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[Intervention Review]

Fitness training for cardiorespiratory conditioning after traumatic brain injury

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ABSTRACT

Background

Reduced cardiorespiratory fitness (cardiorespiratory deconditioning) is a common consequence of traumatic brain injury (TBI). Fitness training may be implemented to address this impairment.

Objectives

The primary objective of this updated review was to evaluate whether fitness training improves cardiorespiratory fitness in people who have sustained a TBI. The secondary objectives were to evaluate whether fitness training improves body function and structure (physical and cognitive impairments, psychological responses resulting from the injury), activity limitations and participation restrictions in people who have sustained a TBI as well as to evaluate its safety, acceptance, feasibility and suitability.

Search methods

We searched 10 electronic databases (the Cochrane Injuries Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Embase; PubMed (MEDLINE); CINAHL; AMED; SPORTDiscus; PsycINFO; PEDro and PsycBITE) and the International Clinical Trials Registry Platform for relevant trials. In addition we screened reference lists from systematic reviews related to the topic that we identified from our search, and from the included studies, and contacted trialists to identify further studies. The search was run in August 2017.

Selection criteria

Randomised controlled studies with TBI participants were eligible if they compared an exercise programme incorporating cardiorespiratory fitness training to usual care, a non-exercise intervention, or no intervention.

Data collection and analysis

Two authors independently screened the search results, extracted data and assessed bias. We contacted all trialists for additional information. We calculated mean difference (MD) or standardised mean difference (SMD) and 95% confidence intervals (CI) for continuous data, and odds ratio with 95% CI for dichotomous data. We pooled data when there were sufficient studies with homogeneity.

Main results

Two new studies incorporating 96 participants were identified in this update and were added to the six previously included studies. A total of eight studies incorporating 399 participants are included in the updated review. The participants were primarily men aged in their mid-thirties who had sustained a severe TBI. No studies included children. The studies were clinically diverse with regard to the interventions,

time postinjury and the outcome measures used. At the end of intervention, the mean difference in peak power output was 35.47 watts (W) in favour of fitness training (MD 35.47 W, 95% CI 2.53 to 68.41 W; 3 studies, 67 participants; low-quality evidence). The CIs include both a possible clinically important effect and a possible negligible effect, and there was moderate heterogeneity among the studies.

Five of the secondary outcomes had sufficient data at the end of intervention to enable meta-analysis: body composition (SMD 0.29 standard deviations (favouring control), 95% CI -0.22 to 0.79; 2 studies, 61 participants; low-quality evidence), strength (SMD -0.02 (favouring control), 95% CI -0.86 to 0.83; 2 studies, 23 participants; very low-quality evidence), fatigue (SMD -0.32 (favouring fitness training), 95% CI -0.90 to 0.26; 3 studies, 130 participants; very low-quality evidence), depression (SMD -0.43 (favouring fitness training), 95% CI -0.92 to 0.06; 4 studies, 220 participants; very low-quality evidence), and neuromotor function (MD 0.01 m (favouring fitness training), 95% CI -0.25 to 0.27; 2 studies, 109 participants; moderate-quality evidence). It was uncertain whether fitness training was more or less effective at improving these secondary outcomes compared to the control interventions. Quality of life was assessed in three trials, but we did not pool the data because of substantial heterogeneity. Five of the eight included studies had no dropouts from their intervention group and no adverse events were reported in any study.

Authors' conclusions

There is low-quality evidence that fitness training is effective at improving cardiorespiratory deconditioning after TBI; there is insufficient evidence to draw any definitive conclusions about the other outcomes. Whilst the intervention appears to be accepted by people with TBI, and there is no evidence of harm, more adequately powered and well-designed studies are required to determine a more precise estimate of the effect on cardiorespiratory fitness, as well as the effects across a range of important outcome measures and in people with different characteristics (e.g. children). In the absence of high quality evidence, clinicians may be guided by pre-exercise screening checklists to ensure the person with traumatic brain injury is safe to exercise, and set training parameters using guidelines established by the American College of Sports Medicine for people who have suffered a brain injury.

PLAIN LANGUAGE SUMMARY

Fitness training to support recovery for people with traumatic brain injury

Background

People with traumatic brain injury often have fitness levels well below the lowest fitness levels of adults of similar age and sex. Reduced fitness causes increased tiredness, which makes everyday activities harder to do. Health professionals use fitness training to address this problem. This is an update to a review first published in 2008, which aimed to evaluate how effective fitness training is at improving fitness, other outcomes such as depression, cognition (e.g. memory, attention and problem solving) and return to everyday activities.

Study characteristics

We searched for studies in August 2017. We included eight studies, involving 399 adults with traumatic brain injuries, in this review. Most study participants were men in their mid-thirties who had severe brain injuries. We found no studies that included children. The fitness training programmes were conducted in a range of settings including hospital, community and at home. In six of the eight studies all fitness training sessions were supervised. The type of fitness training varied, and included exercising on a fixed cycling machine, in water, on gym equipment such as a treadmill, home-based exercise, and a fitness group in the military. In six of the eight studies the prescribed intensity, duration and frequency of fitness training met the guidelines set by the American College of Sports Medicine.

Key results

Three of the eight studies, with 67 participants, assessed change in fitness at the end of the treatment programme. Exercise was conducted on a fixed cycling machine in two studies, and in water in the third, and all sessions were supervised. The fitness training was compared to non-exercise interventions in two of these studies, and to no intervention in the third study. We combined the results of the three studies, which demonstrated an average (mean) improvement of 35 watts on an exercise test in the fitness training groups compared to the non-exercise intervention and no intervention groups. This improvement represents approximately a 36% improvement in fitness from the start of the study, which is a large effect. However, this estimate is uncertain and the difference is likely to be between 3 to 68 watts, which may or may not be important clinically.

More than one study reported on six other outcomes; body composition, strength, tiredness, depression, quality of life and walking. It was unclear whether fitness training was better or worse than the non-exercise interventions or no intervention at improving these outcomes. Measures of cognition, activities of daily living, and return to everyday activities were only measured in one study, and there were no studies that measured the effect of fitness training on levels of physical activity and motivation. Only three studies examined the effect of fitness training beyond the end of the programme, but these could not provide a clear answer regarding the long-term effects of fitness training.

In the five studies that provided supervision for all fitness training sessions, all participants in the fitness training groups completed the studies. Treatment attendance varied between studies, and was reported as ranging from 59% to 100%, and was not reported for two studies. There was no evidence of harm caused by fitness training in any study.

Quality of evidence

Fitness training for cardiorespiratory conditioning after traumatic brain injury (Review)

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Our certainty in these findings is reduced due to the low quality of the evidence caused by small numbers of study participants, poor reporting of some study details, and possible errors in the way some of the studies were carried out.

Authors' conclusions

It is unclear whether fitness training after a traumatic brain injury improves physical fitness. There is not enough evidence to understand the effect of fitness training on other important outcomes. Whilst fitness training appears to be well attended by people with traumatic brain injury, particularly when supervised, and there is no evidence of harm, further well-designed studies are required before we can draw any definite conclusions. In the absence of high quality evidence, health professionals may be guided by pre-exercise screening checklists to ensure the person with traumatic brain injury is safe to exercise, and to set training parameters using guidelines established by the American College of Sports Medicine for people who have suffered a brain injury.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Cardiorespiratory exercise programmes prescribed alone compared with a non-exercise intervention or no intervention for people after traumatic brain injury

Cardiorespiratory exercise programmes prescribed alone compared with usual care, a non-exercise intervention, or no intervention for people after traumatic brain injury

Patient or population: people with traumatic brain injury of any age or severity

Setting: any setting, including inpatient, outpatient, community and home

Intervention: exercise using large muscle groups prescribed at least three times a week for a duration of at least 20 minutes at an intensity that represented a clear attempt to improve cardiorespiratory fitness

Comparison: usual care, a non-exercise intervention, or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	No fitness training	Fitness training			
Cardiorespiratory fitness - peak power output (W) - end of intervention	The mean peak power output ranged across control groups from 85 W to 145 W	The mean peak power output in the intervention groups was on average 35 W higher (95% CI 3 to 68)	67 (3 studies)	⊕⊕ low^{a,b}	The MCID has not been determined for this outcome in this or a similar population, however in people with severe COPD, the MCID is 4 W (Puhan 2011).
Depression - SMD - end of intervention	The mean depression score ranged across control groups from 1.1 to 21.2 points on various depression scales	The SMD between groups was on average 0.43 lower in the intervention group (95% CI 0.92 to -0.06)	220 (4 studies)	⊕ very low^{a,b,c}	An SMD of 0.43 represents a difference between groups in scores on the depression subscale of the Hospital Anxiety Depression Scale (0 to 21) of a 1.7 point reduction in depression with the 95% confidence intervals indicating an effect between a 3.7 reduction in depression to a 0.2 point increase in depression. Post hoc analysis pooling the data from the 3 studies that included subacute and chronic participants at home, the SMD indicated a moderate reduction in depression with fitness training with the 95% CIs indicating between a large and small reduction in depression with fitness training compared to the control interventions (SMD -0.61, 95% CI -1.1 to -0.11; 3 studies, 178 participants; low-quality evidence).

Cognition	See comment	See comment	111 (2 studies)	See comment	Data could not be pooled because the outcome measures from both studies did not measure the same domains of cognition. There were no immediate or long-term effects in either study.
Fatigue - SMD - end of intervention	The mean fatigue score ranged among control groups from 1.3 to 6.6 points on various fatigue scales	The SMD between groups was on average 0.32 lower in the intervention group (95% CI 0.90 to -0.26)	130 (3 studies)	⊕ very low a,b,c	An SMD of 0.32 represents a difference between groups in scores on a VAS fatigue scale (0 to 10) of approximately 0.9 points (95% CI -0.7 to 2.6), with a lower score indicating a reduction in fatigue.
Community integration	See comment	See comment	76 (1 study)	See comment	Data only available from one study; no clear evidence of effect.
Safety	See comment	See comment	183 (5 studies)	See comment	Trialists reported no adverse events occurred during the intervention phase in these studies.

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **COPD:** chronic obstructive pulmonary disease; **MCID:** minimal clinically important difference; **SMD:** standardised mean difference; **VAS:** visual analogue scale; **W:** watts

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a Downgraded once because of risk of bias.

^b Downgraded once because of imprecision of results.

^c Downgraded once because of heterogeneity among included studies.

BACKGROUND

Description of the condition

Traumatic brain injury (TBI) is a leading cause of death and long-term limitation of activity globally (Hyder 2007). The reported incidence of TBI ranges from 108 to 392 per 100,000 population (Abelson-Mitchell 2008), with most of these injuries classified as mild (Hyder 2007). Although TBI has a lower incidence than some other health conditions, such as stroke, it primarily affects people in the prime of their life. The prevalence, economic and social cost of TBI is extensive, with an estimated total direct and indirect cost in the USA of between USD 34 and 76 billion annually (Ma 2014). In addition, the World Health Organization anticipates the incidence of TBI will grow due to motor vehicle accidents in developing countries and ongoing military conflicts (Ma 2014). It is therefore important to optimise the health of people with TBI throughout their lives.

Description of the intervention

Cardiorespiratory fitness training is one method of optimising health. Fitness training is a type of leisure-time physical activity that is planned, structured, repetitive, and purposive in the sense that it has as an objective the improvement or maintenance of one or more components of physical fitness (Caspersen 1985). The American College of Sports Medicine has published exercise guidelines for people with a brain injury; these recommend exercising at a frequency of three to five times per week, at an intensity of 40% to 70% of peak oxygen uptake, or a 13/20 Rating of Perceived Exertion (RPE), and for a duration of 20 to 60 minutes using an appropriate mode of exercise (e.g. walking, swimming, cycling) that will depend upon the individual's physical ability (Palmer-McLean 2009).

How the intervention might work

Regular physical activity and a high fitness level are associated with a reduced risk of morbidity and mortality globally (Lee 2012; Williams 2001). However, people with TBI have been shown to be less physically active than the able-bodied population (Hassett 2015), and to have low fitness (Hassett 2016). In a recent narrative review conducted by our team that proposed a causative model of reduced fitness in people with TBI, we pooled data from 11 studies that measured peak oxygen uptake in 234 adults with TBI (Hassett 2016). The average peak oxygen uptake was $27.2 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ which is well below the lowest fitness levels for adults of a similar age and gender (ACSM 2014). Reasons why people with TBI may be less physically active and unfit are multifactorial and can include the physical and cognitive impairments and psychological responses that result from their injury, as well as environmental and societal barriers (Hassett 2016). For example, it may be difficult to go outside to walk due to both the physical impairment of poor balance and an environmental barrier such as an uneven footpath. The cognitive impairment of diminished drive and the emotional disorder of depression may also make those with TBI less likely to initiate exercise or want to leave their home to go for a walk. It is therefore necessary to investigate fitness training interventions to increase physical activity for people who have sustained a TBI.

Fitness training programmes in unfit - but otherwise healthy - individuals have demonstrated improvements in cardiorespiratory fitness of approximately 12% for light (24% to 39% heart rate

reserve) to moderate (40% to 59% heart rate reserve) intensity programmes (Swain 2005). In healthy able-bodied people, fitness training improves cardiorespiratory fitness by improving both central and peripheral determinants (Rowell 1974). Centrally, cardiorespiratory fitness training of sufficient intensity increases heart stroke volume and decreases heart rate at a set submaximal load; and peripherally, training increases muscle oxidative capacity (Rowell 1974). It is likely that similar mechanisms would increase fitness in people with TBI, but this has not been tested empirically.

Participation in regular fitness training may not only improve cardiorespiratory fitness (thereby reducing the risk of morbidity and mortality), but may also specifically improve some of the common physical and psychosocial sequelae of TBI. These include fatigue (Bushnik 2008; Ponsford 2014), impaired cognition (Novack 2000), depression (Rosenthal 1998), and poor community integration (Doig 2001). Physical fatigue is associated with impairments in physiological efficiency, muscle strength and oxidative capacity (Jankowski 1990). Improvements in fitness (i.e. improvements in the oxidative capacity) increase the reserve capacity (i.e. peak oxygen capacity minus resting oxygen capacity); thus, for the same given activity a fitter person will be working at a lower percentage of their peak oxygen capacity and, as such, will report the activity as less fatiguing.

Cognitive impairments after TBI have a characteristic form, with a pattern of deficits in memory functioning, cognitive processing speeds, reasoning skills and concentration, although individual differences are evident (Novack 2000). These impairments are a direct result of the trauma to the brain and are associated with neuronal activity disruption and changes in oxidative metabolism (Grealy 1999). The rationale for the possibility that cardiorespiratory fitness training might improve cognition comes from animal and neuropsychological research. This shows that regular physical activity can affect cognition positively by increasing cerebral blood flow and neurotransmitter levels and bringing about structural changes in the brain (Etnier 1997). Thus it seems plausible that cardiorespiratory fitness training may improve cognitive function in people with TBI.

Depression is one of the major emotional disorders that can follow moderate to severe TBI (Satz 1998); it is thought to be a primary barrier to achieving optimal rehabilitation goals (Rosenthal 1998). The reported incidence of depression after TBI varies, ranging from 10% to 77% (Rosenthal 1998). The mechanism for the development of depression has been difficult to determine, due to the diverse sequelae seen after TBI and, in some cases, the complicating premorbid factors such as unemployment and substance abuse (Rosenthal 1998). It has been postulated that fitness training may be an under-used adjunct to current pharmacological and psychological therapies that address depression (Paluska 2000). Cardiorespiratory fitness training may have psychological effects such as positive feedback from other people, an increased sense of self-worth, mastery of a new skill and social contact (Lawlor 2001). Physiological mechanisms may also contribute, particularly as exercise increases the release of endorphins and monoamines, which increase feelings of well-being. It is probably a combination of these psychological and physiological components in a psychobiological model that best explains the potential mechanisms of fitness training on depression (Paluska 2000).

'Community integration' refers to effective performance of a role in the community setting (Burleigh 1998), and encompasses

integration in three areas, namely social network, home, and productive activities (Willer 1993). A study of TBI survivors two to five years after discharge from rehabilitation showed that 40% still performed poorly in all three areas of community integration (Doig 2001). Cardiorespiratory fitness training can serve an important role in improving community integration. Firstly, it has an impact on societal and familial re-integration by improving the person's ability to perform regular physical activity with family or friends, such as walking or jogging, and generally participating in socially acceptable activities regardless of their other deficits (Sullivan 1990). Secondly, by reducing fatigue levels and improving cardiorespiratory fitness, the person with TBI may be more able to cope with returning to their everyday activities including vocational activities (Jankowski 1990).

Why it is important to do this review

Several randomised controlled studies have examined the effects of cardiorespiratory fitness training as an intervention for people who have sustained a TBI (e.g. Bateman 2001; Driver 2004), however this intervention has not been subject to rigorous review. For this reason a systematic review was required to investigate these studies comprehensively to determine whether there are any benefits or harms of cardiorespiratory fitness training in this population, and to highlight gaps in the evidence. The original version of this review was published on the Cochrane Library in 2008 and the findings were unclear (Hassett 2008). Given the time since the original review, we considered an update to be appropriate to determine whether the evidence is any clearer regarding the effectiveness of fitness training in this population.

OBJECTIVES

The primary objective of this updated review was to evaluate whether fitness training improves cardiorespiratory fitness in people who have sustained a TBI.

The secondary objectives were to evaluate whether fitness training improves body function and structure (physical and cognitive impairments, psychological responses resulting from the injury) activity limitations and participation restrictions in people who have sustained a TBI as well as to evaluate its safety, acceptance, feasibility and suitability.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled studies that addressed one of the two following comparisons:

- Comparison 1: any exercise programme (as described in [Types of interventions](#)) prescribed alone versus usual care, a non-exercise intervention, or no intervention.
- Comparison 2: any exercise programme (as described in [Types of interventions](#)) as a component of an intervention versus usual care, or no intervention.

Types of participants

We included studies with participants of either sex and any age who had sustained a TBI (the condition where a person is hit by, or runs into, an external force great enough to cause damage to

the brain (NIH 1998)), with or without skull fracture, diagnosed by a medical practitioner with or without confirmation by radiological evidence. Participants could have any severity of injury; where there were data available, we have indicated the injury severity of participants in each study. Injury severity rating was based on the duration of post-traumatic amnesia (Russell 1961), and coma, as measured by the Glasgow Coma Scale (Jennett 1981). The three severity categories were:

- mild: post-traumatic amnesia of less than one hour, with or without loss of consciousness, or amnesia for the event;
- moderate: post-traumatic amnesia between one and 24 hours, with or without an altered level of consciousness (Glasgow Coma Scale score 9 to 12), between one and six hours post-trauma; and
- severe: duration of post-traumatic amnesia longer than 24 hours, a neurosurgical procedure required, or a period of coma with a Glasgow Coma Scale score of 8 or less at six hours post-trauma.

Where a study included a mixed sample of participants with TBI and participants with other health conditions such as a stroke, we used the outcomes from the TBI participants only. Where the data were not separately identifiable, we contacted the trialists to obtain the TBI only data.

Types of interventions

For the purpose of this review, we included studies of any intervention that incorporated exercise that uses large muscle groups in a rhythmical and continuous nature, prescribed at a frequency of at least three times a week for a duration of at least 20 minutes (continuous or intermittent) at an intensity that represented a clear attempt to improve cardiorespiratory fitness (Palmer-McLean 2009). While we did not exclude studies if they did not report exercise intensity of at least 40% peak oxygen uptake or a rate of perceived exertion of 13/20, it had to be clear that the intention of the exercise programme was cardiorespiratory fitness training. If this information was not clear in the study publications, we contacted the trialists regarding the training parameters of the exercise programme.

The exercise was implemented as an inpatient, outpatient or community-based programme, was supervised or self-led, and was set in the hospital, rehabilitation unit, home or community. We included studies that included other types of exercise such as resistance, flexibility or neuromotor exercises in conjunction with cardiorespiratory fitness training. The exercise programme was either prescribed in isolation or as a component of a rehabilitation package.

