We will pool data in meta-analyses where appropriate (see Assessment of heterogeneity).

We will convert analyses using SMDs to MDs using the pooled estimate, re-expressed in the raw units of an outcome, to aid clinical interpretation (by multiplying the SMD by the baseline standard deviation of the control group (Deeks 2023)). We will choose this outcome by identifying the trial with a large weighting in the meta-analysis if the trial used a population that would be of interest, and an outcome measure with which review readers would be familiar.

Unit of analysis issues

We will consider unit of analysis issues in the following four cases.

Cross-over trials

Initially, we will consider whether a cross-over trial is a suitable design for assessing the effects of physical exercise training on CRF. We will base this decision on the length of the wash-out period. If the wash-out period is less than the period of the intervention, then we will consider a cross-over design as inadequate, because any possible effects of the physical exercise training are unlikely to have returned to baseline. In this case, we will analyse only the data from the first period, and will treat the trial as a parallel design (Higgins 2023b). If the wash-out period is longer than the period of the intervention, we will use the reported effect estimate when the trialists used an appropriate analysis (e.g. a paired t-test). We will include this in a meta-analysis using an inverse-variance approach. If the effect estimate was not provided, we will derive this if the authors provide:

- individual participant data; the mean and SD (or SE) of the participant-level differences between the two groups;
- the mean difference and a t-statistic from the paired t-test, or a P-value from a paired t-test of a confidence interval from a paired analysis; or
- graphed data that indicate the individual data, provided the repeat measurement for each participant can be isolated (Higgins 2023b).

If the authors do not provide the effect estimate or data to derive this, we will only extract data from the first period of the trial.

Trials with three or more groups, in which more than one type of physical exercise training is provided

In trials with three or more groups, in which more than one type of physical exercise training is provided to two of the groups, we will include data from all groups. We will only combine the data from the experimental groups if the interventions are considered similar. Otherwise, we will analyse the data from the experimental groups separately, after ensuring that the data from the control group are not double-counted. We will do this by dividing data from the control groups by the number of physical exercise training groups for each analysis.

Trials where outcomes are measured on multiple occasions

In trials where outcomes are measured on multiple occasions, we will extract only one set of data that reflects the short-term (< 6 weeks) and long-term (6 weeks or more) effects. We will prioritise outcomes measured sooner rather than later to reflect the short-term effects. For example, if outcomes are collected one week and four weeks after the end of the intervention, we will prioritise data collected at one week. This is when the effect of the intervention is likely to be greatest, because once physical exercise training ceases, CRF gradually declines due to the effects of de-training (Chen 2022; Coyle 1986). In contrast, we will prioritise outcomes measured later rather than sooner to reflect the long-term effect. For example, if outcomes are collected six weeks and six months after the end of the intervention, we will prioritise data collected at six months.

Cluster and step-wedge randomised controlled trial

In cluster and step-wedge randomised controlled trials in which sites (centres, communities) are randomised rather than individuals, we will use the cluster as the unit of allocation, and the effect measure (e.g. an odds ratio, or mean between-group difference, plus confidence intervals) for meta-analysis, if it is provided from an appropriate analysis (e.g. a multilevel model or generalised estimating equation (Higgins 2023b)). If the trialists did not use an appropriate analysis to determine an effect measure, and the trial did not properly account for clustering, we will repeat the analyses if the following information is available:

- the number of clusters randomised to each group, and the total number of participants in the trial or the average (mean) size of each cluster;
- the outcome data for the total number of individuals, ignoring the cluster design (e.g. the total number or proportion of

individuals with events, or means and standard deviations for continuous data); and
- an estimate of the intracluster (or intraclass) correlation coefficient (ICC). If the ICC estimates are not available, we will estimate them from similar trials or reported patterns in ICCs for similar types of clusters or outcomes.

Dealing with missing data

If an included trial does not report all the necessary data (e.g. it does not provide a mean or median, or a measure of variability for a group), we will contact the authors to request the data. We will record this clearly when data were obtained in this way. If the authors cannot be contacted, or fail to respond to requests for additional data, we will report all available data, and convert available data as possible (as outlined in Measures of treatment effect), but we will not use methods to impute data that are not provided by the authors. If a trial provides insufficient data to include in a meta-analysis, we will describe the results of the trial in a narrative format.