For studies to be included in the review, the comparator intervention had to be usual care, a non-exercise intervention or no intervention. Usual care could include physical rehabilitation, however it could not include fitness training prescribed at a similar dose to the exercise intervention. As for the exercise intervention, the comparator interventions could be implemented as an inpatient, outpatient or community-based programme, supervised or self-led, and set in the hospital, rehabilitation unit, home or community.

Types of outcome measures

The types of outcome measures used in each study did not form part of the inclusion criteria for this review. For each comparison, the primary analyses included all identified studies for each outcome both at the end of the intervention period and at the end of the scheduled follow-up.

Primary outcomes

The primary outcome was cardiorespiratory fitness. This was assessed by direct and indirect measures, for example:

- laboratory-based measures for maximal tests such as peak oxygen uptake (direct) and peak power output (indirect). Other measures such as peak heart rate, stroke volume and peak respiratory exchange ratio during exercise were used to evaluate whether performances were of a maximal nature (ACSM 2014);
- laboratory-based measures for submaximal tests such as oxygen uptake, carbon dioxide production, minute ventilation, respiratory exchange ratio (direct) and peak power output, test duration, and heart rate and stroke volume (indirect) at set submaximal work rates (ACSM 2014); and
- field-based measures (indirect) such as Rating of Perceived Exertion (RPE) (Borg 1982), and distance or level achieved in walk/run tests such as the modified version of the 20-metre shuttle test (Vitale 1997), or 12-minute walk/run test (Cooper 1968).

Reliability for most of these measures has been established in a TBI population (Bhambhani 2003; Mossberg 2003; Mossberg 2005; Rossi 1996; Vitale 1997).

We calculated the information size required to detect a treatment effect reliably using a power analysis for a single trial (Bateman 2001). If we assume a minimal clinically important difference of 4 W for peak power output and a standard deviation of 56 W, 148 people need to be randomised to receive either fitness training or control to obtain a reliable estimate of the treatment effect (significance level = 0.05, power = 90%).

Secondary outcomes

The secondary outcomes included measures of body function and structure (six outcomes), activity limitation (two outcomes) participation restriction (three outcomes), safety, acceptance, feasibility and suitability.

Body function and structure measures

Impairment (four outcomes)

- Body composition assessed using any relevant measure such as body mass index or skin fold thickness (ACSM 2014).
- Strength assessed using any relevant measure such as dynamometer grip strength or one repetition maximum (ACSM 2014); or peak force, torque, or total work normalised to body weight (Palmer-McLean 2009).
- Fatigue (physical and mental) assessed using any relevant physiological measure or any relevant scale such as the Chalder modified fatigue scale (Chalder 1993), or the Fatigue Severity Scale, the Visual Analogue Scale-Fatigue or the Causes of Fatigue Questionnaire (Ziino 2005).
- Cognition (attention and memory domains) assessed using any relevant scale such as the Sunderland Memory Questionnaire

(Sunderland 1984), Adult Memory and Information Processing Battery (Coughlan 1985), Paced Auditory Serial Addition Test (Gronwall 1977), the Buschke Selective Reminding Test (Buschke 1973), the Wechsler Adult Intelligence Scale (Wechsler 1981), Wechsler Memory Scale (Wechsler 1987), Neurobehavioural Rating Scale (Levin 1987), the Rivermead Behavioural Memory Test (Wilson 1989), or the Behavioural Assessment of the Dysexecutive Syndrome (Wilson 1996).

Psychological functioning (two outcomes)

- Depression assessed using any relevant scale such as the Hospital Anxiety and Depression Scale (Zigmond 1983), Depression Anxiety Stress Scale (Lovibond 1996), Profile of Moods Scale (McNair 1992), Zung Depression Scale (Zung 1965), or the Beck's Depression Inventory (Beck 1987).
- Motivation assessed using any relevant scale such as the Motivation for Traumatic Brain Injury Rehabilitation Questionnaire (Chervinsky 1998), or the Apathy Evaluation Scale (Marin 1991).

Activity limitation measures

- Global measures of function assessed using any relevant scale such as the Barthel Index (Mahoney 1965), the Functional Independence Measure (Keith 1987), or the Brain Injury Community Rehabilitation Outcome Scale (Powell 1998).
- Neuromotor function assessed using any relevant measure such as the 10-metre indoor walk (van Loo 2003), or any relevant scale such as the Berg Balance Scale (Berg 1995), Motor Assessment Scale (Carr 1985), High Level Mobility Assessment Tool (Williams 2005), the Rivermead Mobility Index (Collen 1991), or the 6-minute walk test (Butland 1982).

Participation restriction measures

- Community integration assessed using any relevant measure such as return to work rates or any relevant scale such as the Sydney Psychosocial Reintegration Scale (Tate 1999), Community Integration Questionnaire (Willer 1993), or Craig Handicap Assessment Reporting Technique (Whiteneck 1992).
- Global measures of quality of life assessed using any relevant scale such as the General Health Questionnaire (Goldberg 1988), the Health Promoting Lifestyle Profile II (Walker 1995), the Bigelow Quality of Life Questionnaire (Bigelow 1991), Sickness Impact Profile (Temkin 1988), or Satisfaction with Life Scale (Diener 1985).
- Physical activity assessed using any relevant measure such as number of self-reported physical activities or any relevant scale such as the International Physical Activity Questionnaire or the Active Australia (Brown 2004), or the Physical Activity Scale for Individuals with a Physical Disability (Washburn 2002).

Safety

- We classified adverse events as injurious falls, other injury, major cardiovascular events or any other adverse outcome.

Acceptance

- We used dropout rates for each trial as a surrogate measure of the acceptance of the intervention.

Feasibility

- We defined adherence as the number of exercise sessions completed compared to the prescribed number of exercise sessions.

Suitability

- We defined suitability of the intervention as the ability to achieve the prescribed training parameters (i.e. intensity, frequency, duration).

Search methods for identification of studies

No language or publication restriction was applied to any component of the search strategy. Studies were searched for by combining the health condition of TBI, the intervention of cardiorespiratory fitness training and the method of controlled clinical trials.

Electronic searches

The latest search for studies was conducted in August 2017. The Cochrane Injuries Group Information Specialist searched the following:

- The Cochrane Injuries Group's Trial Register (4 August 2017);
- CENTRAL (the Cochrane Library; 2017, Issue 7);
- PubMed (MEDLINE) (4 August 2017);
- Embase Classic + Embase (1947 to 4 August 2017);
- CINAHL Plus (EBSCO) (1937 to 4 August 2017); and
- PsycINFO (OvidSP) (1806 to 4 August 2017).

The review authors searched the following:

- AMED (OvidSP) (2007 to 8 August 2017);
- SPORTDiscus (EBSCO) (May 2007 to 8 August 2017);
- PEDro (www.pedro.org.au) (last searched 8 August 2017); and
- PsycBITE (www.psycbite.com) (last searched 8 August 2017).

Updated search strategies are listed in [Appendix 1](#).

Searching other resources

Reference lists

We checked reference lists of included studies and systematic reviews identified from our search for previously unidentified relevant studies.

Personal communication

We sent a letter containing a list of the eligible studies and the inclusion criteria for the review to the first author of included studies to see if they were aware of any other published or unpublished studies.

Handsearching

Brain Injury and the *Journal of Head Trauma Rehabilitation* have been handsearched by the Cochrane Injuries Group. No additional handsearching was performed.

Grey literature

We searched the International Clinical Trials Registry Platform for ongoing studies in this review update (apps.who.int/trialsearch).

Where we identified relevant studies, we made contact with the first author in accordance with the method described for 'Personal communication'.

Data collection and analysis

Selection of studies

Two review authors (LMH and AMM) independently reviewed the search results and screened the title, abstract or both the title and abstract of identified references to select potentially eligible studies. These were then compared and there were no disagreements. We obtained full copies of all studies that potentially met the inclusion criteria. All potentially eligible studies were entered into the Covidence software program (www.covidence.org), accessed as part of a pilot project through the National Trauma Research Institute, Australia. Covidence required two review authors (LMH and ARH) to determine eligibility independently; once both review authors entered their decision, data comparison was completed within the program. Any disagreements were resolved through discussion. Any unresolved disagreements were resolved by a third party (AMM), but no arbitration was required for this review update. Since we retrieved no potentially eligible articles written in languages other than English, no additional reviewers were required.

Data extraction and management

Two independent review authors (LMH and ARH or AMM) completed data extraction and assessed risk of bias for the included studies. We modified the checklist from the 2008 version of this review and used it independently to record all information required from each study. Two review authors compared the checklists and agreed on the data to be extracted. Outcome data from the newly identified included studies were also entered into Covidence. Covidence again required two review authors (LMH and ARH) to complete data extraction independently and data comparison was completed within the program. Any discrepancies were resolved through discussion. Any unresolved disagreements from the checklist or Covidence system were resolved by a third party (AMM), but no arbitration was required for this review update. Every attempt was made to contact trialists for any missing data. The data extracted included:

- methods (study design, method of generating randomisation schedule, method of concealment of allocation, blinding of therapists, participants and assessors, and number of randomised participants from each group who were not included in the analyses with reasons);
- risk of bias (using the Cochrane 'Risk of bias' tool, and determined from trial publications and correspondence with trialists);
- participants (country, number of participants, inclusion and exclusion criteria, age, sex, injury severity, cause of injury, time from injury to entry to study, and ambulatory status);
- intervention for the experimental group (type of exercise programme (cardiorespiratory alone or combined with strength, flexibility, and/or neuromotor), length of programme, exercise mode, training intensity, frequency and duration, evidence of exercise progression, evidence of training adherence and co-intervention);
- intervention for the control group, as well as categorising it as usual care, non-exercise or no intervention (type

of intervention, length of programme, frequency, duration, evidence of intervention progression and adherence and co-intervention);

- setting (inpatient or outpatient, supervised or self-led, home-based or hospital/unit-based or community-based); and
- outcomes (number of participants in each group, outcome measures, when outcomes were assessed, number of participants experiencing the event (dichotomous outcomes) at each assessment point, and mean and standard deviation (continuous outcomes) at each time point). Outcomes for all available participants were included, regardless of adherence. Whether the data were change-from-baseline or final value scores was noted for each continuous outcome. For this version of the review, we used final value scores for all analyses.

All data were entered into Review Manager 5 ([Review Manager 2014](#)). Data for all outcomes were cross-checked when entered. For each comparison, the primary analysis included all identified studies for each outcome, both at the end of the intervention period and at the end of the scheduled follow-up.

Assessment of risk of bias in included studies

Two review authors (LMH and ARH or AMM) independently assessed the risk of bias of each study using the Cochrane 'Risk of bias' tool ([Higgins 2011](#)). Each study was assessed for:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment for objective outcomes (detection bias);
- blinding of outcome assessment for self-reported outcomes (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting bias); and
- any other bias.

For each possible bias a rating was given of low risk, unclear risk or high risk, as defined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Measures of treatment effect

We used Review Manager 5 for all analyses ([Review Manager 2014](#)). We calculated the mean difference (MD) and the 95% confidence interval (CI) for continuous data that we pooled. Different studies used different measurement tools to measure an outcome. When this occurred, we converted the data to standardised scores with dimensionless units and calculated the standardised mean difference (SMD) and the 95% CI. For this review update, we used standardised scores for the following outcomes within Comparison 1: body composition, strength, fatigue, depression and quality of life. Within Comparison 1 we also calculated the odds ratio (OR) and 95% CI for the dichotomous data of dropouts as a surrogate measure of acceptance. Within Comparison 2, we calculated ORs and 95% CI for depression, community integration (return to work) and acceptance (dropout rates).

Unit of analysis issues

There were no unit of analysis issues because the level of analysis and randomisation was the participant.

Dealing with missing data

We planned to perform our analyses using data from all randomised participants. We attempted to obtain missing data or to clarify data by contacting the trialists; however, outcomes were not available for participants who had dropped out, so we performed analyses using the available case data.

Assessment of heterogeneity

For the outcomes that were measured in more than one study, two authors (LMH and AMM) examined the clinical diversity (variability in participants, interventions and outcomes) and methodological diversity (study design, risk of bias) of the studies and discussed whether it was appropriate to combine data. For outcomes that we considered suitable for pooling, we carried out meta-analysis using the random-effects model, as we expected a lot of variation between studies. We assessed heterogeneity using both the χ^2 and I^2 tests. Because the χ^2 test has low power when small sample sizes are involved, we used the more conservative 90% significance level. The observed heterogeneity from the I^2 test was considered low if I^2 was less than 40%, moderate for values between 40% and 70%, and substantial if I^2 exceeded 70% ([Higgins 2011](#)). When there was substantial heterogeneity we considered whether or not to report the pooled result by checking the magnitude and direction of effects and the strength of evidence for heterogeneity from the P value of the χ^2 test ([Higgins 2011](#)).

Assessment of reporting biases

We did not construct a funnel plot to detect publication bias for this review update because there were too few included studies to detect asymmetry ([Light 1984](#)).

Data synthesis

We used Review Manager 5 for all analyses ([Review Manager 2014](#)).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were not possible for this review update because there were too few included studies for this to be feasible. The planned subgroup analyses were:

- injury severity (categorised as mild, moderate and severe TBI as defined by [Russell 1961](#) and [Jennett 1981](#));
- age (categorised as children (aged < 18 years) and adults (aged $\geq$ 18 years));
- setting (categorised as hospital-based, home-based and community-based);
- time since injury (categorised as early intervention (< 6 months postinjury) and late intervention ($\geq$ 6 months postinjury)); and
- the intensity of the prescribed cardiorespiratory programme, comparing studies which clearly met the American College of Sports Medicine (ACSM) recommended guidelines for TBI versus those that did not meet ACSM recommended guidelines for TBI ([ACSM 2014](#)).

Sensitivity analysis

We planned to conduct sensitivity analyses to examine how robust any pooled results were when the risk of bias of the studies was taken into account, or to explore reasons for heterogeneity if data were not pooled. The planned sensitivity analyses were for concealed allocation (by removing studies with unclear or high risk

of bias for allocation concealment), assessor blinding (by removing studies with unclear or high risk of bias for blinding of outcome assessors), and acceptable loss to follow-up (by removing studies with a dropout rate of $\geq 15\%$). Because of the low number of studies in this review update, a sensitivity analysis was only relevant for one outcome (depression) for concealed allocation.

'Summary of findings' tables

We created a 'Summary of findings' table for comparisons and outcomes with at least two studies. The following six outcomes were selected as the most important and included in [Summary of findings for the main comparison](#): cardiorespiratory fitness; depression; cognition; fatigue; community integration; safety. We summarised the available data on these outcomes, the magnitude of effect of the interventions examined, and the quality of evidence in [Summary of findings for the main comparison](#). We decided an overall grading of the evidence related to each outcome using the GRADE approach as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For continuous outcomes, the after-intervention score (range in studies included in the comparison) was used to illustrate the assumed risk in the control group and the MD or SMD and 95% CI were used to illustrate the corresponding risk with fitness training. The minimal clinically important difference (MCID) has not been determined for the primary outcome (cardiorespiratory fitness - peak power output) in people with TBI or a similar population. We therefore used a MCID value established for people with severe chronic obstructive pulmonary disease, which is 4 W (Puhan

2011). For the GRADE assessment, because all included studies are randomised controlled trials, all evidence was initially rated as 'high'. We downgraded the evidence on the basis of risk of bias in study design, inconsistency in study results, indirectness of evidence, imprecision of results, and publication bias.

RESULTS

Description of studies

Results of the search

The full details of the search results are presented in the PRISMA flow diagram ([Figure 1](#)). Six studies were included from the previous version of the review. The search strategy for this update yielded 10,711 records. Of those, 10,677 were ineligible; 28 records describing 26 studies were excluded and added to the previous nine studies described in [Characteristics of excluded studies](#); one, [NCT02276079](#), is ongoing and is described in [Characteristics of ongoing studies](#); and one is awaiting assessment to confirm eligibility, [McClanachan 2013](#), and is described in [Characteristics of studies awaiting classification](#). Four records describing two new studies were eligible for inclusion ([Driver 2009](#); [Hoffman 2010](#)), and were added to the six studies included in our 2008 review ([Hassett 2008](#)). A total of eight studies were included in this review update and described in [Characteristics of included studies](#) ([Bateman 2001](#); [Driver 2004](#); [Driver 2006](#); [Driver 2009](#); [Hoffman 2010](#); [Laskin 2001](#); [McMillan 2002](#); [Salazar 2000](#)). Additional information about all eight studies was obtained from correspondence with the trialists and incorporated in [Characteristics of included studies](#).

Figure 1. Study flow diagram

Included studies

All eight included studies used true randomised, parallel group design. Six studies used a two-group design, one study randomised to three groups (McMillan 2002), and one study randomised to four groups (Laskin 2001). For the McMillan 2002 study, participants were randomised to an attentional training group, a cardiorespiratory fitness training group or a no intervention group. For analysis we compared the cardiorespiratory fitness training group to the no intervention group. For the Laskin 2001 study, participants were randomised to one of three intervention groups (cardiorespiratory fitness training alone, combined cardiorespiratory fitness and resistance training, resistance training alone) or a control group (no intervention). For analysis we combined the first two intervention groups as the experimental group, and compared this to the control group.

The eight included studies populated the following comparisons:

- Comparison 1: seven studies (279 participants) compared an exercise programme prescribed alone versus a non-exercise intervention (Bateman 2001 (47 participants); Driver 2004 (16 participants); Driver 2006 (18 participants); Driver 2009 (16 participants)), or no intervention (Hoffman 2010 (80 participants); Laskin 2001 (7 participants); McMillan 2002 (95 participants));
- Comparison 2: one study (120 participants) compared an exercise programme as a component of an intervention versus usual care (Salazar 2000).

Five studies were conducted in the USA (Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Salazar 2000), two in the UK (Bateman 2001; McMillan 2002), and one in Canada (Laskin 2001). The experimental intervention was implemented in an inpatient setting for two studies (Bateman 2001; Salazar 2000), in an outpatient setting at a rehabilitation centre for one study (Laskin 2001), in a community setting for three studies (Driver 2004; Driver 2006; Driver 2009), in the home for one study (McMillan 2002), and

a combination of community and home settings for one study (Hoffman 2010).

Participants

The eight included studies provide data for a total of 399 participants with TBI. Six studies included only TBI participants (Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; McMillan 2002; Salazar 2000). One study included participants with a single brain injury of any cause (Bateman 2001), and another study included participants with any physical disability who attended the study centre (Laskin 2001). For these two studies, we were able to obtain the data for the TBI participants from the trialists and only these data were included in the review (Bateman 2001 for 47/175 participants; Laskin 2001 for 7/37 participants).

The participants were mainly young adult men who had sustained severe TBIs in road traffic accidents. No studies recruited children. We were unable to determine demographic or injury-related data for the TBI-only participants in one study (Laskin 2001). For the remaining seven studies, the average age of participants was 35 years and most were male (71%). However, all studies included women and one study included more women than men (Hoffman 2010). Injury severity was classified as severe for most participants (58%); the remainder were classified as either moderate (13%), mild (3%) or indeterminate (26%). Road traffic accident was the most common cause of TBI (41%), followed by acts of violence (13%), falls (8%), sport (1%), other (3%), or unknown causes (35%). The average time from injury to entry into the study ranged from 1.3 months in Salazar 2000 to 40.8 months for Driver 2006. Three studies recruited participants within the first year of sustaining their injury (Bateman 2001; McMillan 2002; Salazar 2000), three studies recruited participants after the first year of their injury (Driver 2004; Driver 2006; Driver 2009), and one study recruited participants between six months and five years after their injury (Hoffman 2010). Almost half (46%) of participants were ambulatory and 9% were non-ambulatory; the ambulatory status could not be determined for 45% of participants. Because only three studies reported use of walking aids, we did not differentiate between walking unaided and walking with an aid.