When studies fail to collect data on all participants at the time points of interest, we will use all available data, but we will not impute missing data. The number of participants in all meta-analyses will reflect the number of participants contributing data. For example, if 15 participants dropped out of a trial randomising 100 participants, and their missing data were not imputed, we will use a sample size of 85 (not 100) in the meta-analysis. However, if the authors imputed the missing data to derive a between-group difference and corresponding 95% CI, we will use a sample size of 100 (not 85) in the meta-analysis. In either case, our assessments of the risk of bias domain, incomplete outcome data, will reflect the likely risk of bias in our results.

We do not intend to perform sensitivity analyses to address the possible impact of data that authors failed to report, or missing data. However, we will describe the results of any trials that cannot be included in the meta-analyses because the authors did not provide sufficient data. We will address the potential impact of this and other sources of missing data on the review results in the Discussion section of the review.

Assessment of heterogeneity

We will assess for both clinical and statistical heterogeneity. We will determinre clinical heterogeneity by looking for important differences between interventions, participants, and outcomes. We will determine atatistical heterogeneity by I^2 values, where I^2 values > 75% will be considered indicative of statistical heterogeneity.

Assessment of reporting biases

We will assess the presence of non-reporting bias using a funnel plot, provided there are at least 10 trials reporting on the same outcome measure and comparison (Page 2023). Reasons for any observed asymmetry will be explored and detailed in the review.

We will also assess the presence of selective outcome reporting by comparing the published reports against either the trial registration, or a published or unpublished protocol. Selective reporting of outcomes will be reported in the review.

Data synthesis

We will pool data in a meta-analysis if:

- there are two or more trials for each outcome measure;
- there is clinical homogeneity (trials with similar interventions, participants, and outcomes); and
- there is no excessive statistical heterogeneity (i.e. I^2 values < 75%).

We will use a random-effects model to obtain the pooled estimate of the effect of the intervention (Deeks 2023). This model assumes that the trials are drawn from populations that differ from each other in ways that could impact the treatment effect. We will include all eligible trials regardless of the risk of bias. We will perform the meta-analyses using RevMan 2024.

When pooling is not possible, we will report the outcome of the between-groups analysis with a 95% confidence interval.

Subgroup analysis and investigation of heterogeneity

When there are sufficient trials, we will perform the subgroup analyses below on the short-term effects of the primary outcome, CRF. We will use the tests for interaction in RevMan 2024 to test for differences between subgroups.

- **Duration of physical exercise training programme (< 12 weeks and > 12 weeks):** the response to physical exercise training may depend on the duration of the exercise programme, because regular exercise should be continued for a sustained period of time before any benefits become apparent (MacInnis 2017). Therefore, short exercise programmes may not be as effective as long exercise programmes. Programmes longer than 12 weeks are commonly considered long-term programmes (Strauss 2020).
- **Frequency of physical exercise training (less than 3 times a week and 3 times or more a week):** the response to physical exercise training may depend on the frequency of exercising. Current guidelines for non-disabled people recommend that physical exercise training be performed at least three times a week (Garber 2011). However, there is some suggestion that less than three times per week may also have positive health effects (Martin Ginis 2018; Warburton 2016).
- **Intensity of physical exercise training (light and moderate-to-vigorous intensity):** the response to physical exercise training may depend on the intensity of the physical exercise (Garber 2011). For this review, moderate-to-vigorous intensity training refers to physical exercise training that meets any of these criteria:
  - more than three metabolic equivalents of task (METs);
  - at least a score of 12 on the Rate of Perceived Exertion (RPE) scale of 6 to 20;
  - more than 40% of heart rate reserve (HRR) or oxygen uptake reserve (VO_2R (ACSM 2021)).

If these details are not provided, we will use all available information to gauge the intensity of the physical exercise training.

- **Type of physical exercise training (upper limb exercise and lower limb/combined limbs exercises):** the response to physical exercise training may depend on the size of the recruited muscle mass, because there is a greater demand for oxygenated blood with the use of large muscle masses (Theisen 2012). This leads to concerns that exercise only involving the

small muscle masses (such as the upper limbs) may not be sufficient to increase CRF.

Table 3 provides a summary of all the proposed analyses, including the subgroup analyses.