Interventions

A summary of the experimental interventions (i.e. exercise programmes) is detailed in Table 1. Three studies led by the same author provided the same intervention (a community-based aquatic exercise programme) across all three studies (Driver 2004; Driver 2006; Driver 2009). Six studies (184 participants) had fitness training as the primary focus of the study (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Laskin 2001). The other two studies (215 participants) had cognitive training as their primary focus and included fitness training as a control group (McMillan 2002), or as a component of their experimental intervention (Salazar 2000).

The length of the exercise programme was four weeks (McMillan 2002), eight weeks (Driver 2004; Driver 2006; Driver 2009; Salazar 2000), 10 weeks (Hoffman 2010), or 12 weeks (Bateman 2001; Laskin 2001). Supervision of the exercise programme was provided for six of the eight studies (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Laskin 2001; Salazar 2000); the other two studies had a mix of supervised and independent sessions over the duration of the programme (Hoffman 2010; McMillan 2002). The exercise programme included a combination of cardiorespiratory

fitness and resistance training for four studies (Driver 2004; Driver 2006; Driver 2009; Laskin 2001), cardiorespiratory fitness training alone for two studies (Bateman 2001; Hoffman 2010), and was unclear for two studies (McMillan 2002; Salazar 2000). The exercise programme was compared to a non-exercise intervention in four studies (Bateman 2001; Driver 2004; Driver 2006; Driver 2009), no intervention in two studies (Laskin 2001; McMillan 2002), a usual care intervention in one study (Salazar 2000), and a waiting-list control group who were offered the programme at the end of the wait-list period (Hoffman 2010).

The six studies with fitness training as their primary focus prescribed the cardiorespiratory fitness component of the exercise programme (type, intensity, duration, frequency) within the ACSM guidelines for people who have sustained a brain injury (Palmer-McLean 2009). Only one of the six studies reported the actual exercise dose delivered (Bateman 2001), which was below the ACSM recommendations (Palmer-McLean 2009). In the two studies for which fitness training was not the primary focus, it was not possible to determine if the exercise programme met the ACSM guidelines; however, it was clear that the intention of the intervention was cardiorespiratory fitness training (McMillan 2002; Salazar 2000). Training load was progressed in one study by increasing the duration and power output (Laskin 2001), in another study by increasing the duration (Bateman 2001), and was not reported for the other six studies. From correspondence with one trialist, the exercise programme focused on reaching a perceived exertion level and the training load was progressed by the participant by increasing the difficulty as their exertion level allowed (Hoffman 2010).

Outcomes

Only the immediate effects of intervention were examined for five studies (Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Laskin 2001), with outcomes being measured at baseline and at the end of intervention. A follow-up period between 12 weeks and 12 months was used to determine the sustained effects of the intervention in two studies (Bateman 2001; McMillan 2002). Only long-term effects were examined for one study, with the trial's primary outcome measures (i.e. return to employment and fitness for duty) being reported at one year follow-up only (Salazar 2000).

The primary outcome of cardiorespiratory fitness was measured in three studies (Bateman 2001; Driver 2004; Laskin 2001). The eight included studies measured a mix of outcomes in the body function and structure, activity limitation and participation restriction domains, but the outcomes measured varied considerably among studies. At the body function and structure level, the secondary outcome of body composition was measured in two studies (Bateman 2001; Driver 2004), strength in two studies (Driver 2004; Laskin 2001), fatigue in three studies (Bateman 2001; Driver 2009; Hoffman 2010), cognition in three studies (Driver 2009; McMillan 2002; Salazar 2000), and depression in five studies (Bateman 2001; Driver 2009; Hoffman 2010; McMillan 2002; Salazar 2000). For activity limitation, the secondary outcome measure of global function was measured in one study (Bateman 2001), and neuromotor function was measured in two studies (Bateman 2001; Hoffman 2010). For participation restriction, the secondary outcome of community integration was measured in two studies (Hoffman 2010; Salazar 2000), and quality of life in three studies (Driver 2006; Hoffman 2010; McMillan 2002). The secondary

outcome measures of motivation and physical activity were not measured in any of the eight included studies.

Safety (adverse events) was not reported in the eight studies. Trialists were contacted and adverse events data were provided for six studies (Bateman 2001; Driver 2004; Driver 2006; Hoffman 2010; Laskin 2001; Salazar 2000). Acceptance data (i.e. dropout data) were available for all studies. Feasibility data (adherence to the prescribed exercise programme) were available for six studies (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Laskin 2001). Only one study provided data to determine the suitability of fitness training in people with TBI (Bateman 2001).

Excluded studies

We excluded 35 studies for the following reasons:

- 10 did not fulfil our [Types of studies](#) criteria (Corral 2014; Dault 2002; Dresen 1985; Driver 2003; Driver 2016; Esquenazi 2013; Esquenazi 2017; Freivogel 2009; Hassett 2009; Kim 2014);
- six did not fulfil our [Types of participants](#) criteria (Calder 2008; Elsworth 2011; McAuley 2001; Rarick 1968; Sherrington 2008; Varela 2012);
- 15 did not fulfil our [Types of interventions](#) criteria (Baque 2017; Bellon 2015; Bender 2016; Berrol 1997; Blake 2009; Canning

2003; Clanchy 2016; Hassett 2012; Haworth 2009; Katz-Leurer 2009; Kurowski 2017; Maerlender 2015; Shiel 2001; Slade 2002; Zhu 2007);

- three trials provided too little information, even after correspondence with authors, for us to be certain that they met our inclusion criteria (Froehlich-Grobe 2004; Herterich 2002; Zhu 2004); and
- one trial was terminated due to recruitment issues (Reed 2015).

Further details of these trials are provided in [Characteristics of excluded studies](#).

Risk of bias in included studies

The risk of bias is reported for each study following each [Characteristics of included studies](#) table and is summarised across all the included studies in [Figure 2](#) and for each included study in [Figure 3](#). We required clarification from trialists for seven of the eight studies for at least one of the eight risk of bias domains to confirm our judgements (Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Laskin 2001; McMillan 2002; Salazar 2000). All studies had high and low risk of bias judgements for the different domains, and five studies had at least one domain that was rated at unclear risk of bias (Bateman 2001; Driver 2009; Hoffman 2010; McMillan 2002; Salazar 2000).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Eight studies are included in this review.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): Objective outcomes	Blinding of outcome assessment (detection bias): Self-reported outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bateman 2001	+	+	-	+	?	+	-	+
Driver 2004	+	-	-	+	+	+	-	+
Driver 2006	+	-	-	+	-	+	-	+
Driver 2009	+	?	-	+	-	+	-	+
Hoffman 2010	+	+	-	+	?	+	-	+
Laskin 2001	+	+	-	-	+	+	-	+
McMillan 2002	?	-	-	+	?	-	-	+
Salazar 2000	?	+	-	+	+	-	-	?

Allocation

All studies randomised participants to study groups, however there was uncertainty regarding the method used to generate the random sequence for two studies (McMillan 2002; Salazar 2000). Four studies reported using allocation concealment when assigning participants to study groups (Bateman 2001; Hoffman 2010; Laskin 2001; Salazar 2000), three studies did not use allocation concealment (Driver 2004; Driver 2006; McMillan 2002), and allocation was unclear for one study (Driver 2009).

Blinding

Blinding of participants and personnel delivering the intervention (performance bias) is not possible in exercise studies; therefore, we judged this domain to be at high risk of bias for all studies. Detection bias was split into objective and self-report measures. For the outcomes included in this review, six studies included objective measures (Bateman 2001; Driver 2004; Hoffman 2010; Laskin 2001; McMillan 2002; Salazar 2000), and five studies included self-reported measures (Bateman 2001; Driver 2006; Driver 2009; Hoffman 2010; McMillan 2002). Four of the six studies that measured objective outcomes used blinded assessors to measure the key outcomes and we judged these to be at low risk of detection bias (Bateman 2001; Driver 2004; Hoffman 2010; McMillan 2002). One of the remaining two studies that measured objective outcomes did not use a blinded assessor and was assessed at high risk of detection bias (Laskin 2001). Salazar 2000 was not able to use blinded assessors for the primary outcome measure of return to work (this outcome was determined independently of the study and in accordance with army regulations) and was judged to have a low risk of detection bias. Three of the five studies that measured self-reported outcomes used blinded assessors to collect these data (Bateman 2001; Hoffman 2010; McMillan 2002); however, because participants were not blinded to group allocation, detection bias was rated as unclear. We rated detection bias as high for the two studies that did not use a blinded assessor and where the participants were unblinded to group allocation (Driver 2006; Driver 2009).

Incomplete outcome data

Seven of the eight included studies measured their outcomes at the end of intervention. Four of these studies had no dropouts and complete data at the end of intervention for primary outcome measures (Driver 2004; Driver 2006; Driver 2009; Laskin 2001); we therefore rated these studies at low risk of attrition bias. Two of the remaining three studies had a small proportion of dropouts and the completeness of data at the end of intervention for the primary outcome measure ranged from 90% to 94% (Bateman 2001; Hoffman 2010). We also rated these studies at low risk of attrition bias. One study had a 19% dropout rate in the fitness training group (but did not report the reasons) and no dropouts in the control group (McMillan 2002); we rated this trial at high risk of attrition bias.

Three of the included studies conducted follow-up assessments. The completeness of data for the primary outcome measure at follow-up ranged from 77% to 100% (Bateman 2001; McMillan 2002; Salazar 2000). Although Salazar 2000 reported 89% follow-up for the trial's primary outcomes (return to work and fitness for duty), only 63% of participants were followed up in person to conduct the cognitive outcome measures; we therefore rated this study at high risk of attrition bias.

Selective reporting

None of the included studies was registered on clinical trial registries, so we could not confirm that all outcome measures were reported. We therefore rated all studies at high risk of reporting bias.

Other potential sources of bias

We were unable to identify any other potential sources of bias for seven of the eight studies. For one study (Salazar 2000), bias may have been introduced from potential contamination of the control group in which participants were instructed to resume their usual physical activity. This study's participants came from the armed forces and so usual physical activity for some may have included exercising at the same or an even higher dosage of exercise than the experimental group. We rated this study as being at an unclear risk of bias for this domain.

Effects of interventions

See: [Summary of findings for the main comparison](#) [Cardiorespiratory exercise programmes prescribed alone compared with a non-exercise intervention or no intervention for people after traumatic brain injury](#)

See: [Summary of findings for the main comparison](#) for the main comparison, Comparison 1: cardiorespiratory exercise programmes prescribed alone compared with a non-exercise intervention or no intervention for people after TBI.

We pooled data from the end of the intervention for seven outcomes within Comparison 1 (cardiorespiratory fitness, body composition, strength, fatigue, depression, neuromotor function and dropouts) and pooled data for a post hoc analysis for a eighth outcome (depression). For five of the eight pooled outcomes (body composition, strength, fatigue, depression and post hoc depression), different studies used different outcome measures. In these instances, we calculated the standardised mean difference (SMD) and 95% confidence intervals (CI). For each of the pooled outcomes we applied the GRADE criteria to rate the quality of the evidence and the justification for each rating is provided in [Table 2](#). The remaining outcomes were not pooled due to a large number of single study outcomes, due to substantial heterogeneity, or due to no events being reported (one outcome). It is likely that heterogeneity existed due to both clinical and methodological diversity among studies.

Comparison 1: exercise programme prescribed alone versus usual care, non-exercise intervention or no intervention

Cardiorespiratory fitness (primary outcome)

Only one study assessed cardiorespiratory fitness using peak oxygen uptake at the endpoint of an incremental cycle ergometer test, however, this study included only seven TBI participants (Laskin 2001). Three of the seven studies assessed cardiorespiratory fitness indirectly at the end of intervention using power output at the endpoint of an incremental cycle ergometer test; these data were pooled using a random-effects model (Bateman 2001; Driver 2004; Laskin 2001; 67 participants; [Analysis 1.1](#)). One study also measured power output at follow-up (Bateman 2001; [Analysis 1.1](#)). We downgraded the quality of the evidence for this outcome to low due to risk of bias of the included studies and imprecision of the estimate of effect. There

was a mean improvement of 35.47 W on an exercise test in the fitness training intervention compared to the control intervention, however this estimate was imprecise with 95% CI 2.53 to 68.41 W. The mean improvement of 35 W represents approximately a 36% improvement in fitness from baseline measurement (average baseline peak power output across the three studies = 97 W). Although a minimal clinically important difference (MCID) has not been determined for this measure in this or similar populations, in people with severe chronic obstructive pulmonary disease - whose baseline power output is approximately one-third of the baseline power output in the included studies - MCID has been determined to be 4 W (Puhan 2011). Taking this into consideration, the confidence intervals are likely to include both a substantial clinically important effect and a possible negligible effect. There was no clear long-term effect of fitness training on cardiorespiratory fitness (MD 3.27 W, 95% CI -34.21 to 40.75; 1 study, 40 participants; Analysis 1.1).

Body function and structure (impairment): body composition (secondary outcome)

Two studies measured body composition at the end of the intervention (Bateman 2001; Driver 2004); Bateman 2001 also measured body composition at the end of follow-up. We pooled the immediate effect of intervention using a random-effects model. The effect size was small and in favour of the control intervention, however the wide confidence intervals (suggesting a positive or negative effect) mean we are uncertain about the effects of fitness training on body composition (SMD 0.29, 95% CI -0.22 to 0.79; 2 studies, 61 participants; low-quality evidence; Analysis 1.2). No clear long-term effect of fitness training on body composition was evident (SMD 0.52, 95% CI -0.11 to 1.14; 1 study, 41 participants; Analysis 1.2).

Body function and structure (impairment): strength (secondary outcome)

Two studies measured strength at the end of intervention (Driver 2004; Laskin 2001). We pooled the immediate effect of intervention using a random-effects model. The between-group difference was negligible and the confidence intervals indicate considerable uncertainty about whether fitness training is effective at increasing muscle strength (SMD -0.02, 95% CI -0.86 to 0.83; 2 studies, 23 participants; very low-quality evidence; Analysis 1.3).

Body function and structure (impairment): fatigue (secondary outcome)

Three studies measured fatigue at the end of intervention (Bateman 2001; Driver 2009; Hoffman 2010); Bateman 2001 also measured fatigue at end of follow-up. The three studies used different measures of fatigue including a visual analogue scale (VAS) (Hoffman 2010), the fatigue subscale of the Profile of Moods State (Driver 2009), and the modified version of the Chalder Fatigue Scale (Bateman 2001). The Chalder Fatigue Scale provides both a physical and mental fatigue score; we pooled the physical subscale score with the measures from the other two studies because these were more in the physical fatigue domain. We downgraded the quality of the evidence for this outcome to very low due to risk of bias, heterogeneity and imprecision. There was a small reduction in self-reported fatigue with fitness training compared to the control interventions, however the wide confidence intervals indicated imprecision for this estimate and a potentially positive or negative effect of fitness training on fatigue (SMD -0.32, 95% CI -0.90 to 0.26;

3 studies, 130 participants; very low-quality evidence; Analysis 1.4). We transformed this SMD into a score on the VAS-fatigue scale (score 0 to 10, using the average baseline score from Hoffman 2010), which showed this result would equate to an average reduction in fatigue of 0.9 points, with the 95% confidence intervals indicating an effect between a 2.6 point reduction in fatigue to a 0.7 point increase in fatigue with fitness training compared to the control interventions. There was no clear long-term effect of fitness training on physical fatigue (SMD 0.35, 95% CI -0.28 to 0.97; 1 study, 40 participants; Analysis 1.4).

Body function and structure (impairment): cognition (secondary outcome)

One study measured the cognitive domains of memory and attention at the end of intervention and at the end of follow-up (McMillan 2002; Table 3). In addition, the Profile of Moods State measured in Driver 2009 included a confusion subscale which could be classified as a measure of cognitive function. However, we felt it did not measure cognition in the same detail as the neuropsychological tests used in McMillan 2002, and so we did not pool this outcome. There were no immediate or long-term effects of fitness training on cognitive function compared to the control interventions in either study (Table 3).

Body function and structure (psychological functioning): depression (secondary outcome)

Four studies measured depression at the end of intervention (Bateman 2001; Driver 2009; Hoffman 2010; McMillan 2002); Bateman 2001 and McMillan 2002 also measured depression at the end of follow-up. The four studies used three different outcome measures of depression; the depression subscale of the Hospital Anxiety Depression Scale (Bateman 2001; McMillan 2002), the depression-dejection subscale of the Profile of Moods States (Driver 2009) and the Beck Depression Inventory (Hoffman 2010). The quality of the evidence for this outcome was downgraded to very low due to risk of bias, heterogeneity and imprecision. There was a small reduction in self-reported depression with fitness training compared to the control interventions, however the wide confidence intervals indicated imprecision of this estimate and potentially a positive or negative effect of fitness training on depression (SMD -0.43, 95% CI -0.92 to 0.06; 4 studies, 220 participants; very low-quality evidence; Analysis 1.5). Transforming the SMD into a score on the depression subscale of the Hospital Anxiety Depression Scale (score 0 to 21 with a higher score indicating greater depression, using the average baseline score from Bateman 2001 and McMillan 2002), this result would equate to an average reduction in depression of 1.7 points with the 95% confidence intervals indicating an effect between a 3.7 point reduction in depression to a 0.2 point increase in depression with fitness training compared to the control interventions. At the end of follow-up there was substantial heterogeneity ($I^2 = 74\%$, $P = 0.05$), therefore we did not pool the data. There was no clear long-term effect of fitness training on depression for either study (SMD -0.44, 95% CI -0.90 to 0.03; McMillan 2002, 73 participants; SMD 0.35, 95% CI -0.28 to 0.97; Bateman 2001, 40 participants; Analysis 1.5).

There was moderate heterogeneity for depression at the end of intervention ($I^2 = 64\%$, $P = 0.04$), however this was not explained by methodological diversity (studies with low risk of bias from allocation concealment; $I^2 = 60\%$, $P = 0.11$; Bateman 2001; Hoffman 2010). Our post hoc analysis, in which we pooled the data from

the three studies that included subacute and chronic participants at home only (Driver 2009; Hoffman 2010; McMillan 2002), yielded an SMD that indicated a moderate reduction in depression with fitness training immediately after intervention, with the 95% CIs indicating that the effect lay between a large and small reduction in depression with fitness training compared to the control interventions (SMD -0.61, 95% CI -1.1 to -0.11; 3 studies, 178 participants; low-quality evidence; Analysis 1.9). The fourth study, which included participants who were still participating in inpatient rehabilitation, showed a small reduction in depression in favour of the control intervention (relaxation therapy), however the 95% CIs were wide indicating uncertainty regarding which intervention was more effective at reducing depression (SMD 0.19, 95% CI -0.42 to 0.80, 42 participants; Bateman 2001).

Body function and structure (psychological functioning): motivation (secondary outcome)

No studies measured motivation.

Activity limitation: global (secondary outcome)

Only one study measured the effect of the intervention on a global measure of function (Bateman 2001; Table 3). There was no clear immediate or long-term effect of fitness training on function globally.

Activity limitation: neuromotor function (secondary outcome)

Two studies measured neuromotor function at the end of intervention during a walking test in metres per second (m/s) (Bateman 2001; Hoffman 2010; Analysis 1.6). We pooled the immediate effect of fitness training on neuromotor function using a random-effects model. There was uncertainty regarding the effect of fitness training on walking speed with the confidence intervals spanning a difference of approximately 0.3 m/s in either direction (MD 0.01 m/s, 95% CI -0.25 to 0.27; 2 studies, 109 participants; moderate-quality evidence; Analysis 1.6). A minimal clinically important difference (MCID) in people with TBI was determined to be 0.15 m/s for a comfortable walking speed over 10 m (van Loo 2004).

Participation restriction: community integration (secondary outcome)

One study measured community integration at the end of intervention with no clear evidence of effect (Hoffman 2010; Table 3).

Participation restriction: quality of life (secondary outcome)

Three studies measured quality of life at the end of intervention (Driver 2006; Hoffman 2010; McMillan 2002), with only one measuring it also at end of follow-up (McMillan 2002). The outcome measure used in the McMillan 2002 study (General Health Questionnaire) gives a higher score for a worse outcome. To match the other two studies where a higher score equals a better outcome, we subtracted the mean scores for each group in the McMillan 2002 study from the maximum possible score for this outcome measure. There was substantial heterogeneity for this outcome ($I^2 = 93\%$; $P < 0.01$); and so we did not pool data. We could not test the effect of allocation concealment on heterogeneity, as two of the three studies did not conceal allocation, indicating considerable risk of bias for this outcome. There were mixed results among studies for this outcome. Self-reported quality of life was rated as

better in the intervention group than the control group at the end of intervention for one of the three studies (SMD 26.04, 95% CI 16.37 to 35.71; Driver 2006, 18 participants; Analysis 1.7), however this was not measured at end of follow-up to determine if this effect was sustained. For the other two studies, it was uncertain whether quality of life was rated as better or worse at the end of the intervention for participants who completed fitness training compared to control interventions (SMD 0.42, 95% CI -0.03 to 0.88; 76 participants, Hoffman 2010; SMD 0.38, 95% CI -0.05 to 0.81; 86 participants, McMillan 2002), and at end of follow-up (SMD 0.15, 95% CI -0.31 to 0.61; 73 participants, McMillan 2002).

Participation restriction: physical activity (secondary outcome)

No studies measured physical activity.

Safety

The trial publications reported no adverse events for the intervention group in any of the seven studies included in Comparison 1. Correspondence with trialists produced confirmation of no adverse events for five studies (Bateman 2001; Driver 2004; Driver 2006; Laskin 2001; McMillan 2002), and no clarification for two studies (Driver 2009; Hoffman 2010), which indicated that there was no evidence of harm of providing cardiorespiratory fitness training for participants.

Acceptance

The five studies that provided supervised fitness training sessions had no dropouts from their intervention groups at the end of intervention (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Laskin 2001). The other two studies had a mix of supervised and unsupervised sessions and had a dropout rate of 19% (9/47) for McMillan 2002 (reasons not documented) and 8% (3/40) for Hoffman 2010 (unable to contact participants) from the fitness training group. For the three studies with dropouts in either group (Bateman 2001; Hoffman 2010; McMillan 2002), we pooled the dropout rate data using a random-effects model (222 participants, 3 studies; very low-quality evidence; Analysis 1.8). Participants were three times less likely to drop out of the control group than the intervention group, however this odds ratio estimate was imprecise, with the 95% confidence intervals spanning a range between 0.32 in favour of the fitness training group to 30 times more in favour of the control intervention. The overall low rate of dropouts indicates that an exercise programme incorporating cardiorespiratory fitness training is an acceptable intervention for participants.

Feasibility

Training adherence was reported as 69% in Bateman 2001, 84% in Driver 2006 and Driver 2009, and 100% in Driver 2004 and Laskin 2001, and was not reported for McMillan 2002. The seventh study, Hoffman 2010, reported mean attendance of the once a week supervised session as 5.9 sessions out of 10, with more than half of the intervention group attending seven or more of the 10 supervised sessions and four attending none of the sessions. These results indicated that an exercise programme incorporating cardiorespiratory fitness training is a feasible intervention.

Suitability

Only one study reported how well the participants achieved the training parameters (Bateman 2001). In this study, fitness training

was set at an intensity of 60% to 80% of age-predicted maximal heart rate, for a duration of 30 minutes, with a frequency of three times per week, for 12 weeks (36 sessions). On average, the participants in the experimental group spent 66% (16.2 minutes out of 24.5 minutes) of exercise time within or above their training heart rate zone for an average of 2.1 sessions per week. Overall, there was insufficient evidence to determine how suitable the prescribed interventions (i.e. training parameters) were for participants.

Comparison 2: exercise programme as a component of an intervention versus usual care

Only one study with 120 participants was included in Comparison 2 (Salazar 2000). No data were available to assess the immediate effects of intervention; only the long-term effects were reported and the data are reported in Table 4.

Cardiorespiratory fitness (primary outcome)

No data available.

Body function and structure (impairment): body composition, strength, fatigue (secondary outcomes)

No data available.

Body function and structure (impairment): cognition (secondary outcome)

Two outcome measures were used to measure cognition; the Paced Auditory Serial Addition Test (PASAT) and the Buschke Selective Reminding Test. At the end of follow-up, it was uncertain whether cognition was rated as better or worse for participants in the intervention and control groups (Table 4).

Body function and structure (psychological functioning): depression (secondary outcome)

Twenty-one per cent (16/76) of participants were diagnosed with major depression at the end of follow-up, with no difference in depression between the intervention and control groups (Table 4).

Body function and structure (psychological functioning): motivation (secondary outcome)

No data available.

Activity limitation: global and neuromotor function (secondary outcomes)

No data available.

Participation restriction: community integration (secondary outcome)

Most participants had returned to work at the end of follow-up (92%). There was no difference in return to work rates between the intervention and control groups (Table 4).

Participation restriction: quality of life and physical activity (secondary outcomes)

No data available.

Safety

No adverse events were reported for the intervention group although six were reported in the control group. These adverse events were classified in the 'any other adverse events' category

(i.e. they required supplemental therapy either during or straight after the control intervention because of persisting behaviour or mood problems). The control intervention for that study was an independent home programme (including cognitive training and an exercise programme), so it is unlikely that the need for additional intervention was strongly related to the independent home exercise programme.

Acceptance

There was a 10% (7/67) dropout rate in this study, two for medical reasons and five voluntary withdrawals. There were no differences in dropout rates between the intervention and control groups (Table 4).

Feasibility

No data available.

Suitability

No data available.

DISCUSSION

Two new studies are included in this updated review, bringing the total to eight randomised controlled studies (399 participants) that have investigated the effects of cardiorespiratory fitness training for people who have sustained a traumatic brain injury (TBI). The identified studies incorporated clinically diverse interventions implemented at incongruent times postinjury, and measured an array of outcomes using a number of different measurement tools. The clinical and methodological diversity among studies and the number of single study outcomes prevented pooling of the results for all but seven of the outcomes evaluated in the included studies. In addition, when studies were pooled, the quality of evidence was downgraded from high to moderate, low or very low. Consequently, there is uncertainty regarding our results, which renders it difficult to draw any definitive conclusions regarding the effectiveness of cardiorespiratory fitness training after TBI.

Summary of main results

Primary outcome

The primary objective was to investigate whether fitness training improves cardiorespiratory fitness in people who have sustained a TBI. The gold standard measure for cardiorespiratory fitness in this population is peak oxygen uptake, but only one of the three included studies that assessed cardiorespiratory fitness used this measure (Laskin 2001). The other two studies (and the Laskin 2001 study) used an indirect measure of cardiorespiratory fitness, i.e. peak power output achieved during a submaximal incremental test to a predetermined endpoint (i.e. percentage of predicted maximum heart rate) (Bateman 2001; Driver 2004; Laskin 2001). The mean difference between groups for the three included studies in this analysis was 35.5 W which is probably a clinically important difference. However the 95% confidence interval ranged from 2.5 to 68.4 W, highlighting the imprecision of this estimate and that the effect may not be clinically relevant. Only one of the three studies showed a positive effect; this study recruited participants who were in the chronic phase, and were more than three years postinjury on average (Driver 2004). In contrast, one of the studies that did not show a clear effect implemented fitness training during acute inpatient rehabilitation (Bateman 2001), with participants

who were, on average, less than six months postinjury. Participants in both the intervention and control groups of that study may still have been improving acutely, since the first three to six months postinjury is considered to be the period with the most rapid recovery (Ponsford 2014). Hence, this may have reduced any potential difference between groups. Further studies are required to investigate fitness training in both the acute and chronic stages of recovery and to measure peak oxygen uptake to determine if fitness training is more effective at particular times in the rehabilitation process.

Secondary outcomes (impairments in body function and structure, activity limitation, participation restriction)

The secondary objectives were to investigate whether fitness training improves impairments in body function and structure, activity limitation and participation restriction in people who have sustained a TBI. We were unable to determine a clear effect of the intervention on any of the secondary outcomes, primarily because of the lack of data. Within our secondary outcomes, we were able to pool data for only five outcomes (depression, fatigue, strength, body composition and neuromotor function), and we pooled data in a post hoc analysis for depression. No studies included measures of motivation or physical activity. The confidence intervals were wide for the five outcomes that were pooled, and it was uncertain whether fitness training was more or less effective at improving the outcome compared to the control interventions. This highlights the need for adequately powered studies that incorporate measures of body function and structure, activity limitation, and participation restriction to assess satisfactorily the benefits of cardiorespiratory fitness training for people who have sustained a TBI.

Secondary outcomes (safety, acceptance, feasibility, suitability)

The secondary objectives also aimed to evaluate the safety, acceptance, feasibility and suitability of fitness training in people with TBI. No adverse events were reported in the included studies; thus there is no evidence of harm when providing cardiorespiratory fitness training as an intervention for people with TBI. However, participant screening and supervision during training may have influenced this finding. Five of the eight included studies used heart rate monitors and one-to-one supervision during each training session (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Laskin 2001), and a sixth study provided one-to-one supervision for one session per week (Hoffman 2010), thus participants were monitored to ensure they were exercising safely and at a suitable exercise intensity. It should also be considered that the finding of no adverse events may be because participants were not specifically questioned regarding this, so minor adverse events such as a muscle strain may have gone unreported. Screening of potential participants for suitability to exercise was also conducted by six of the eight included studies (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Hoffman 2010; Laskin 2001), which may have avoided adverse events. It should be noted however, that none of the studies reported using a standardised screening checklist such as described by Vitale 1996 or the American College of Sports Medicine (ACSM 2014). Use of checklists such as these before commencing fitness testing and training provides rigorous screening to ensure the risk of adverse events is minimised.

We examined the dropout and adherence rates to determine how acceptable and feasible carrying out a cardiorespiratory fitness

programme is for people after TBI. All eight studies reported a low dropout rate, demonstrating that this intervention was considered acceptable to the participants. Adherence was defined as the number of exercise sessions completed compared to the number prescribed. Five of the eight studies reported adherence rates (Bateman 2001; Driver 2004; Driver 2006; Driver 2009; Laskin 2001), these ranged from 69% in Bateman 2001, to 100% in Driver 2004 and Laskin 2001. In these five studies each exercise session was supervised, hence the adherence rates reported should be accurate. The study with the lowest adherence was an inpatient study and poor adherence was primarily because participants were discharged from hospital before the end of the programme, and had difficulty returning for each session. Interestingly, the two studies with 100% adherence and no dropouts comprised participants who were community-dwelling. Cardiorespiratory fitness training prescribed after discharge home thus appears to be both acceptable and feasible.

We examined the ability to achieve the training parameters to determine how suitable a cardiorespiratory fitness programme is for people after TBI. However, only one study reported the actual training parameters achieved (Bateman 2001). In this study, participants in the intervention group spent on average 16 minutes per session within or above their training heart rate zone and only exercised for an average 24.5 minutes per session. This study was conducted in people early after TBI (< 6 months) and there was uncertainty regarding the effect of fitness training compared to relaxation therapy on cardiorespiratory fitness (MD 21.5 W, 95% CI -12.3 to 55.3). In comparison, in the fitness programme for the study that showed a clear positive effect, participants who were more than one year postinjury were required to work for 60 minutes within their training heart rate zone. However, because Bateman 2001 did not report the actual training intensity and duration achieved, we can only speculate that a longer duration of exercise at sufficient intensity may have contributed to the difference in effect size between these two studies. In an observational study conducted by our team we were able to demonstrate that early after TBI (average time since injury was 3.7 months) people can meet the exercise dosage recommended in the American College of Sports Medicine (ACSM) guidelines for people after stroke or TBI (Palmer-McLean 2009). However, this could only be achieved by participating in exercise of longer duration and lower intensity (52 minutes) because of the difficulty of sustaining moderate intensity workloads (Hassett 2012). This would suggest the importance in clinical situations of monitoring the intensity and duration of exercise to ensure a sufficient dosage of exercise is provided, and highlights the need for future studies to monitor and record actual training data systematically for each of the parameters to enable valid interpretation of results.

Overall completeness and applicability of evidence

None of the included studies investigated the effect of fitness training in children who had sustained a TBI. This is a major gap in the literature when it is considered that one of the goals of children's rehabilitation teams is the successful reintegration of these children into sport and physical activities (Rossi 1996). It was not possible to perform subgroup analyses due to too few included studies, thus generalisation to the TBI population is difficult. Most participants in the eight included studies were ambulant adult males who had sustained a severe TBI, thus results may not be applicable to other TBI subgroups (e.g. teenage females with a mild

TBI). One of our planned subgroup analyses was time since injury. The disparate findings between the [Bateman 2001](#) and [Driver 2004](#) studies for cardiorespiratory fitness, as well as the post hoc analysis that included only chronic TBI participants for depression, suggest that time postinjury may be important. Future studies investigating the effects of fitness training in the acute and chronic stage after TBI would enable subgroup analyses to be conducted to determine if fitness training is indeed effective at improving cardiorespiratory fitness, depression and other outcomes early and late after TBI.

Quality of the evidence

This review included only randomised controlled trials, thus each outcome was initially rated as high quality evidence. Applying the GRADE criteria, one outcome was downgraded to moderate-quality evidence (neuromotor function), four to low-quality evidence (cardiorespiratory fitness, body composition, depression sensitivity analysis, dropouts), and three were downgraded to very low-quality evidence (fatigue, depression, strength). The evidence was downgraded due to the risk of bias of study design, heterogeneity among studies and imprecision of the estimate of effect. For the primary outcome (cardiorespiratory fitness), the two studies providing most data had different effect sizes. One of the hypothesised reasons for this difference was the difference in time postinjury of the participants. However, the study with the larger effect size did not use allocation concealment, which has been shown to increase the effect size of trials when compared to trials with adequate allocation concealment ([Savovic 2012](#)). This could have contributed to the difference in effect sizes. This reinforces the need for future trials to incorporate design features known to minimise bias.

Potential biases in the review process

Our search strategy was thorough, and incorporated 10 electronic databases, the International Clinical Trials Registry Platform (the central database for 16 trial registries), a review of reference lists from relevant systematic reviews and any full copy articles obtained, and personal communication with the first authors of included studies. We excluded five studies because we could not confirm their eligibility ([Froehlich-Grobe 2004](#); [Herterich 2002](#); [Kurowski 2017](#); [Rarick 1968](#); [Zhu 2004](#)), and we have yet to confirm eligibility for one study ([McClanachan 2013](#)), thus we cannot be certain that we have not missed some data. However for four of the studies that were excluded, it was unclear whether any TBI participants were included, and for four of the five studies it was unclear whether the intervention met our criteria for fitness training. As such, we believe that it is likely these studies would have been excluded or contributed few participants to the review. While we did not do any handsearching, the Cochrane Injuries Group undertakes handsearching; thus any further relevant references should have been identified from the Cochrane Injuries Group Trials Register. We therefore feel confident that this review contains all the relevant studies on this topic.

Agreements and disagreements with other studies or reviews

There have been no other systematic reviews published that have evaluated fitness training in people with TBI, although there are systematic reviews that have evaluated fitness training in a similar population (i.e. people after stroke; [Saunders 2016](#)) and in populations with similar impairments (e.g. people with depression;

[Cooney 2013](#)). The results of the review for people after stroke were similar to ours; there were small improvements in cardiorespiratory fitness with fitness training at the end of intervention (peak oxygen uptake (VO₂ peak) MD 2.86, 95% CI 1.76 to 3.96 mL/kg/min; 9 studies, 425 participants) and mixed findings for other outcomes, such as small improvements in walking speed and endurance and unclear effects on depression ([Saunders 2016](#)). As with our review, the small number of studies, few participants and the variety of outcome measures used limited the conclusions that could be drawn for many of the secondary outcomes. A Cochrane Review that evaluated the effect of exercise on depression in both clinical and non-clinical populations - 33 studies used fitness training - reported a moderate effect of exercise on depression (SMD -0.62, 95% CI -0.81 to -0.42; 35 studies, 1356 participants) ([Cooney 2013](#)). However, a sensitivity analysis that incorporated only studies at low risk of bias showed a dilution of this effect, so there is still some uncertainty regarding the effect size of fitness training on depression.

AUTHORS' CONCLUSIONS

Implications for practice

In summary, cardiorespiratory fitness training appears to be effective at improving cardiorespiratory fitness in people with traumatic brain injury (TBI), however whether this effect is clinically worthwhile is not clear. The certainty of this result is limited due to the small number of relevant studies plus the diversity of interventions and methodological biases in some studies. Nonetheless, fitness training appears to be an acceptable and feasible intervention and there is no evidence of harm for people with TBI. However, its effect on other secondary outcomes (impairments in body function and structure, activity limitation and participation restriction as well as its suitability) is unclear, again due to the small number of studies plus the diversity of interventions, participants and outcomes. The very few studies investigating this intervention make it difficult for clinicians to make an evidence-based decision about the implementation of a fitness training programme for a person with TBI. Although this review has not been able to provide a definitive answer regarding the effects of fitness training in this group, it has provided some evidence to suggest it is an intervention with no documented harms, that is well accepted and feasible to implement. In light of insufficient data, clinicians may be guided by the pre-exercise screening checklists ([ACSM 2014](#); [Vitale 1996](#)), and set training parameters using the American College of Sports Medicine (ACSM) guidelines for people who have sustained a brain injury ([Palmer-McLean 2009](#)).

Implications for research

The effectiveness of cardiorespiratory fitness training among people with TBI needs to be evaluated with adequately powered, well-designed, randomised controlled studies that incorporate measures of cardiorespiratory fitness (using blood gas analysis, if feasible), as well as measures of body function and structure, activity limitation and participation restriction. In addition, studies should investigate the effectiveness of fitness training in different subgroups of people with TBI (e.g. children and people with different severities of injury) as well as at different times postinjury. To investigate the relative importance and the suitability of implementing each training parameter in accordance with the ACSM guidelines ([Palmer-McLean 2009](#)), experimental

interventions ought to be set within these guidelines and then each training parameter monitored and recorded throughout the intervention. Monitoring and questioning for adverse events should also be incorporated into the study design to confirm the safety of cardiorespiratory fitness training.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bateman 2001

Methods	2 parallel groups, multicentre RCT. Block allocation (block size 10) for each centre; used computer-generated random numbers. 2/24 dropouts from Intervention group (both in follow-up phase), 3/23 dropouts from Control group (1 in intervention phase plus 2 in follow-up phase).
Participants	Country: United Kingdom Mean (SD) age (years): Intervention group: 35 (14); Control group: 36 (13) Sex (male:female): Intervention group: 18:6; Control group: 20:3 Injury severity: Intervention group: 0 mild: 0 moderate: 14 severe: 10 unknown; Control group: 0 mild: 0 moderate: 12 severe: 11 unknown Cause of injury: Intervention group: 9 RTAs: 6 falls: 1 act of violence: 0 sport: 0 other: 8 unknown; Control group: 10 RTAs: 4 falls: 1 act of violence: 0 sport: 0 other: 8 unknown Mean (SD) time since injury (months): Intervention group: 5 (3); Control group: 5 (2) Ambulatory status at entry to study: Intervention group: 8 non-ambulant: 15 ambulant ± aid: 1 unknown; Control group: 8 non-ambulant: 15 ambulant ± aid: 0 unknown Inclusion criteria: admitted to 1 of 4 inpatient regional rehabilitation units for younger patients with complex disability; 16 to 65 years of age; sustained single-incident brain injury of any cause; able to comply with planned interventions; able to sit on cycle ergometer; provided informed consent; expected that they would remain an inpatient for most of the training period (3 months); no physical, cognitive, or behavioural impairments that were sufficiently severe to prevent compliance with and participation in training; no known cardiac disease or other comorbidities precluding exercise training

Bateman 2001 (Continued)

Interventions	<p>Participants in both groups participated in the usual inpatient individually designed multidisciplinary therapy programme. In addition, both groups had 3 x 30 minute extra sessions per week for 12 weeks (36 sessions).</p> <p>Intervention group: completed a hospital-based individual cardiorespiratory fitness programme on a cycle ergometer supervised by a physiotherapist. The intensity was set at 60% to 80% of the individual's age-predicted maximal heart rate ($210 - 0.65 \times \text{age}$). On average, 66% of the training time was within or above the training zone set. On average participants completed 25 (SD = 5) sessions over 12 weeks for an average time of 24.5 minutes per session. Exercise was progressed as tolerated by individual participants until the participant was able to cycle for 30 minutes.</p> <p>Control group (non-exercise intervention): completed a hospital-based relaxation therapy programme consisting of breathing exercises, progressive muscle relaxation techniques, autogenic exercises and visualisation techniques, supervised by a clinical psychologist. On average participants attended 23 (SD = 7) sessions over 12 weeks for an average of 28.8 minutes per session.</p>	
Outcomes	<p>Assessed at baseline, the end of intervention (12 weeks) and at follow-up (24 weeks).</p> <ul style="list-style-type: none">• Cardiorespiratory fitness measured by a submaximal incremental cycle ergometer test (participant was stopped if they reached 80% of their age predicted maximum heart rate ($210 - 0.65 \times \text{age}$)) recording peak power output (W).• Body composition measured by body mass index (kg/m^2)• Fatigue measured by the Chalder modified fatigue scale, physical subscale (8 items, scale 0 to 24 with a higher score indicating more physical fatigue)• Depression measured by the Hospital Anxiety Depression Scale (HADS) depression subscale (scale 0 to 21; 0 to 7 = normal, 8 to 10 mild, 11 to 14 moderate and 15 to 21 severe depression)• Global measure of function, the Barthel Index (score 0 to 100 with higher score indicating greater independence)• Neuromotor function measured by the timed 10-m walk (m/s) (not measured at follow-up)• Other measurement tools used that were not assessed for this review included peak heart rate; modified Ashworth Scale; Berg Balance Scale; Functional Independence Measure (FIM); Nottingham Extended Activities of Daily Living Index (NEADLI); HADS anxiety subscale; Chalder modified fatigue scale mental subscale and Rivermead Mobility Index (RMI).	
Source of funding	"Supported by the Research and Development Directorate of the National Health Service Executive, North Thames. Supported also by Remedi (pilot study)"	
Notes	This study recruited a mixed sample; data for participants with TBI were obtained by correspondence with the author. Confirmed by correspondence with the author.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated random numbers, restricted randomisation in blocks of 10: p. 175, Recruitment and Allocation.
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment: consecutively numbered and sealed brown opaque envelopes containing the intervention group were prepared at the beginning of the study and opened by the study physiotherapist at each centre. Information from trial report: p. 175 Recruitment and Allocation, and from correspondence with author (i.e. that brown opaque envelopes were drawn up at the beginning of the study)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded, however it was not possible to blind for this intervention.