Sensitivity analysis

If there are sufficient trials, we will conduct the following sensitivity analyses on the short-term effects on the primary outcome, CRF, to determine the robustness of our results (Deeks 2023).

- **Influence of a trial:** we will remove trials that are overwhelming the pooled estimate because of their weight, one at a time, and rerun the meta-analysis to determine their influence. We will do the same with trials that seem different visually, for example, their effect is in a different direction to that of most trials in the analysis. If the exclusion of any one trial makes a notable difference to the interpretation of the results, we will explore possible explanations for this (e.g. differences in the characteristics of the participants, methodology, outcomes, and endpoints from the other included trials). We will provide a narrative summary and then include a section in the Discussion as a caution to the interpretation of the primary analysis.
- **Influence of bias:** we will restrict the analysis to trials at low risk of bias, excluding those at high risk of bias or with other valid concerns. This will be based on the RoB 2 judgements for each trial of the short-term effects of physical exercise training on CRF.

Summary of findings and assessment of the certainty of the evidence

We will develop a summary of findings table using GRADEpro GDT online software for the comparison, physical exercise training versus control (i.e. no intervention or placebo intervention), for the primary outcome, CRF, and four of the secondary outcomes, functional fitness, quality of life, depression/anxiety, and adverse events (Schünemann 2023).We will only present these data for one time point, reflecting the short-term effects.

We will assess the certainty of the body of evidence for each outcome using the GRADE approach (Schünemann 2013; Schünemann 2023). This includes an assessment considering the:

- risk of bias;
- indirectness of evidence;
- inconsistency of results;
- imprecision of effect estimates; and
- reporting bias.

We will use the RoB 2 judgements to determine the overall risk of bias in the body of evidence for each outcome.

Two review authors (JI and LAH) will independently assess the evidence for each outcome, and rate the certainty as high, moderate, low, or very low, according to the perfomance against the aforementioned five listed criteria. We will justify all decisions to downgrade the certainty of evidence using footnotes.

We will import data from RevMan 2024 into GRADEpro GDT. We will generate tables to provide information about the:

- overall certainty of the available evidence for each outcome;
- magnitude of the effect of the intervention; and
- sum of the available data for each outcome.

Reaching conclusions

We will base the review conclusions on findings from the quantitative and narrative synthesis of the included trials. This section will contain subsections on Implications for practice and Implications for research. We will avoid making clinical recommendations in the Implications for practice subsection. Rather, we will provide a summary of the evidence about the benefits and harms of physical exercise training for increasing CRF in people with SCI. We will compare and contrast our findings with the findings of other recent systematic reviews. In the Implications for research subsection, we will suggest priorities for future research, and outline the remaining uncertainties in the area.

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• Sign-off Editor (final editorial decision): Stefano Negrini, Department of Biomedical, Surgical and Dental Sciences, University La Statale, Milan and Director of Cochrane Rehabilitation

• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Anupa Shah, Cochrane Central Editorial Service

• Assistant Editor (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Justin Mann, Cochrane Central Editorial Service

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ADDITIONAL TABLES

Table 1. Summary of trial inclusion and exclusion criteria

Criteria	P Participants	I Intervention	C Comparison	O Outcome	S Study design
Inclusion	• People with SCI • Traumatic or non-traumatic injuries • Any time post-onset SCI • Adults (> 16 years)	• Physical exercise training for CRF • Inpatient, outpatient, or community programmes • Supervised or unsupervised programmes	• No intervention • Placebo intervention • Usual care (if also provided to experimental group)	• CRF measure (VO_2max, VO_2peak and peak power output)	• Randomised controlled trials • Randomised cross-over trials
Exclusion	• Trial with mixed populations if < 80% are people with SCI • Congenital conditions (e.g. spina bifida) • Progressive diseases (e.g. multiple sclerosis)	• < 2 weeks of training • Interventions that solely promote an active lifestyle or physical activity • Movement solely driven by robotic devices or through the hands of another person	• Different types of physical exercise training • Different doses of physical exercise training	• No CRF measure	• Quasi-randomised trials

Abbreviations: CRF: cardiorespiratory fitness; SCI: spinal cord injury; VO_2max: maximal volume of oxygen consumed per minute; VO_2peak: peak oxygen consumption/uptake