Bateman 2001 (Continued)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Assessors were blinded to group allocation and were not involved in the treatment. Steps were taken to ensure assessors remained blinded, e.g. participants were not asked about information that might indirectly provide information about the training condition: p. 176 Outcomes Assessments.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	Chalder modified fatigue scale and HADS are self-reported outcome measures and participants were not blinded to group allocation. However scales were administered by an assessor blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	TBI only data (47 participants): primary outcome (fitness) 91% of Control group and 96% of Intervention group participants had complete data. For other outcome measures Intervention group: 96% to 100%, Control group: 70% to 100% had complete data. The authors stated that some participants were unable to complete the modified fatigue scale due to language impairments.
Selective reporting (reporting bias)	High risk	The trial was not registered, so we cannot confirm all outcomes that were measured were reported. Detailed outcomes were described in the Methods section and reported in the Results section. There was mention in study text regarding measures of muscle function and VO ₂ for a subset of participants, to be reported elsewhere; however, these data have not been published to our knowledge.
Other bias	Low risk	We identified no other sources of bias.

Driver 2004

Methods	2-parallel group, single-centre RCT. Stratified random sampling technique. The random sample was taken from a generated list of individuals who met the inclusion criteria. No allocation concealment The assessor was blinded. 8/8 participants in the Intervention group and 8/8 participants in the Control group completed the interventions and assessments.
Participants	Country: USA. Mean (SD) age (years): Intervention group: 39 (5); Control group: 38 (4) Sex (male:female): 8:8 Injury severity: all participants had sustained a severe TBI. Cause of injury: 9 RTAs; 2 falls; 2 acts of violence; 1 sport; 2 other Mean (SD) time since injury (months): Intervention group: 41(17); Control group: 37(14) Ambulatory status at entry to study: 7 non-ambulant; 5 with walking aids; 4 ambulant Inclusion criteria: outpatients at a Midwest rehabilitation centre; above level 6 on the Ranchos Los Amigos Scale of Cognitive Functioning; > 1 year post brain injury; aged > 18 years; required physician's approval to participate
Interventions	Both groups were treated as outpatients for 3 x 60-minute sessions per week for 8 weeks (24 sessions). Intervention group: attended a community-based swimming group with a 1-on-1 instructor and completed cardiorespiratory and resistance aquatic exercises. The intensity was set at 50% to 70% of the individual's maximal heart rate (using Karvonen method). Adherence was 100%.

Driver 2004 (Continued)

Control group (non-exercise intervention): attended a unit-based vocational rehabilitation group based on improving reading and writing skills. Adherence was 95%.

Outcomes	<p>Assessed at baseline and at the end of intervention (8 weeks). No follow-up assessments were taken.</p> <ul style="list-style-type: none"> Cardiorespiratory fitness measured by a submaximal incremental cycle ergometer test (participant was stopped if he or she reached 75% of predicted maximum heart rate (using Karvonen method)) recording peak power output (W) Body composition measured by skin fold thickness (percentage body fat) Strength measured by dynamometer grip strength (kg) Other measurement tools not included in this review: length of time of submaximal cycle ergometry test; modified curl-up; sit and reach test; range of motion
Source of funding	No funding reported in the publication.
Notes	Confirmed published information and obtained unpublished data by correspondence with the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A stratified random sampling technique was used." A pool of participants was created who had a certain level of cognitive function and were more than 1 year postinjury. Participants were then randomly sampled from this pool: p. 850 Methods, Participants. From correspondence with the author, a random number table was used.
Allocation concealment (selection bias)	High risk	Allocation concealment was not reported in the paper. It was confirmed with the author this was not done.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, it was not possible to blind for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Not stated in paper. Communication with author: "Yes, blinded for all measures"
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	No self-reported outcomes were reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in the publication. Communication with author: "no dropouts"
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. Detailed outcomes were described in the Methods section and reported in the Results section.
Other bias	Low risk	We identified no other sources of bias.

Driver 2006

Methods	<p>2 parallel groups, single-centre RCT. Stratified random sampling technique. The random sample was taken from a generated list of individuals who met the inclusion criteria.</p> <p>No allocation concealment The assessor was not blinded. 9/9 participants in the Intervention group and 9/9 participants in the Control group completed the interventions and assessments.</p>
Participants	<p>Country: USA</p> <p>Mean (SD) age (years): Intervention group: 38 (4); Control group: 35 (4)</p> <p>Sex (male:female): 10:8</p> <p>Injury severity: all participants had sustained a severe TBI.</p> <p>Cause of injury: 9 RTAs; 3 falls; 2 acts of violence; 1 sport; 3 other</p> <p>Mean time since injury (months): Intervention group: 40 (15); Control group: 41 (14)</p> <p>Ambulatory status at entry to study: 8 non-ambulatory; 6 with walking aids; 4 ambulatory</p> <p>Inclusion criteria: outpatients at a (USA) Midwest rehabilitation centre; above level 6 on the Ranchos Los Amigos Scale of Cognitive Functioning; > 1 year post brain injury; required physician's approval to participate</p>
Interventions	<p>Both groups were treated as outpatients for 3 x 60 minute sessions per week for 8 weeks (24 sessions).</p> <p>Intervention group: attended a community-based swimming group with a 1-on-1 instructor and completed cardiorespiratory and resistance aquatic exercises. The intensity was set at 50% to 70% of the individual's maximal heart rate. Adherence was 84%.</p> <p>Control group (non-exercise intervention): attended a unit-based vocational rehabilitation group based on improving reading and writing skills. Adherence was 81%.</p>
Outcomes	<p>Assessed at baseline and at the end of intervention (8 weeks). No follow-up assessments were taken.</p> <ul style="list-style-type: none"> Global measure of quality of life measured by the Health Promoting Lifestyle Profile-II (HPLP-II) (52-item scale, 1 to 4 on each item; 1 = never, 4 = routinely. Final score obtained by calculating a mean of the individual's responses to all 52 items, yielding a final score between 1 and 4, with a higher score indicating a better outcome) A measurement tool not included in this review was the Physical Self-Description Questionnaire (PSDQ)
Source of funding	No funding reported in the publication.
Notes	Confirmed published information and obtained unpublished data by correspondence with the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A stratified random sampling technique was adopted." A pool of participants was created who had a certain level of cognitive function and were more than 1 year postinjury. Participants were then randomly sampled from this pool: pp. 135-6 Methods, Participants. From correspondence with the author, purposive random sampling was used.
Allocation concealment (selection bias)	High risk	Allocation concealment was not reported in the publication. The study author confirmed this was not done.

Driver 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, it was not possible to blind for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No objective outcomes were reported.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	The participants and outcome assessor were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in the publication. Communication with the lead author confirmed 100% data completeness.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. Two self-report measures were described in the Methods section and reported in the Results section.
Other bias	Low risk	We identified no other sources of bias.

Driver 2009

Methods	2 parallel groups, single-centre RCT. Stratified random sampling technique. The random sample was taken from a generated list of individuals who met the inclusion criteria. No allocation concealment The assessor was not blinded. 8/8 participants in the Intervention group and 8/8 participants in the Control group completed the interventions and assessments (100%).
Participants	Country: USA Mean (SD) age (years): Intervention group: 39 (2); Control group: 38 (2) Sex (male:female): Intervention group: 5:3; Control group: 4:4 Injury severity: all participants sustained a moderate TBI. Cause of injury: unknown Mean time since injury (months): Intervention group: 41 (15); Control group: 36 (14) Ambulatory status at entry to study: Intervention group: 4 ambulatory: 2 with walking aid: 2 non-ambulatory: 0 unknown; Control group: 3 ambulatory: 3 with walking aid: 2 non-ambulatory: 0 unknown Inclusion criteria: outpatients at a rehabilitation centre; above level 6 on the Ranchos Los Amigos Scale of Cognitive Functioning; > 1 year post brain injury; required physician's approval to participate
Interventions	Both groups were treated as outpatients for 3 x 60 minute sessions per week for 8 weeks (24 sessions). Intervention group: had 3 initial sessions before commencement of the programme to set the training parameters. Participants then attended a community-based swimming group with a 1-on-1 instructor and completed cardiorespiratory and resistance aquatic exercises. The intensity was set at 50% to 70% of the individual's maximal heart rate. Adherence was 84%.

Driver 2009 (Continued)

Control group (non-exercise intervention): attended a unit-based vocational rehabilitation group based on improving reading and writing skills. Adherence was 87%.

Outcomes	<p>Assessed at baseline and at the end of intervention (8 weeks). No follow-up assessments were taken.</p> <ul style="list-style-type: none"> Fatigue measured using the Profile of Mood States (POMS): fatigue-inertia subscale (7-item subscale, score range 0 to 28). Cognition measured using POMS: confusion-bewilderment subscale (7-item subscale, score range 0 to 28). Depression measured using POMS: depression dejection subscale (15-item subscale, score range 0 to 60). Each item in the 3 subscales of the POMS is scored from 0 to 4 (0 = not at all and 4 = extremely). In this study each subscale score was obtained by calculating a mean of the individual's responses to all items in that subscale, meaning a final score was between 0 to 4, with a higher score indicating a worse outcome). Other measurement tools used but not included in this review: POMS subscales for: tension-anxiety, anger-hostility, vigour-activity, and friendliness.
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Source of funding	None stated in published paper.
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Notes	Confirmed published information and obtained unpublished data by correspondence with the author.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified random sampling was utilized within this investigation." A pool of participants was created who had a certain level of cognitive function and more than 1 year postinjury. Participants were then randomly sampled from this pool: p. 205 Methods, Participants. From correspondence with author: "block randomization (1:1) by placing individuals who met the inclusion criteria into either Intervention or Control group"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported in the publication. Correspondence with the author confirmed that randomisation was computer-generated and investigators were not aware of group allocation. How allocation concealment was achieved was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, it was not possible to blind for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No objective outcomes were reported.
Blinding of outcome assessment (detection bias) Self-reported outcomes	High risk	The participants and outcome assessor were not blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in publication. Communication with lead author confirmed data were 100% complete.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. 1 self-report measure with 7 subscales described in the

Driver 2009 (Continued)

Methods section and reported in the Results section. Correspondence with the author confirmed that no other measures were taken.

Other bias	Low risk	We identified no other sources of bias.
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Hoffman 2010

Methods	<p>2 parallel group, single-centre RCT. Computer-generated random number list</p> <p>Adequate allocation concealment (consecutively numbered and sealed opaque envelopes were prepared before the start of the study)</p> <p>The assessors were blinded.</p> <p>5/42 dropouts from Intervention group (2 excluded prior to intervention; 3 lost to follow-up at 10 weeks), 3/42 dropouts from Control group (2 excluded prior to intervention; 1 lost to follow-up at 10 weeks)</p>
Participants	<p>Country: USA</p> <p>Mean (SD) age years: Intervention group: 39.7 (12.6); Control group: 37.1 (12.3)</p> <p>Sex (male:female): Intervention group: 15:25; Control group: 20:20</p> <p>Injury severity: unknown</p> <p>Cause of injury: unknown</p> <p>Median (IQR) time since injury (months): Intervention group: 22.1 (9.7 to 37.6); Control group: 20.0 (12.2 to 42.6)</p> <p>Ambulatory status at entry to study: unknown</p> <p>Inclusion criteria: self-reported TBI sufficiently severe to have required medical evaluation or hospital admission immediately after injury; TBI from 6 months to 5 years before enrolment; score ≥ 5 on the Patient Health Questionnaire-9 indicating at least a mild level of depressive symptoms; sufficient cognitive ability to maintain an exercise log and independently participate in the study or to have an involved support person for assistance</p> <p>Exclusion criteria: having a medical condition that would limit or preclude exercise; current suicidal ideation with intent or plan; current pregnancy; current regular exercise programme 3 times per week or more; any physical barrier to the use of standard aerobic exercise equipment; non-English speaker</p>
Interventions	<p>Intervention group: attended a community-based college gymnasium with a 1-on-1 research educational trainer and a certified athletic trainer 1 x per week for 1¼ hours for 10 weeks. The session incorporated 15 minutes of education and review of home programme logs, 15 minutes warm-up, 30 minutes aerobic exercise (choice of modes from available equipment including treadmill, stair-stepper, rowing machine, stationary bicycle or an indoor track) at 60% of participant's estimated maximal heart rate ($60\% \times 220 - \text{age}$) or 12/20 rating of perceived exertion scale, followed by 15 minutes cool down. Also ≥ 4 x per week 30 minutes of aerobic exercise at home, of any mode but of the same prescribed intensity. Mean number of supervised sessions attended was 5.88 (minimum = 0; maximum = 10; mode = 9). More than half of the exercise group attended 7 or more of the 10 supervised sessions; 4 participants attended none of the sessions after enrolment. Mean (SD) exercise recall total time per week at 10 weeks 252 (278). Mean (SD) exercise recall total frequency per week at 10 weeks 3.68 (2.53)</p> <p>Control group (no intervention): wait-list control; participants were offered experimental programme after 10 week assessment. Mean (SD) exercise recall total time per week at 10 weeks 143 (190). Mean (SD) exercise recall total frequency per week at 10 weeks 2.05 (2.21)</p>
Outcomes	Assessed at baseline and at the end of intervention (10 weeks). No follow-up assessment were taken.

Hoffman 2010 (Continued)

- Fatigue assessed using the analogue assessment of fatigue (VAS 0 to 10 with a higher score indicating greater fatigue).
- Depression measured using the Beck Depression Inventory (21 questions each scoring between 0 = "I do not feel sad" to 3 = "I am so sad or unhappy that I can't stand it". Total score between 0 to 63 with 0 to 9 = minimal depression, 10 to 18 = mild depression, 19 to 29 = moderate depression and > 30 = severe depression).
- Neuromotor function assessed using the 6-minute walk test (converted to average walking speed in m/s).
- Community Integration assessed using the Craig Handicap Assessment and Reporting Technique-Short Form (19 questions in 5 domains, each domain maximum score = 100 indicating no participation limitation. Total score maximum = 500).
- Quality of life assessed using the Perceived Quality of Life (19 items each scoring between 0 = extremely dissatisfied to 10 = extremely satisfied. Total score between 0 to 190 with a higher score indicating greater perceived satisfaction with quality of life).
- Other measurement tools used that were not included in this review include pain assessed using the analogue assessment of pain and Brief Pain Inventory, sleep measured using the Pittsburgh Sleep Inventory, symptoms of head injury assessed using the Head Injury Symptom checklist, fatigue assessed using the analogue assessment of fatigue interference and general health assessed using SF-12 Health Survey.

Source of funding	Quote: "8B, NIDILRR [National Institute on Disability, Independent Living, and Rehabilitation Research], Department of Education grant #H133A070032"
Notes	Additional data and clarification of data (methodology, participants, intervention and outcomes) presented in the study publication were provided by the author.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Correspondence with author: "Randomisation was computer generated."
Allocation concealment (selection bias)	Low risk	Correspondence with author: "The randomisation schedule was given to the study coordinator who prepared sealed opaque envelopes which were opened after participants completed their enrolment and baseline assessment. The study coordinator was not involved in recruitment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, blinding was not possible for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Correspondence with author: "Assessors were blinded to group allocation."
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	All outcome measures except 6-minute walk test were self-reported outcome measures. Participants were not blinded to group allocation. However, the measures were administered by an assessor blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 (10%) randomised participants were not included in the final analysis (5 Intervention; 3 Control). Reasons for not including participants were stated and were not related to adherence to the programme.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. Many outcomes were described in the Methods section and reported in the Results section. Correspondence with the author: "Addi-

Hoffman 2010 (Continued)

tional measures of heart rate, blood pressure, weight and cognition (RBANS [Repeatable Battery for the Assessment of Neuropsychological Status] and the Trials A and B) were collected but not reported in the primary paper."