Table 2. Table template for the characteristics of included studies

Methods	**Design:** (e.g. parallel RCT, cross-over RCT, cluster-RCT)

Participants	**Sample size**
	• Randomisation:
	• Randomised (overall number of participants)
	  ○ Experimental:
	  ○ Control:
	• Analysed (participants included in the analysis)
	  ○ Experimental:

Table 2. Table template for the characteristics of included studies *(Continued)*

	○ Control:
	Setting: (e.g. outpatient, inpatient, multicentre, national/international)
	Inclusion criteria *List*
	Exclusion criteria *List*
	SCI information • Experimental group ○ Neurological level of SCI (N/N paraplegia/tetraplegia) ○ AIS classification (% AIS A, B, C, and D) ○ Type of SCI (N/N traumatic/non-traumatic) ○ Motor score (points) ○ Time since injury (years) • Control group ○ Neurological level of SCI (N/N paraplegia/tetraplegia) ○ AIS classification (% AIS A, B, C, and D) ○ Type of SCI (N/N traumatic/non-traumatic) ○ Motor score (points) ○ Time since injury (years)
	Mean age (years) (SD) • Overall: • Experimental: • Control:
	Gender/Sex (N/N male/female) • Overall: • Experimental: • Control:
Intervention	**Total groups:**
	Experimental: physical exercise training for CRF • Mode of training (the use of the upper and lower limbs, use of electrical stimulation and the modalities of physical exercise) • Training period (weeks) • Overall number of training sessions • Frequency (sessions/day; sessions/week) • Intensity (RPE score; power output; % HRR; or $\%\dot{V}O_2R$) • Time (session duration; minutes) • Volume of training (session duration x number of sessions; hours) • Progression (any details of progression training parameters) • Adherence (number of sessions completed; %)
	Control:

Table 2. Table template for the characteristics of included studies *(Continued)*

	Relevant information about control group intervention
	Co-intervention: *Relevant information about any co-interventions, including usual care, provided to both groups*
Outcomes	**Primary outcomes** *List* **Secondary outcomes** *List* *Note: describe details about when each outcome was taken.*
Notes	**Dropouts/withdrawals (n, reason)** • Experimental: • Control:
	Funding sources:
	Trial registration or published protocol:
	Other relevant information:

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Randomisation process	*Rated risk*	*Quote/comment*
Deviations from the intended intervention	*Rated risk*	*Quote/comment*
Missing outcome data	*Rated risk*	*Quote/comment*
Measurement of the outcome	*Rated risk*	*Quote/comment*
Selection of the reported result	*Rated risk*	*Quote/comment*
Identification/recruitment of individual participants[a]	*Rated risk*	*Quote/comment*

Abbreviations: AIS: American Spinal Injury Association (ASIA) Impairment Scale; HRR: heart rate reserve; RCT: randomised controlled trial; RPE: rate of perceived exertion; SCI: spinal cord injury; $\dot{V}O_2R$: oxygen consumption/uptake reserve

[a]Bias only related to cluster-RCTs

Table 3. Planned analyses and forest plots

Major analysis	Outcome(s)	Subgroup analyses on primary outcome

Table 3. Planned analyses and forest plots *(Continued)*

Physical exercise training versus control *(i.e. no intervention or placebo intervention)*	**Primary (short-term and long-term effects)**	• Cardiorespiratory fitness	1. Duration of physical exercise training programme (< 12 weeks and > 12 weeks) 2. Frequency of physical exercise training (less than 3 times a week and 3 times or more a week) 3. Intensity of physical exercise training (light and moderate-to-vigorous intensity) 4. Type of physical exercise training (upper limb exercise and lower limb/combined limbs exercises)
	Secondary (short-term and long-term effects)	• Functional fitness • Perceived exercise exertion • Independence • Quality of life • Physical activity level • Fatigue • Sleep quality • Depression and anxiety • Adverse events	

APPENDICES

Appendix 1. Search strategies

CENTRAL (Cochrane Library)	
#1	MeSH descriptor: [Spinal Cord Injuries] explode all trees
#2	MeSH descriptor: [Spinal Cord Ischemia] explode all trees
#3	MeSH descriptor: [Central Cord Syndrome] explode all trees
#4	((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*))
#5	(spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia))
#6	central cord injury syndrome
#7	central spinal cord syndrome
#8	MeSH descriptor: [Spinal Cord] explode all trees
#9	MeSH descriptor: [Cervical Vertebrae] explode all trees and with qualifier(s): [injuries - IN]
#10	MeSH descriptor: [Paraplegia] explode all trees
#11	MeSH descriptor: [Quadriplegia] explode all trees
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Exercise] explode all trees

(Continued)

#14	MeSH descriptor: [Exercise Therapy] explode all trees
#15	MeSH descriptor: [Physical Education and Training] explode all trees
#16	MeSH descriptor: [Physical Fitness] explode all trees
#17	MeSH descriptor: [Sports] explode all trees
#18	MeSH descriptor: [Sports for Persons with Disabilities] explode all trees
#19	MeSH descriptor: [High-Intensity Interval Training] explode all trees
#20	MeSH descriptor: [Endurance Training] explode all trees
#21	MeSH descriptor: [Ergometry] explode all trees
#22	(wheelchair* adj3 prop*)
#23	(gait adj train*)
#24	MeSH descriptor: [Exergaming] explode all trees
#25	MeSH descriptor: [Circuit-Based Exercise] explode all trees
#26	(resistan* adj2 (training* or exercise*))
#27	(aerobic* adj2 (training* or exercise*))
#28	MeSH descriptor: [Cardiorespiratory Fitness] explode all trees
#29	MeSH descriptor: [Swimming] explode all trees
#30	MeSH descriptor: [Boxing] explode all trees
#31	MeSH descriptor: [Gymnastics] explode all trees
#32	rowing
#33	#13 or#14 or #15 or #16 or #17 or #18 or #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 #32
#34	#12 AND #33
MEDLINE(R) Ovid ALL (1946 - present, including In-Process & Other Non-Indexed Citations)	
1	exp Spinal Cord Injuries/
2	exp Spinal Cord Ischemia/
3	exp Central Cord Syndrome/
4	(myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
5	((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).ab,ti.
6	(spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.

(Continued)

7	central cord injury syndrome.ab,ti.
8	central spinal cord syndrome.ab,ti.
9	tetrate [Injuries]
10	exp Spinal Cord/
11	SCI.ab,ti.
12	exp Paraplegia/
13	exp Quadriplegia/
14	(paraplegia* or quadriplegia* or tetraplegia*).ab,ti.
15	or/1-14
16	*Exercise/
17	*Exercise Therapy/
18	*"Physical Education and Training"/
19	*Physical Fitness/
20	*Sports/
21	Sports for Persons with Disabilities/
22	exp Endurance Training/
23	High-Intensity Interval Training/
24	Ergometry/
25	(wheelchair$ adj3 prop$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26	(gait adj train$).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27	Exergaming/
28	exp Video Games/
29	Circuit-Based Exercise/
30	sports training.mp.
31	(resistan$ adj2 (training$ or exercise$)).mp.

(Continued)

32	(aerobic$ adj2 (training$ or exercise$)).mp.
33	boxing
34	exp swimming/
35	exp rowing/
36	exp boxing/
37	exp Gymnastics/
38	16 or 17 or 18 or 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 or 33 or 34 or 35 or 36 or 37
39	randomi?ed.ab,ti.
40	randomized controlled trial.pt.
41	controlled clinical trial.pt.
42	placebo.ab.
43	clinical trials as topic.sh.
44	randomly.ab.
45	trial.ti.
46	Comparative Study/
47	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	(animals not (humans and animals)).sh.
49	47 not 48
50	15 and 38 and 49
Embase Ovid (1974 to present)	
1	exp Spinal Cord Injury/
2	exp Spinal Cord Ischemia/
3	exp Central Cord Syndrome/
4	(myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
5	((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).ab,ti.
6	(spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
7	central cord injury syndrome.ab,ti.
8	central spinal cord syndrome.ab,ti.