Other bias	Low risk	We identified no other sources of bias.
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Laskin 2001

Methods	<p>4 parallel groups, single-centre RCT. Participants stratified by gender and a disability-specific sport classification. Once stratified, each participant was randomly assigned to 1 of 4 treatment groups using a computer-generated list; randomisation performed by an individual not associated with the study.</p> <p>The assessor was not blinded.</p> <p>In the full study there was a mixed sample with 10 participants in the strength group (S), 10 participants in the endurance group (E), 8 participants in the strength plus endurance group (S&E) and 9 participants in the control group. For this review data from 5/5 TBI participants in the Intervention group (combined E and S&E groups) and 2/2 TBI participants in the Control group (C group) who completed the intervention and assessments were included.</p>
Participants	<p>Country: Canada</p> <p>Mean age, sex and ambulatory status unknown for TBI sample.</p> <p>Injury severity: cause of injury and time since injury were not recorded as part of this study.</p> <p>Inclusion criteria: participants with various types and severities of physical disabilities who attended a rehabilitation centre at a university in Alberta, Canada; provided informed consent; no musculoskeletal problems such as chronic rotator cuff dysfunction that might predispose participants to exercise-related injuries</p>
Interventions	<p>This study included 4 groups: strength training (S); endurance training (E); combined strength and endurance training (S&E), and control.</p> <p>The 3 exercise groups completed a 12 week supervised individualised programme conducted at a rehabilitation centre.</p> <p>S group (not included in this review): attended 3 sessions per week which entailed use of weight machines. The strength sessions involved completing 8 exercises: chest press, pullover, rowing, biceps curl, triceps extension, knee extensions, hamstring curls and leg press at an increasing percentage of their calculated 1 repetition maximum; 2 to 10 repetitions ranging from 3 to 6 sets.</p> <p>E group: attended 3 sessions per week (2 continuous, 1 intermittent) during which cycle or arm crank ergometry was used. The duration of the continuous session was gradually progressed from 15 minutes in week 1 to 29 minutes by week 12. The initial power output elicited the heart rate achieved at the second ventilatory threshold (VT2), and was increased at weeks 4, 7 and 10. The intermittent session started with 6 sets of 90 s work (with 90 s rest in between bouts) at a power output halfway between the individual's power output at VT2 and peak oxygen consumption; and progressed to 13 sets by week 12. Power output was increased as for the continuous component.</p> <p>S&E group: trained 5 days per week with 2.5 strength sessions and 2.5 endurance sessions. The same endurance and strength training protocols as for the E and S groups were followed in this group.</p> <p>Control group (no intervention): were requested to continue their current exercise regimen at a maintenance level.</p> <p>Intervention group: for the purpose of this review we combined the E and S&E groups as the intervention group</p>

Laskin 2001 (Continued)

Outcomes	Assessed at baseline and end of intervention (12 weeks) for all groups. No follow-up assessments were made. <ul style="list-style-type: none">• Cardiorespiratory fitness measured by a peak incremental cycle (or arm crank) ergometer test (participant was asked to continue to fatigue) recording peak power output (W).• Strength measured by 1 repetition maximum upper extremity (kg).• Other measurement tools not included in this review were peak oxygen consumption (unable to obtain TBI data); oxygen consumption at VT2; respiratory exchange ratio at peak oxygen consumption and VT2; power output at VT2; heart rate at peak oxygen consumption and VT2; upper and lower extremity girths; skin fold measurements (unable to obtain TBI data); muscle cross sectional area (biceps brachii and rectus femoris); creatine kinase; serum total testosterone; urinary free cortisol; sex hormone binding globulin.	
Source of funding	Acknowledgement from thesis: "I would like to recognize the financial assistance provided by the Rick Hansen Center and the Alberta Paraplegic Association"	
Notes	This study recruited a mixed sample of participants, data for participants with TBI were obtained by correspondence with the author. We confirmed information through correspondence with the author.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From thesis and author correspondence: stratified by gender and a disability specific sport classification. Once stratified, each participant was randomly assigned to 1 of 4 groups via computer-generated list.
Allocation concealment (selection bias)	Low risk	Quote: "An individual not associated with the study randomly assigned participants to the 4 training groups" p. 62 of thesis
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, blinding was not possible for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	Not stated in thesis. From correspondence with the author we learned that the outcome assessor was not blinded to group allocation.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	No self-reported outcomes were reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full data available for all TBI participants (7) for cardiorespiratory fitness and strength measures.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. Results have not to our knowledge been published in a peer reviewed journal. A full copy of the thesis was provided by the author. Detailed outcomes were described in the Methods section and reported in the Results section.
Other bias	Low risk	We identified no other sources of bias.

McMillan 2002

Methods	<p>3 parallel groups, single-centre RCT</p> <p>There was no adequate allocation concealment (participants were allocated to groups by use of tickets indicating group allocation drawn by the therapist from an opaque bag). The assessor was blinded.</p> <p>12/47 dropouts from the Intervention group (9 in the intervention phase, 3 in follow-up phase) and 10/48 dropouts from Control group (all in the follow-up phase)</p>
Participants	<p>Country: United Kingdom</p> <p>Mean (SD) age: Intervention group (N = 38): 31 (13); Control group (N = 48): 36 (13)</p> <p>Sex (m/f): Intervention group: 30/8; control group: 36/12</p> <p>Injury severity: Intervention: 5 mild: 11 moderate: 31 severe: 0 unknown; Control: 2 mild: 9 moderate: 36 severe: 1 unknown</p> <p>Cause of injury: Intervention: 24 RTAs: 7 falls: 12 acts of violence: 4 other (including sports): 0 unknown; control: 27 RTAs: 9 falls: 10 acts of violence: 1 other (including sports): 1 unknown</p> <p>Mean (SD) time since injury (months): not reported</p> <p>Ambulatory status at entry to study: unknown</p> <p>Inclusion criteria: admitted to hospital; showed problems of attention on neuropsychological testing, or reported attentional problems in everyday life; aged 16 to 65 years; no previous head injuries or major neurological disease; no history of drug or alcohol abuse; between 3 months and 1 year postinjury and living at home; no significant language problems; fully oriented in time, place and person; willing and able to give informed consent; aware of cognitive problems including concentration difficulties</p>
Interventions	<p>This study included 3 groups: attentional control training (ACT); physical exercise (PE) and control.</p> <p>ACT group (not included in this review): participated in 5 x 45 minute supervised sessions and were expected to complete the rest of the therapy independently daily, with the aid of an audio recording for 4 weeks (5 supervised and 15 independent sessions). This intervention incorporated breathing-based techniques for treatment of sustained attention problems where the participant learnt to control attention by concentrating on breathing over extended periods.</p> <p>PE group: participated in 5 x 45 minute supervised sessions and were expected to complete the rest of the therapy independently daily, with the aid of an audio recording for 4 weeks (5 supervised and 15 independent sessions). This intervention was a home-based exercise programme in which participants completed basic fitness exercises (with no equipment) and was based on cardiorespiratory exercise principles. The intensity and adherence was not monitored.</p> <p>Control group: no intervention</p> <p>Intervention group: for the purpose of this review we used the PE group as the intervention group and did not include the ACT group.</p>
Outcomes	<p>Assessed at baseline, end of intervention (4 weeks) and at follow-up (12 months).</p> <ul style="list-style-type: none"> Cognition measured by: <ul style="list-style-type: none"> Paced Auditory Serial Addition Test (PASAT) (2-s spacing; score between 0 to 60 with a higher score indicating higher cognitive function); Sunderland Memory Questionnaire (28-item scale with a higher score indicating greater memory failures); Adult Memory and Information Processing Battery (AMIPB) story recall (delayed) (maximum score possible = 58; a higher score indicates a better outcome). Depression measured by the Hospital Anxiety Depression Scale (HADS) depression subscale (scale 0 to 21 with 0 to 7 = normal, 8 to 10 mild, 11 to 14 moderate and 15 to 21 severe depression). Community Integration measured by readiness/fitness for return to work.

McMillan 2002 (Continued)

- Global measure of quality of life measured by the General Health Questionnaire (each item scored on 4-point Likert scale 0 to 3; with a higher score indicating a worse outcome).
- Other measurement tools not included in this review included: self-reported cognitive failures; other-reported cognitive failures; Rivermead Post Concussional Symptoms Questionnaire (PCS) (self-reported); Rivermead PCS (relative) HADS (anxiety subscale); Test of Everyday Attention (TEA); AMIPB list learning and story recall (immediate); Trials A and B.

Source of funding	National NHS Research and Development Programme Grant for People with Physical Disabilities (PCD/A1/97)
Notes	This study randomised participants to 1 of 3 groups; an attentional training group, an active control group receiving physical exercise, and a no intervention control group. For the purpose of this review we compared the two control groups and renamed the active control group the Intervention group. We confirmed information and obtained unpublished by correspondence with the author. The author was unable to provide more detailed information regarding physical exercise intervention, as primary interest of this study was the attention training.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	In the publication the term "randomization" was used. From email correspondence with the lead author: "tickets indicating group allocation prepared by assessor who was not involved in the treatment"
Allocation concealment (selection bias)	High risk	No information provided in publication. From email correspondence: "Tickets indicating group allocation drawn by therapist from opaque bag"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, it was not possible to blind for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	The assessor was blinded for the cognitive measures.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Unclear risk	The assessor was blinded to group allocation. However participants were not blinded for the self-reported General Health Questionnaire and HADS.
Incomplete outcome data (attrition bias) All outcomes	High risk	145 participants initially recruited and randomised into 3 groups. Only 2 groups included in this review (95 participants); Control group and Intervention (exercise) group. From those two groups, 86/95 (90.5%) completed intervention and thus had data presented (38/47 Intervention group, 48/48 Control group). Email correspondence with the author confirmed that no information about reasons for dropping out was available. 12-month follow-up: 73/95 (76.8%) had follow-up data reported (35/47 exercise group, 38/48 control group). Appears only attempted to follow up those who had end of intervention measurements.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm that all outcomes that were measured were reported; trial authors only reported data for participants who completed the treatment protocols and follow-up assessments.
Other bias	Low risk	We identified no other sources of bias.

Salazar 2000

Methods	<p>2 parallel groups, single-centre RCT, block randomisation</p> <p>Adequate allocation concealment (randomisation scheme controlled by person independent of the treatment teams and with no interaction with potential participants) Complete assessor blinding was not possible.</p> <p>7/67 dropouts from Intervention group (during intervention; 2 for medical reasons, 5 voluntarily); 2/53 dropouts from Control group (during intervention; required supplementary therapy)</p>
Participants	<p>Country: USA</p> <p>Mean (SD) age (years): Intervention group: 25 (7); Control group: 26 (6)</p> <p>Sex (male:female): Intervention group: 62:5; Control group: 51:2</p> <p>Injury severity: 3 mild: 17 moderate: 99 severe: 1 unknown</p> <p>Cause of injury: Intervention group: 31 RTAs: 10 falls: 18 acts of violence: 7 sports: 1 other; Control group: 38 RTAs: 9 falls: 4 acts of violence: 1 sports: 1 other</p> <p>Mean (SD) time since injury (months): Intervention group: 1 (1); Control group: 1 (1)</p> <p>All participants could ambulate independently.</p> <p>Inclusion criteria: active-duty military personnel with moderate-to-severe closed head injury (measured by admission Glasgow Coma Scale score of ≤ 13, or post-traumatic amnesia of ≥ 24 hours, or focal cerebral contusion or haemorrhage on computed tomography or MRI); head injury within 3 months of randomisation; Rancho Los Amigos cognitive level of 7; active duty military member not pending military separation; accompanied home setting with at least 1 responsible adult available; an ability to ambulate independently; no prior severe TBI or other severe disability that would preclude return to active duty after study treatment; and voluntary informed consent</p>
Interventions	<p>Both groups participated in an 8-week programme followed by a 6-month return to work trial.</p> <p>Intervention group: participated in a hospital-based programme which included attending a 1-hour fitness group 5 days per week for 60 minutes, led by a rehabilitation assistant. The fitness group was designed to prepare the participants for the physical fitness requirements of active duty. An alternative physical activities programme was organised if the participant was not able to participate in this group. The participants were prescribed a cautious return to the rigorous army physical fitness standards. All participants in this group participated in a multidisciplinary inpatient programme with a neurological focus and integrated work-based treatment intervention consisting of group and individual therapies.</p> <p>Control group: participated in a home-based programme which included a gradual return to physical activity. They were provided with instructions to exercise for at least 30 minutes twice a week, at their own pace. They were supported in this programme by a weekly 30-minute phone call by a nurse to inquire about the week's events and offering support and advice. The participants in this group were given TBI educational materials, trained in various card game exercises, encouraged to watch the news and read magazines and books, all strategies for enhancing cognitive functioning.</p>
Outcomes	<p>Assessed at baseline and at follow-up (12 months post treatment). Also re-evaluated at 6 months and 24 months (results not available). Structured telephone interviews and review of military records to collect selected essential outcome data were used for 42 participants who were unable to return for their 1-year follow-up.</p> <ul style="list-style-type: none"> Cognition measured by: <ul style="list-style-type: none"> Buschke Selective Reminding Test: consistent long term retrieval (Consistent Long Term Retrieval: reference mean (SD) value = 115 (19.7)); Paced Auditory Serial Addition Test (4 trial sum total: reference mean = 134 with a higher score indicating higher cognitive function). Depression measured by diagnosis of major depression (based on definition from Diagnostic and Statistical Manual of Mental Disorders, 4th Edition).

Salazar 2000 (Continued)

- Community integration measured by return to work at end of scheduled follow-up determined independently of the study and in accordance with army regulations.
- Other measures not included in this review included: fitness for duty; Paced Auditory Serial Addition Test (PASAT) (4 trial); Trahan Continuous Visual Memory Test; Wisconsin Card Sorting; Wechsler Memory Scale, revised; Auditory Consonant Trigrams; Halstead-Reitan Neuropsychological Impairment Index; generalised anxiety; diagnosis of aggression (verbal or physical); Katz Adjustment Scale.

Source of funding	Support for this research, data monitoring, and analysis were provided by the Defense and Veterans Head Injury Program and by the Medical Research Service of the USA Department of Veterans Affairs.
Notes	Information and published data were confirmed and unpublished data were obtained by correspondence with the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned using block randomisation, method of generating random sequence not specified.
Allocation concealment (selection bias)	Low risk	Block randomisation was done by an independent study statistician using variable-sized blocks to prevent investigators from guessing the code: p. 3076 Methods, Study Interventions.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and therapists were not blinded. However, blinding was not possible for this intervention.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	The outcome assessor was not blinded for fitness to return to work/duty. However, this outcome was determined independently of the study (from interview, military records or both) and in accordance with army regulations.
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low risk	No subjective outcomes were included in this review.
Incomplete outcome data (attrition bias) All outcomes	High risk	120 participants randomised. 60/67 received hospital intervention (7 withdrew (2 for medical reasons, 5 voluntarily)) and 47/53 received home intervention (6 received supplemental therapy, 2 during the intervention phase). ITT was used for the primary outcome (return to work/duty). Cognitive measures that required participant follow-up at 12 months was 63%.
Selective reporting (reporting bias)	High risk	The trial was not registered so we cannot confirm all outcomes that were measured were reported. 3 papers reviewed: Warden 2000; Braverman 1999; Salazar 2000. Braverman paper indicated cognitive measures were taken at end of intervention and both Braverman and Warden papers indicate participants were evaluated at 6, 12 and 24 months. Only 12-month data (primary time point) were reported in primary paper by Salazar 2000.
Other bias	Unclear risk	Participants in Control group could have been exercising at the same or an even higher exercise dosage as they were told to resume usual physical activity. Not assessed until 12 months after completion of programme, unclear what exercise programme any of participants completed during this time.

Abbreviations

IQR = interquartile range

ITT = intention-to-treat analysis

MRI = magnetic resonance imaging
 RCT = randomised controlled trial
 RTA = road traffic accident
 SD = standard deviation
 TBI = traumatic brain injury
 VO₂ = peak oxygen uptake
 VT₂ = second ventilatory threshold
 W = watts

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baque 2017	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with acquired brain injury participants (including some with TBI), however the intervention was not of sufficient duration (12 minutes of gross motor activities within 30 minutes) for a cardiorespiratory fitness effect.</p>
Bellon 2015	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with TBI participants, however through correspondence with the author it was determined that the physical activity intervention was not prescribed with the purpose of having a cardiorespiratory fitness effect.</p>
Bender 2016	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with acquired brain injury participants (including 7 with TBI). However, the intervention was focused on participation and most therapy hours involved the use of Affolter tactical interaction therapy, thus the intervention was not prescribed with the purpose of having a cardiorespiratory fitness effect.</p>
Berrol 1997	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with TBI participants. However, the intervention was only twice a week and did not report cardiorespiratory fitness as an aim for their dance intervention.</p>
Blake 2009	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with TBI participants, however the exercise intervention was only provided once a week and the type of exercise (Qigong instruction) does not appear to be of sufficient intensity for a cardiorespiratory fitness effect.</p>
Calder 2008	<p>Did not fulfil Types of participants criteria.</p> <p>This study was conducted in people who had suffered a stroke.</p>
Canning 2003	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with TBI participants. However, through correspondence with the author it was determined that the motor retraining intervention was not prescribed with the purpose of having a cardiorespiratory fitness effect.</p>
Clanchy 2016	<p>Did not fulfil Types of interventions criteria.</p> <p>This study was an RCT with TBI participants. However, through correspondence with the author it was determined that the physical activity intervention was not prescribed with the purpose of having a cardiorespiratory fitness effect.</p>
Corral 2014	<p>Did not fulfil Types of studies criteria.</p>

Study	Reason for exclusion
	This study was with TBI participants. However, through correspondence with the author it was determined that group assignment was based on preference for the intervention (1 required more trips back to the hospital) due to difficulties with recruitment.
Dault 2002	Did not fulfil Types of interventions criteria or Types of studies criteria. This study was with TBI participants. However, group assignment was based on availability and the intervention was only twice a week.
Dresen 1985	Did not fulfil Types of studies criteria. This study was an RCT with mixed diagnoses. However, the Control group received the same exercise intervention as the Intervention group, but without feedback.
Driver 2003	Did not fulfil Types of studies criteria. This was a pilot study with 3 participants who had sustained brain injuries who participated in an appropriate fitness programme. However, there was no randomisation to different interventions.
Driver 2016	Did not fulfil Types of studies criteria and Types of interventions criteria. This study was with acquired brain injury participants (including people with TBI). However group assignment was not randomised for pragmatic reasons and participants were consecutively enrolled for 6 months into the Intervention group and then for 6 months into the Control group. The experimental intervention was twice weekly and utilised strategies e.g. information, behavioural strategies to promote physical activity.
Elsworth 2011	Did not fulfil Types of participants criteria. From correspondence with the senior author, there was only 1 TBI participant included in the study.
Esquenazi 2013	Did not fulfil Types of studies criteria. This was an RCT investigating treadmill walking 3 times per week for 45 minutes each session. However, both groups participated in treadmill training, each with a slight variation.
Esquenazi 2017	Did not fulfil Types of studies criteria. This was an extension of Esquenazi 2013 , adding in a group to evaluate end effector robot (G-EO System) compared to partial bodyweight support treadmill training and Lokomat treadmill training, thus participants were not randomly assigned to groups and the same dose of training was delivered for all groups.
Freivogel 2009	Did not fulfil Types of studies criteria. This was an RCT with TBI participants investigating gait training 3 to 5 times per week for 30 minutes each session. However, both groups participated in gait training, 1 with an electromechanical gait device and the other with treadmill or overground walking.
Froehlich-Grobe 2004	Unable to confirm if this study fulfilled Types of participants and Types of interventions criteria. We were able to confirm with the author that there was at least 1 TBI participant, but could not confirm the total number of TBI participants or whether the dosage of exercise was of sufficient intensity, duration and frequency to meet our specified criteria.
Hassett 2009	Did not fulfil Types of studies criteria. This was an RCT with TBI participants investigating fitness training 3 times per week for 30 minutes. However, both groups completed similar training, the difference between groups being the environment (unsupervised home-based versus supervised fitness-centre based).
Hassett 2012	Did not fulfil Types of interventions criteria.

Study	Reason for exclusion
	This was an RCT with TBI participants investigating circuit class training 3 times per week for 60 minutes. However both groups completed the same training, the difference between groups being that 1 group received feedback about intensity of exercise using a heart rate monitor.
Haworth 2009	Did not fulfil Types of interventions criteria. This was an RCT investigating exercise training in people with neurological impairments. However the frequency of exercise was only twice per week.
Herterich 2002	Unable to confirm if fulfilled Types of participants and Types of interventions criteria. We were unsuccessful in attempts to correspond with the authors via email and mail. We were unable to confirm if any of the participants with acquired brain injuries had sustained a TBI, and we were unable to confirm if the treadmill gait training was at sufficient intensity to achieve a cardiorespiratory fitness effect.
Katz-Leurer 2009	Did not fulfil Types of interventions criteria. This was an RCT investigating exercise training in children with brain injury. However, the duration of exercise (15 minutes) and intensity of exercise (aim for muscular endurance) was below our specified criteria for eliciting a fitness effect.
Kim 2014	Did not fulfil Types of studies criteria. This was an RCT with TBI participants investigating sideways treadmill walking 3 times per week for 20 minutes. However, both groups completed the same dosage of training, the difference between groups being that 1 group had their vision occluded during training.
Kurowski 2017	Unable to confirm if study fulfilled Types of interventions criteria. This study was an RCT with TBI participants. However, we were unsuccessful in attempts to correspond with authors via email. As per Maerlender 2015 , we anticipated that this trial would be excluded, because the focus of training was to work at subthreshold level so as not to elicit postconcussive symptoms with training. Thus the focus was not on increasing cardiorespiratory fitness.
Maerlender 2015	Did not fulfil Types of interventions criteria. This study was an RCT with TBI participants. Correspondence with the author confirmed that the focus of the study was on finding a desirable activity that would not interfere in recovery from postconcussive syndrome. The study criteria for exertion was no greater than 70% maximum heart rate (1 session for 20 minutes every day during recovery) – as measured by RPE - so the exercise was not intended to improve fitness.
McAuley 2001	Did not fulfil Types of participants criteria. This study was an RCT where participants in the experimental group completed an appropriate exercise programme. However correspondence with the author confirmed that none of the participants - who had epilepsy - had sustained a TBI.
Rarick 1968	We were unable to confirm if this study fulfilled Types of participants criteria. No standard deviations were available in the report. We were unsuccessful in our attempts to contact either the authors or the institution via email and mail. This study was an RCT with an appropriate exercise programme. However, we were unable to determine the definition of "minimally brain damaged" to know whether some or all participants in this diagnostic group had sustained a TBI.
Reed 2015	On clinicaltrials.gov. Study was terminated due to recruitment issues.
Sherrington 2008	Did not fulfil Types of participants criteria.