(Continued)

9	exp cervical spine/
10	exp Spinal Cord/
11	SCI.ab,ti.
12	exp Paraplegia/
13	exp Quadriplegia/
14	(paraplegia* or quadriplegia* or tetraplegia*).ab,ti.
15	or/1-14
16	*exercise/
17	aerobic exercise/
18	leg exercise/ or arm exercise/ or muscle exercise/
19	moderate intensity exercise/ or high intensity exercise/
20	*fitness/
21	*training/
22	*sport/
23	exp *ergometry/ or exp *bicycle ergometry/
24	exp wheelchair sport/
25	(wheelchair$ adj3 prop$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
26	treadmill exercise/
27	(gait adj train$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
28	exp exergaming/
29	exp video game console/
30	exp circuit training/
31	sports training.mp.
32	(resistan$ adj2 (training$ or exercise$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

(Continued)

33	(aerobic$ adj2 (training$ or exercise$)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
34	exp cardiorespiratory fitness/
35	exp swimming/
36	exp rowing/
37	exp boxing/
38	exp Gymnastics/
39	16 or 17 or 18 or 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 or 33 or 34 or 35 or 36 or 37 or 38
40	exp Randomized Controlled Trial/
41	exp controlled clinical trial/
42	exp controlled study/
43	comparative study/
44	randomi?ed.ab,ti.
45	placebo.ab.
46	*Clinical Trial/
47	exp major clinical study/
48	randomly.ab.
49	(trial or study).ti.
50	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51	exp animal/ not (exp human/ and exp animal/)
52	50 not 51
53	15 and 39 and 52
54	exp case report/
55	53 not 54

CINAHL Complete	
S42	S23 AND S35 AND S41

(Continued)

S41	S36 OR S37 OR S38 OR S39 OR S40
S40	(MM "Exergames") OR "exergaming"
S39	(MH "Ergometry")
S38	wheelchair propulsion
S37	(MM "Wheelchair Sports")
S36	(MH "Exercise+") OR (MM "Resistance Training") OR (MM "Group Exercise") OR (MM "Exercise Intensity") OR (MH "Aerobic Exercises") OR (MH "Upper Extremity Exercises") OR (MH "Lower Extremity Exercises") OR (MH "Arm Exercises") OR (MH "High-Intensity Interval Training") OR (MH "Endurance Training")
S35	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S34	(cervical vertebrae)(fracture* or injur*)
S33	(spine or spinal) (contusion or laceration or transaction or trauma or isch*))
S32	((spine or spinal) (fracture* or wound* or trauma* or injur* or damag*))
S31	MH (quadraplegia)
S30	MH (quadraplegia)
S29	quadriplegi* or paraplegi* or tetrapleg*
S28	MH (spinal cord injuries)
S27	spinal cord ischemia
S26	central cord syndrome
S25	spinal cord injur*
S24	spinal injur*
S23	S22 NOT S21
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S21	S19 NOT S20
S20	MH (human)
S19	S16 OR S17 OR S18
S18	TI (animal model*)
S17	MH (animal studies)
S16	MH animals+

(Continued)

S15	AB (cluster W3 RCT)
S14	MH (crossover design) OR MH (comparative studies)
S13	AB (control W5 group)
S12	PT (randomized controlled trial)
S11	MH (placebos)
S10	MH (sample size) AND AB (assigned OR allocated OR control)
S9	TI (trial)
S8	AB (random*)
S7	TI (randomised OR randomized)
S6	MH cluster sample
S5	MH pretest-posttest design
S4	MH random assignment
S3	MH single-blind studies
S2	MH double-blind studies
S1	MH randomized controlled trials
PEDro	
1	"spinal injur*' AND exercis*
2	"spinal injur*' AND training
3	"spinal injur*' AND fitness
4	"spinal injur* AND 'sport*
5	"spinal cord injur*' AND exercis*
6	"spinal cord injur*' AND training
7	"spinal cord injur*' AND fitness
8	"spinal cord injur* AND 'sport*

CONTRIBUTIONS OF AUTHORS

Jocemar Ilha, Joanne V Glinsky, and Lisa A Harvey were responsible for designing and writing the review protocol.

Jackie Chu, Elizabeth Bye, and Sean Tweedy provided feedback on the protocol.

DECLARATIONS OF INTEREST

JI has no conflicts of interest to declare.

JVG has no conflicts of interest to declare.

JC has no conflicts of interest to declare.

EB has no conflicts of interest to declare.

ST has no conflicts of interest to declare.

LAH has no conflicts of interest to declare.

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  The State Insurance Regulatory Authority (SIRA) and icare fund Professor Harvey's position. They are New South Wales Government organisations responsible for regulating insurance companies and providing treatment and care for people after injury.