Study	Reason for exclusion
	This study was an RCT investigating circuit-style exercise in rehabilitation. However, the frequency was only twice per week, and correspondence with the lead author established there were no participants who had sustained a TBI.
Shiel 2001	Did not fulfil Types of interventions criteria. This study was an RCT investigating increased intensity of inpatient rehabilitation. However, the intervention was focused on functional improvement and was not aimed, or of sufficient type and duration of exercise, to provide a cardiorespiratory fitness effect.
Slade 2002	Did not fulfil Types of interventions criteria. This RCT had some participants who had sustained a TBI. However, from correspondence with the author, the intensive therapy programme did not include a cardiorespiratory fitness component and was focused on neuromotor rehabilitation.
Varela 2012	Did not fulfil Types of participants criteria. Correspondence with the lead author confirmed that no participants had sustained a TBI.
Zhu 2004	We were unable to confirm if this study fulfilled Types of participants and Types of interventions criteria. We were unsuccessful in attempts to correspond with the authors via email and mail. This study was an RCT, however we were unable to confirm if any of the participants with brain injuries had sustained a TBI, and we were unable to confirm if the treadmill gait training was at sufficient intensity for a cardiorespiratory fitness effect.
Zhu 2007	Did not fulfil Types of interventions criteria. This study was an RCT investigating intensity of inpatient rehabilitation in participants with TBI. However, the intervention was focused on functional improvement and included physiotherapy, occupational therapy and speech pathology.

Abbreviations

RCT = randomised controlled trial

RPE = rating of perceived exertion

TBI = traumatic brain injury

Characteristics of studies awaiting assessment *[ordered by study ID]*

McClanachan 2013

Methods	Randomised cross-over trial
Participants	Participants had a diagnosis of an acquired brain injury, were able to walk with supervision (with or without an aid), had the ability to understand and follow simple instructions and were receiving inpatient rehabilitation. 10/21 participants randomised had sustained a TBI.
Interventions	Intervention group: WiiFit in addition to usual therapy; WiiFit sessions incorporated aerobic and balance activities selected according to the abilities, deficits and interests of the participant; 3 times per week for 4 weeks for 30 minutes each session. Mean heart rate during Wii-Fit sessions was between 52% and 64% of maximum heart rate. Control group: usual therapy alone
Outcomes	Feasibility: number and duration of sessions attended. Level of enjoyment using 10 cm VAS. Fatigue using 10 cm VAS.

Fitness training for cardiorespiratory conditioning after traumatic brain injury (Review)

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McClanachan 2013 (Continued)

Workload using 10 cm VAS.

Perception of intensity using Borg RPE.

Gait using 6-minute walk test.

Spatiotemporal gait parameters (speed, step length, step width) using the GAITRite system.

Balance using the Balance Outcome Measure for Elder Rehabilitation (BOOMER).

High-level mobility was measured using the high-level mobility assessment tool (HiMat).

Readiness to engage in therapy was measured using the Change Assessment Questionnaire.

Notes	Correspondence with the senior author confirmed inclusion of 10 TBI participants and that data could be provided. Author also confirmed they were trying to get participants to reach a moderate intensity measured using the 0-10 Borg scale. Data needs to be obtained for participant demographics, intervention dose and outcomes for TBI participants.
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Abbreviations

RPE = rate of perceived exertion
TBI = traumatic brain injury
VAS = visual analogue scale

Characteristics of ongoing studies [ordered by study ID]

NCT02276079

Trial name or title	The effect of exercise on neurorecovery following mild traumatic brain injury
Methods	RCT
Participants	<p>Inclusion criteria: 37 people aged 18 to 40 years with confirmed diagnosis of mild traumatic brain injury (mTBI) sustained 14-25 days before beginning the exercise intervention</p> <p>Exclusion criteria: comorbid orthopaedic injury that inhibits movement; history of serious psychiatric disturbance with hospitalisation; prior history of neurologic disease; current or past history of substance abuse disorder; diabetes; previous history of moderate or severe head injury; neurological disorder unrelated to TBI (e.g. seizure disorder); physician recommendations against exercise; non-English speakers</p>
Interventions	<p>Intervention: aerobic exercise consisting of riding a stationary bicycle at moderate intensity for 2 consecutive, 20-minute periods with a 5-minute break in between, daily for 1 week. Moderate intensity is defined as maintaining 65% to 75% of estimated maximum heart rate based on the calculation ($HR_{max} = 208 - 0.7 \times \text{age}$).</p> <p>Control: non-aerobic exercise consisting of very low-intensity movements including static stretching and toning exercises. Participants complete 2 consecutive, 20-minute periods with a 5-minute break in between, daily for 1 week, mirroring the aerobic exercise condition. Heart rate will be monitored by research staff to ensure that it remains below 50% of estimated maximum heart rate.</p>
Outcomes	<p>The primary outcomes of interest are:</p> <ul style="list-style-type: none"> change in symptom score and severity measured on the Sport Concussion Assessment Tool (SCAT3); sleep quality (Medical Outcomes Sleep Scale); postural stability (Balance Error Scoring System); verbal learning and memory (California Verbal Learning Test, 2nd Edition); auditory-linguistic memory (Wechsler Memory Scale, 3rd Edition); word-fluency (Controlled Oral Word Association);

NCT02276079 (Continued)

- semantic fluency (Verbal Fluency Test);
- psychomotor/executive functioning (Delis-Kaplan Executive Functioning System (D-KEFS), Trail Making Test; problem solving and abstract reasoning (Wisconsin Card Sorting Test);
- attention and processing speed (Wechsler Adult Intelligence Scale, 3rd Edition);
- visual memory (Wechsler Memory Scale, 3rd Edition);
- sustained and selective attention (Ruff 2 & 7 Selective Attention Test);
- working memory and attention (Paced Auditory Serial Addition Test);
- depression symptoms (Beck Depression Inventory); and
- anxiety symptoms (State Trait Anxiety Inventory).

Secondary outcome measures include:

- functional neuroimaging activation (functional resting state sequences will be performed on the Phillips 3 Tesla magnetic resonance (MR) research scanner);
- aerobic fitness (3-minute step test);
- body weight (body weight measured in kilograms); and
- minutes of physical activity outside the exercise programme (measured by a digital fitness monitor that will be worn 24 hours per day during the 7-day exercise programme)

Starting date	17 February 2015
Contact information	Principal Investigator: Russell M Bauer, University of Florida: rbauer@phhp.ufl.edu
Notes	Clinicaltrials.gov indicates the study was completed 22 December 2016. No publications available at time of writing.

Abbreviations

HRmax = maximum heart rate

RCT = randomised controlled trial

mTBI = mild traumatic brain injury

DATA AND ANALYSES

Comparison 1. Exercise programme prescribed alone versus a non-exercise intervention or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiorespiratory fitness - peak power output	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 End of intervention	3	67	Mean Difference (IV, Random, 95% CI)	35.47 [2.53, 68.41]
1.2 End of follow-up	1	40	Mean Difference (IV, Random, 95% CI)	3.27 [-34.21, 40.75]
2 Body composition - standardised mean difference	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 End of intervention	2	61	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.22, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 End of follow-up	1	41	Std. Mean Difference (IV, Random, 95% CI)	0.52 [-0.11, 1.14]
3 Strength - standardised mean difference	2	23	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.86, 0.83]
4 Fatigue-standardised mean difference	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 End of intervention	3	130	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.90, 0.26]
4.2 End of follow-up	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.28, 0.97]
5 Depression - standardised mean difference	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 End of intervention	4	220	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.92, 0.06]
5.2 End of follow-up	2	113	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.84, 0.69]
6 Neuromotor function - metre/s	2	109	Mean Difference (IV, Random, 95% CI)	0.01 [-0.25, 0.27]
7 Quality of life - standardised mean difference	3		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 End of intervention	3		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 End of follow-up	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Dropouts during the intervention phase	3	222	Odds Ratio (M-H, Random, 95% CI)	3.14 [0.32, 30.80]
9 Depression post hoc analysis (studies with sub-acute to chronic participants at home) - standardised mean difference	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 End of intervention	3	178	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.10, -0.11]

Analysis 1.1. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 1 Cardiorespiratory fitness - peak power output.

Analysis 1.2. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 2 Body composition - standardised mean difference.

Analysis 1.3. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 3 Strength - standardised mean difference.

Analysis 1.4. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 4 Fatigue-standardised mean difference.

Analysis 1.5. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 5 Depression - standardised mean difference.

Analysis 1.6. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 6 Neuromotor function - metre/s.

Analysis 1.7. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 7 Quality of life - standardised mean difference.

Analysis 1.8. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 8 Dropouts during the intervention phase.

Analysis 1.9. Comparison 1 Exercise programme prescribed alone versus a non-exercise intervention or no intervention, Outcome 9 Depression post hoc analysis (studies with sub-acute to chronic participants at home) - standardised mean difference.

ADDITIONAL TABLES

Table 1. Summary of the prescribed exercise programmes

Study	Setting	Supervised	Exercise type	Resistance exercises	Intensity	Duration	Frequency	Length of programme
Bateman 2001	Inpatient	Yes	Cycle ergometer	No	60% to 80% predicted heart rate maximum (210 – 0.65 x age)	Aim 30 minutes; average time 24.5 minutes	Aim 3 x week, average 2.1 x week	12 weeks
Driver 2004 Driver 2006 Driver 2009	Community	Yes	Aquatic	Yes	50% to 70% predicted heart rate maximum (Karvonen method)	60 minutes	3 x week	8 weeks
Hoffman 2010	1 x week community; ≥ 4 x week at home	Yes for 10 sessions, independent for 40 sessions	Participant choice (e.g. treadmill, cycle ergometer, indoor track, rowing machine, stair-stepper)	No	60% heart rate max (220 – age) or 12/20 RPE	15 minutes education, 30 minutes warm-up and cool-down, 30 minutes aerobic	1 x supervised; ≥ 4 x independent	10 weeks
Laskin 2001	Outpatient	Yes	Cycle (or arm crank) ergometer	Yes	Heart rate and power output set to second ventilatory threshold from peak test	Average time 15 minutes week 1 to 28.5 minutes week 12 for continuous fitness component	3 x week	12 weeks
McMillan 2002	Home	Yes for 5 sessions, independent for 15 sessions	Basic fitness exercises, no equipment	Unknown	Not specified	45 minutes	5 x week	4 weeks
Salazar 2000	Inpatient	Yes	Fitness group	Unknown	At own pace	60 minutes	5 x week	8 weeks

Abbreviation RPE = rated perceived exertion

Table 2. Justification of GRADE ratings for pooled outcomes

Outcome	Reasons to downgrade the evidence	Reasons to upgrade the evidence	GRADE rating

Table 2. Justification of GRADE ratings for pooled outcomes (Continued)

	Risk of bias of study design	Indirectness of evidence	Heterogeneity	Imprecision	Publication bias	Large magnitude of effect, dose response, effect of all plausible confounding factors	
Cardiorespiratory fitness (3 studies, 67 participants)	Downgraded x 1 level: allocation concealment at high risk of bias for 1 study; no blinded assessor for 1 study	Nil: not gold standard measure, but still common measure of fitness	Nil: $I^2 = 36\%$; Chi ² P = 0.21	Downgraded x 1 level: wide CI and 2 studies with positive and 1 study with negative mean differences	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 2 levels to LOW
Body composition (2 studies, 61 participants)	Downgraded x 1 level: allocation concealment high for 1 of 2 studies	Nil	Nil: $I^2 = 0\%$ Chi ² P = 0.88	Downgraded x 1 level: wide CI	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 2 levels to LOW
Strength (2 studies, 23 participants)	Downgraded x 2 levels: allocation concealment high for 1 of 2 studies; unblinded assessor for 1 of 2 studies; small number of participants	Nil	Nil: $I^2 = 0\%$ Chi ² P = 0.77	Downgraded x 1 level: wide CI and 1 study with positive and 1 study with negative mean difference	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 3 levels to VERY LOW
Fatigue (3 studies, 130 participants)	Downgraded x 1 level: allocation concealment unclear for 1 study and low for 2 studies; high risk (1 study) or unclear risk (2 studies) of detection bias: participants not blinded for self-reported measure	Nil	Downgraded x 1 level: $I^2 = 56\%$ Chi ² P = 0.11	Downgraded x 1: wide CI and 2 studies with negative and 1 study with positive mean difference	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 3 levels to VERY LOW
Depression (4 studies, 220 participants)	Downgraded x 1 level: allocation concealment high for 1 of 4 studies and unclear for 1 of 4 studies; high risk (1 study) or unclear risk (3 studies) of detection bias: participants not blinded for self-reported measure	Nil	Downgraded x 1 level: $I^2 = 64\%$ Chi ² P = 0.04	Downgraded x 1: wide CI and 3 studies with negative and 1 study with positive mean difference	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 3 levels to VERY LOW

Table 2. Justification of GRADE ratings for pooled outcomes (Continued)

Depression post hoc analysis (3 studies, 178 participants)	Downgraded x 1 level: allocation concealment high for 1 of 4 studies; high risk (1 study) or unclear risk (3 studies) of detection bias: participants not blinded for self-reported measure	Nil	Downgraded x 1 level: $I^2 = 53\%$ Chi ² P = 0.04	Nil	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 2 levels to LOW
Neuromotor function (2 studies, 109 participants)	Nil	Nil	Nil: $I^2 = 28\%$ Chi ² P = 0.24	Downgraded x 1 level: wide CI and 1 study with positive and 1 study with negative mean difference	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 1 level to MODERATE
Acceptance - dropout rate (3 studies, 222 participants)	Downgraded x 1 level: allocation concealment high for 1 of 3 studies	Nil	Downgraded x 1 level: $I^2 = 50\%$ Chi ² P = 0.13	Downgraded x 1 level: wide CI and 2 studies with negative and 1 study with positive mean difference	Nil: no published protocol, but no bias serious enough to downgrade	Nil	Downgraded 3 levels to VERY LOW

Abbreviation CI = confidence interval

Table 3. Additional data for comparison 1

Outcome	Study	Outcome measure	Timing	Intervention group Mean (SD); N	Control group Mean (SD); N	Mean between group difference (MD), 95% CI
Cognition	McMillan 2002	PASAT	End of intervention	37 (13); 38	32 (14); 48	MD 5, 95% CI -0.7 to 10.7
			End of follow-up	38 (14); 35	34 (15); 38	MD 4, 95% CI -2.7 to 10.7
		Sunderland Memory	End of intervention	52 (35); 38	52 (37); 48	MD 0, 95% CI -15.3 to 15.3
		Questionnaire	End of follow-up	49 (36); 35	47 (34); 38	MD 2, 95% CI -14.1 to 18.1
		Adult Memory & Information Processing Battery	End of intervention	24 (12); 38	23 (12); 48	MD 1, 95% CI -4.1 to 6.1
			End of follow-up	34 (10); 35	31 (13); 38	MD 3, 95% CI -2.3 to 8.3
	Driver 2009	POMS: confusion subscale	End of intervention	0.6 (0.3); 8	0.9 (0.6); 8	MD -0.2, 95% CI -0.7 to 0.2
Community integration	Hoffman 2010	CHART-SF	End of intervention	85 (14); 37	83 (12); 39	MD 1.7, 95% CI -4.1 to 7.5
Global measure of function	Bateman 2001	Barthel Index	End of intervention	17 (4); 24	18 (3); 22	MD -0.9, 95% CI -2.9 to 1.2
			End of follow-up	18 (4); 22	19 (3); 21	MD -1.1, 95% CI -3.3 to 1.2

Abbreviations CHART-SF = Craig Handicap Assessment and Reporting Technique - Short Form; PASAT = Paced Auditory Serial Addition Test; POMS = Profile of Mood States

Table 4. Additional data for comparison 2

Outcome	Study	Outcome measure	Timing	Intervention group Mean (SD); N	Control group Mean (SD); N	Between-group difference
Cognition	Salazar 2000	Buschke Selective Reminding Test	End of follow-up	67 (34); 42	63 (40); 34	MD 4.0, 95% CI -12.9 to 20.9
		PASAT	End of follow-up	42 (14); 42	38 (12); 33	MD 3.5, 95% CI -2.3 to 9.4
Depression		Diagnosis of major depression	End of follow-up	7/42 ^a	9/34 ^a	OR 0.6, 95% CI 0.2 to 1.7
Community integration		Return to work	End of follow-up	60/67 ^a	50/53 ^a	OR 0.5, 95% CI 0.1 to 2.1

Table 4. Additional data for comparison 2 (Continued)

Acceptance	Dropouts	During the inter- vention phase	7/67 ^a	2/53 ^a	OR 3.0, 95% CI 0.6 to 15.0
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^aNumber of events over total number of cases

Abbreviations MD = mean difference; OR = odds ratio; PASAT = Paced Auditory Serial Addition Test

APPENDICES

Appendix 1. Search strategies

Since publication of the initial review in 2008, there have been changes to search interfaces on the databases therefore the strategies were modified. Keywords and medical subject headings remain the same.

Cochrane Injuries Group Specialised Register

#1 ((exercise or circuit or aerobic or cardio* or physiotherapy or locomotion or sport* or athletic* or activit* or recreation)) AND (INREGISTER) [REFERENCE] [STANDARD]
#2 ((baseball or basketball or bicycling or cycle or cycling or boxing or football or golf or bockey or gymnastics or martial arts or mountaineering or tennis or netball or squash or run or running or jog or jogging or skate or skating or ski or skiing or soccer or swim or swimming or walk or walking or aquatic* or surf or surfing or abseiling or dance or dancing or rowing or calisthenics)) AND (INREGISTER) [REFERENCE] [STANDARD]
#3 #1 OR #2 [REFERENCE] [STANDARD]
#4 ((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr*) AND (injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*)) AND (INREGISTER) [REFERENCE] [STANDARD]
#5 #3 AND #4 [REFERENCE] [STANDARD]

CENTRAL (The Cochrane Library)

#1MeSH descriptor: [CranioCerebral Trauma] explode all trees
#2"diffus* axonal injur*":ti,ab,kw (Word variations have been searched)
#3((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr*) near/1 (injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*)):ti,ab,kw (Word variations have been searched)
#4#1 or #2 or #3
#5MeSH descriptor: [Exercise Therapy] explode all trees
#6MeSH descriptor: [Physical Fitness] explode all trees
#7MeSH descriptor: [Sports] explode all trees
#8MeSH descriptor: [Physical Exertion] explode all trees
#9MeSH descriptor: [Locomotion] explode all trees
#10MeSH descriptor: [Exercise] explode all trees
#11"cardiorespiratory fitness training":ti,ab,kw (Word variations have been searched)
#12((exercise or circuit or aerobic or cardio* or fitness or physical) near/1 (therap* or train* or program* or intervention* or protocol* or activit* or regim* or group* or class*)):ti,ab,kw (Word variations have been searched)
#13(physiotherapy or locomotion):ti,ab,kw (Word variations have been searched)
#14(sport* or athletic* or leisure activit* or recreation):ti,ab,kw (Word variations have been searched)
#15(baseball or basketball or bicycling or (cycle or cycling) or boxing or football or golf or gymnastics or hockey or martial arts or mountaineering or tennis or netball or squash or (run or running) or (jog or jogging) or (skate or skating) or (ski or skiing) or soccer or (swim or swimming) or (walk or walking) or aquatic* or (surf or surfing) or abseiling or (dance or dancing)) or rowing or calisthenics:ti,ab,kw (Word variations have been searched)
#16#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17#4 and #16

PubMed (MEDLINE)

((((((("Comparative Study"[Publication Type]) OR "Randomized Controlled Trial"[Publication Type]) OR "Controlled Clinical Trial"[Publication Type])) OR ((((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR study[Title/Abstract]) OR group*[Title/Abstract]))) NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))) AND (((((((sport*[title/abstract] OR athletic*[title/abstract] OR recreation[title/abstract] OR baseball[title/abstract] OR basketball[title/abstract] OR bicycling[title/abstract] OR cycle[title/abstract] OR cycling[title/abstract]

OR boxing[title/abstract] OR football[title/abstract] OR golf[title/abstract] OR gymnastics[title/abstract] OR hockey[title/abstract] OR "martial arts"[title/abstract] OR mountaineering[title/abstract] OR tennis[title/abstract] OR netball[title/abstract] OR squash[title/abstract] OR run[title/abstract] OR running[title/abstract] OR jog[title/abstract] OR jogging[title/abstract] OR skate[title/abstract] OR skating[title/abstract] OR ski[title/abstract] OR skiing[title/abstract] OR soccer[title/abstract] OR swim[title/abstract] OR swimming[title/abstract] OR walk[title/abstract] OR walking[title/abstract] OR aquatic*[title/abstract] OR surf[title/abstract] OR surfing[title/abstract] OR abseiling[title/abstract] OR dance[title/abstract] OR dancing[title/abstract] OR rowing[title/abstract] OR calisthenics[title/abstract])) OR ((physiotherapy[Title/Abstract]) OR locomotion[Title/Abstract])) OR (((therapy[title/abstract] OR therapies[title/abstract] OR training[title/abstract] OR train[title/abstract] OR program*[title/abstract] OR intervention*[title/abstract] OR protocol*[title/abstract] OR activity[title/abstract] OR activities[title/abstract] OR regim*[title/abstract] OR group[title/abstract] OR groups[title/abstract] OR class*[title/abstract])) AND (exercise[title/abstract] OR circuit[title/abstract] OR aerobic[title/abstract] OR cardio*[title/abstract] OR fitness[title/abstract] OR physical[title/abstract])) OR (cardiorespiratory fitness training[Title/Abstract])) OR (((("Exercise Therapy"[Majr]) OR "Physical Fitness"[Majr]) OR "Sports"[Majr]) OR "Physical Exertion"[Majr]) OR "Locomotion"[Majr])) AND (((("Craniocerebral Trauma"[Majr]) OR (diffus* AND axonal injur*[Title/Abstract])) OR ((injur*[title/abstract] OR trauma*[title/abstract] OR lesion*[title/abstract] OR damage*[title/abstract] OR wound*[title/abstract] OR destruction*[title/abstract] OR oedema*[title/abstract] OR edema*[title/abstract] OR fracture*[title/abstract] OR contusion*[title/abstract] OR concus*[title/abstract] OR commotion*[title/abstract] OR pressur*[title/abstract])) AND (head[title/abstract] OR crani*[title/abstract] OR capitis[title/abstract] OR brain*[title/abstract] OR forebrain*[title/abstract] OR skull*[title/abstract] OR hemisphere[title/abstract] OR intracran*[title/abstract] OR orbit*[title/abstract] OR cerebr*[title/abstract]))))

Embase Classic + Embase

1. exp head injury/
2. "diffus* axonal injur*".ti,ab.
3. ((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr*) adj1 (injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*)).ti,ab.
4. exp kinesiotherapy/
5. exp fitness/
6. exp sport/
7. exp exercise/
8. exp locomotion/
9. cardiorespiratory fitness training.ti,ab.
10. ((exercise or circuit or aerobic or cardio* or fitness or physical) adj1 (therap* or train* or program* or intervention* or protocol* or activit* or regim* or group* or class*)).ti,ab.
11. (physiotherapy or locomotion).ti,ab.
12. (sport* or athletic* or leisure activit* or recreation).ti,ab.
13. (baseball or basketball or bicycling or cycle or cycling or boxing or football or golf or gymnastics or hockey or martial arts or mountaineering or tennis or netball or squash or run or running or jog or jogging or skate or skating or ski or skiing or soccer or swim or swimming or walk or walking or aquatic* or surf or surfing or abseiling or dance or dancing or rowing or calisthenics).ti,ab.
14. 1 or 2 or 3
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
16. 14 and 15
17. exp Randomized Controlled Trial/
18. exp controlled clinical trial/
19. exp controlled study/
20. comparative study/
21. randomi?ed.ab,ti.
22. placebo.ab.
23. *Clinical Trial/
24. exp major clinical study/
25. randomly.ab.
26. (trial or study).ti.
27. 17 or 18 or 19 or 21 or 22 or 23 or 24 or 25 or 26
28. exp animal/ not (exp human/ and exp animal/)
29. 27 not 28
30. 16 and 29
31. limit 30 to exclude medline journals

CINAHL Plus

S25S13 AND S24
S24S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S23MH quantitative studies
S22TX random* N3 allocat*

S21(MH "Random Assignment")
 S20TX placebo*
 S19(MH "Placebos")
 S18TX randomi?ed N3 control* N3 trial*
 S17TI ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*) or (tripl* N3 blind*)) or TI ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*)) or AB ((singl* N3 blind*) or (doubl* N3 blind*) or (trebl* N3 blind*)) or AB ((singl* N3 mask*) or (doubl* N3 mask*) or (trebl* N3 mask*) or (tripl* N3 mask*))
 S16TX clinical N3 trial*
 S15PT clinical trial*
 S14(MH "Clinical Trials")
 S13S4 AND S12
 S12S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
 S11TX (baseball or basketball or bicycling or (cycle or cycling) or boxing or football or golf or gymnastics or hockey or martial arts or mountaineering or tennis or netball or squash or (run or running) or (jog or jogging) or (skate or skating) or (ski or skiing) or soccer or (swim or swimming) or (walk or walking) or aquatic* or (surf or surfing) or abseiling or (dance or dancing) or rowing or calisthenics)
 S10AB (sport* or athletic* or "leisure activity" or "leisure activities" or recreation) OR TI(sport* or athletic* or "leisure activity" or "leisure activities" or recreation)
 S9TI physiotherapy OR locomotion
 S8AB physiotherapy OR locomotion
 S7TX ((exercise or circuit or aerobic or cardio* or fitness or physical) N1 (therap* or train* or program* or intervention* or protocol* or activit* or regim* or group* or class*))
 S6AB ("cardiorespiratory fitness training") OR TI ("cardiorespiratory fitness training")
 S5(MH "Exercise+") OR (MH "Therapeutic Exercise+") OR (MH "Physical Fitness") OR (MH "Sports+") OR (MH "Locomotion+") OR (MH "Exertion+")
 S4S1 OR S2 OR S3
 S3AB ((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr*) N1 (injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*))
 OR TI ((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr*) N1 (injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*))
 S2AB (diffus* axonal injur*) OR TI (diffus* axonal injur*)
 S1(MH "Head Injuries+")

AMED

1. exp head injuries/
2. diffus\$ axonal injur\$.ab,ti.
3. ((head or crani\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemisphere or intracran\$ or orbit\$ or cerebr\$) adj1 (injur\$ or trauma\$ or lesion\$ or damage\$ or wound\$ or destruction\$ or oedema\$ or edema\$ or fracture\$ or contusion\$ or concus\$ or commotion\$ or pressur\$)).ab,ti.
4. 1 or 2 or 3
5. exp exercise therapy/ or exp physical fitness/ or exp sports/ or exp exercise/ or exp exertion/ or exp locomotion/
6. cardiorespiratory fitness training.ab,ti.
7. ((exercise or circuit or aerobic or cardio\$ or fitness or physical) adj1 (therap\$ or train\$ or program\$ or intervention\$ or protocol\$ or activit\$ or regim\$ or group\$ or class\$)).ab,ti.
8. (physiotherapy or locomotion).ab,ti.
9. (sport\$ or athletic\$ or leisure activit\$ or recreation).ab,ti.
10. (baseball or basketball or bicycling or (cycle or cycling) or boxing or football or golf or gymnastics or hockey or martial arts or mountaineering or tennis or netball or squash or (run or running) or (jog or jogging) or (skate or skating) or (ski or skiing) or soccer or (swim or swimming) or (walk or walking) or aquatic\$ or (surf or surfing) or abseiling or (dance or dancing) or rowing or calisthenics).ab,ti.
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp clinical trials/ or exp double blind method/ or exp placebos/ or exp random allocation/ or exp comparative study/
13. (clinical trial or clinical trials or randomised controlled trial or randomized controlled trial or controlled clinical trial).pt.
14. (crossover or cross-over or cross over).tw.
15. (random\$ or placebo\$ or (clin\$ adj1 trial\$)).ab,ti.
16. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj1 (blind\$ or mask\$)).ab,ti.
17. 12 or 13 or 14 or 15 or 16
18. 4 and 11 and 17
19. exp animals/ not exp humans/
20. 18 not 19
21. 20 (2007 to current)

SPORTDiscus

S1. DE "BRAIN damage" OR DE "BRAIN -- Concussion" OR DE "POSTCONCUSSION syndrome"
S2. TI diffuse* axonal injur* OR AB diffuse* axonal injur*
S3. TI (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr* adj1 injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*) OR AB (head or crani* or capitis or brain* or forebrain* or skull* or hemisphere or intracran* or orbit* or cerebr* adj1 injur* or trauma* or lesion* or damage* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or concus* or commotion* or pressur*)
S4. S1 OR S2 OR S3
DE "EXERCISE" OR DE "ABDOMINAL exercises" OR DE "AEROBIC exercises" OR DE "ANAEROBIC exercises" OR DE "AQUATIC exercises" OR DE "ARM exercises" OR DE "BACK exercises" OR DE "BREATHING exercises" OR DE "BREEMA" OR DE "BUTTOCKS exercises" OR DE "CALISTHENICS" OR DE "CHAIR exercises" OR DE "CHEST exercises" OR DE "CIRCUIT training" OR DE "COMPOUND exercises" OR DE "DO-in" OR DE "EXERCISE -- Immunological aspects" OR DE "EXERCISE adherence" OR DE "EXERCISE for children" OR DE "EXERCISE for girls" OR DE "EXERCISE for men" OR DE "EXERCISE for middle-aged persons" OR DE "EXERCISE for older people" OR DE "EXERCISE for people with disabilities" OR DE "EXERCISE for women" OR DE "EXERCISE for youth" OR DE "EXERCISE therapy" OR DE "EXERCISE video games" OR DE "FACIAL exercises" OR DE "FALUN gong exercises" OR DE "FOOT exercises" OR DE "GYMNASTICS" OR DE "HAND exercises" OR DE "HATHA yoga" OR DE "HIP exercises" OR DE "ISOKINETIC exercise" OR DE "ISOLATION exercises" OR DE "ISOMETRIC exercise" OR DE "ISOTONIC exercise" OR DE "KNEE exercises" OR DE "LEG exercises" OR DE "LIANGONG" OR DE "METABOLIC equivalent" OR DE "MULAN quan" OR DE "MUSCLE strength" OR DE "PILATES method" OR DE "PLYOMETRICS" OR DE "QI gong" OR DE "REDUCING exercises" OR DE "RUNNING" OR DE "RUNNING -- Social aspects" OR DE "SCHOOLS -- Exercises & recreations" OR DE "SEXUAL exercises" OR DE "SHOULDER exercises" OR DE "STRENGTH training" OR DE "STRESS management exercises" OR DE "STRETCHING exercises" OR DE "TAI chi" OR DE "TREADMILL exercise" OR DE "WHEELCHAIR workouts" OR DE "YOGA"
S5. DE "EXERCISE" OR DE "EXERCISE therapy" OR DE "PHYSICAL fitness" OR DE "SPORTS" OR DE "LOCOMOTION"
S6. TI (exercise OR circuit OR aerobic OR cardio* OR fitness OR physical adj1 therap* OR train* OR program* OR intervention* OR protocol* OR activit* OR regim* OR group* OR class*) OR AB (exercise OR circuit OR aerobic OR cardio* OR fitness OR physical adj1 therap* OR train* OR program* OR intervention* OR protocol* OR activit* OR regim* OR group* OR class*)
S7. TI (physiotherapy OR locomotion) OR AB (physiotherapy OR locomotion)
S8. TI (sport* OR athletic* OR leisure activit* OR recreation) OR AB (sport* OR athletic* OR leisure activit* OR recreation)
S9. TI (baseball OR basketball OR bicycling OR cycle OR cycling OR boxing OR football OR golf OR gymnastics OR hockey OR martial arts OR mountaineering OR tennis OR netball OR squash OR run OR running OR jog OR jogging OR skate OR skating OR ski OR skiing OR soccer OR swim OR swimming OR walk OR walking OR aquatic? OR surf OR surfing OR abseiling OR dance OR dancing OR rowing OR calisthenics) OR AB (baseball OR basketball OR bicycling OR cycle OR cycling OR boxing OR football OR golf OR gymnastics OR hockey OR martial arts OR mountaineering OR tennis OR netball OR squash OR run OR running OR jog OR jogging OR skate OR skating OR ski OR skiing OR soccer OR swim OR swimming OR walk OR walking OR aquatic? OR surf OR surfing OR abseiling OR dance OR dancing OR rowing OR calisthenics)
S10. S5 OR S6 OR S7 OR S8 OR S9
S11. TX (crossover OR cross-over OR cross over)
S12. TI (random* or placebo* or clin* adj1 trial*) OR AB (random* or placebo* or clin* adj1 trial*)
S13. TI (singl* or doubl* or trebl* or tripl* adj1 blind* or mask*) OR AB (singl* or doubl* or trebl* or tripl* adj1 blind* or mask*)
S14. S11 OR S12 OR S13
S15. S4 AND S10 AND S14
S16. S15 limit May 2007 to August 2017

PsycINFO (OvidSP)

1. exp Head Injuries/
2. diffus\$ axonal injur\$.ab,ti.
3. ((head or crani\$ or capitis or brain\$ or forebrain\$ or skull\$ or hemisphere or intracran\$ or orbit\$ or cerebr\$) adj1 (injur\$ or trauma\$ or lesion\$ or damage\$ or wound\$ or destruction\$ or oedema\$ or edema\$ or fracture\$ or contusion\$ or concus\$ or commotion\$ or pressur\$)).ab,ti.
4. 1 or 2 or 3
5. exp exercise/ or exp physical fitness/ or exp sports/
6. cardiorespiratory fitness training.ab,ti.
7. ((exercise or circuit or aerobic or cardio\$ or fitness or physical) adj1 (therap\$ or train\$ or program\$ or intervention\$ or protocol\$ or activit\$ or regim\$ or group\$ or class\$)).ab,ti.
8. (physiotherapy or locomotion).ab,ti.
9. (sport\$ or athletic\$ or leisure activit\$ or recreation).ab,ti.
10. (baseball or basketball or bicycling or (cycle or cycling) or boxing or football or golf or gymnastics or hockey or martial arts or mountaineering or tennis or netball or squash or (run or running) or (jog or jogging) or (skate or skating) or (ski or skiing) or soccer or (swim or swimming) or (walk or walking) or aquatic\$ or (surf or surfing) or abseiling or (dance or dancing) or rowing or calisthenics).ab,ti.
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp clinical trials/
13. exp placebo/
14. exp treatment effectiveness evaluation/

15. exp mental health program evaluation/
16. exp experimental design/
17. exp prospective studies/
18. clinical trial*.ab,ti.
19. controlled clinical trial.ab,ti.
20. randomi?ed controlled trial.ab,ti.
21. randomi?ed.ab,ti.
22. placebo.ab.
23. randomly.ab.
24. trial.ti.
25. ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or dummy or mask*)).ab,ti.
26. ((crossover or clin* or control* or compar* or evaluat* or prospectiv*) adj3 (trial* or studi* or study)).ab,ti.
27. 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. exp animals/
29. exp human females/
30. exp human males/
31. 29 or 30
32. 28 not (28 and 31)
33. 27 not 32
34. 4 and 11 and 33

PEDro

Fitness training [Therapy] AND Neurology [Subdiscipline] AND 08/08/2017 [New records added since]

PsycBITE

(Fitness/ Exercise [Intervention] AND Traumatic Brain Injury (TBI)/ Head Injury [Neurological Group] AND Randomised Controlled Trial [Method] AND 2007 to 2013 [Year]) OR (Recreation/ Leisure [Intervention] AND Traumatic Brain Injury (TBI)/ Head Injury [Neurological Group] AND Randomised Controlled Trial [Method] AND 2007 to 2017 [Year])

WHAT'S NEW

Date	Event	Description
8 August 2017	New citation required and conclusions have changed	Two new studies were included. The conclusions were slightly modified.
4 August 2017	New search has been performed	The search was updated to 4 August 2017.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 2, 2008

Date	Event	Description
11 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

LMH initiated the review. LMH, AMM, ARH (and RLT) designed the protocol. LMH carried out the search strategies for AMED, SPORTDiscus, PEDro and PsychBITE electronic databases and searched other resources. LMH and AMM independently screened the search output. LMH and ARH or AMM extracted data and assessed quality. LMH wrote the first draft of the protocol and review with the assistance of AMM and wrote the update of the review. LMH, AMM, ARH revised the update for important intellectual content and gave approval for the version to be submitted. LMH takes ultimate responsibility for the accuracy and honesty of the report and the morality of the review.

DECLARATIONS OF INTEREST

LMH: no conflict of interest.

AMM: no conflict of interest.

ARH: no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Musculoskeletal Health Sydney, School of Public Health, Sydney Medical School, The University of Sydney, Australia.
- Discipline of Physiotherapy, Faculty of Health Sciences, The University of Sydney, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Author change

Robin Tate was not involved in the update of this review and was removed from the author list.

Background changes

- The background section was updated with some more recent references and adjusted to focus more specifically on cardiorespiratory fitness training rather than more broadly describing physical activity.

Methodological changes

- The means of assessment of bias within studies was changed from the PEDro scale to the Cochrane 'Risk of bias' tool. This change was done to meet current Cochrane recommendations for assessing risk of bias in studies ([Higgins 2011](#)).
- A 'Summary of findings' table was constructed incorporating six outcomes which the authors defined as the six most important outcomes, prior to conducting the analysis. This change was done to meet current Cochrane recommendations for assessing the quality of the evidence ([Higgins 2011](#)).
- Since the original review was published there have been changes to search interfaces on some of the databases therefore some of the search strategies have been modified. Keywords and medical subject headings remain the same. In addition, in this update our grey literature search was modified to search the International Clinical Trials Registry Platform (ICTRP) instead of two online registers: Trials Central (www.trialscentral.org) and Current Controlled Trials (www.controlled-trials.com). The ICTRP enables a single point of access to international clinical trial registries.
- The 6-minute walk test outcome measure was initially named as a measure of cardiorespiratory fitness. After discussion between the authors it was decided that it fitted better as a measure of neuromotor function (i.e. walking endurance).
- The assessment for heterogeneity was modified to meet current Cochrane recommendations for assessing risk of bias in studies ([Higgins 2011](#)).
- The secondary outcome 'adverse event' was renamed 'safety' (measured by number of adverse events reported) to reflect this outcome more accurately.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiovascular Deconditioning; *Exercise Therapy; *Physical Fitness; Brain Injuries [complications] [*rehabilitation]; Physical Conditioning, Human; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Male