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Physical exercise training for type 3 spinalmuscular atrophy (Review)

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Abstract

Background

Physical exercise training might improve muscle and cardiorespiratory function in spinal muscular atrophy (SMA). Optimization of aerobic capacity or other resources in residual muscle tissue through exercise may counteract the muscle deterioration that occurs secondary to motor neuron loss and inactivity in SMA. There is currently no evidence synthesis available on physical exercise training in people with SMA type 3.

Objectives

To assess the effects of physical exercise training on functional performance in people with SMA type 3, and to identify any adverse effects.

Search methods

On 8 May 2018, we searched the Cochrane Neuromuscular Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, AMED, and LILACS. On 25 April 2018 we searched NHSEED, DARE, and ClinicalTrials.gov and WHO ICTRP for ongoing trials.

Selection criteria

We included randomized controlled trials (RCTs) or quasi-RCTs lasting at least 12 weeks that compared physical exercise training (strength training, aerobic exercise training, or both) to placebo, standard or usual care, or another type of non-physical intervention for SMA type 3. Participants were adults and children from the age of five years with a diagnosis of SMA type 3 (Kugelberg-Welander syndrome), confirmed by genetic analysis.

Data collection and analysis

We used standard Cochrane methodological procedures.

Main results

We included one RCT that studied the effects of a six-month, home-based, combined muscle strength and recumbent cycle ergometry training program versus usual care in 14 ambulatory people with SMA. The age range of the participants was between 10 years and 48 years. The study was evaluator-blinded, but personnel and participants could not be blinded to the intervention, which placed the results at a high risk of bias. Participants performed strength training as prescribed, but 50% of the participants did not achieve the intended aerobic exercise training regimen. The trial used change in walking distance on the six-minute walk test as a measure of function; a minimal detectable change is 24.0 m. The change from baseline to six months' follow-up in the training group (9.4 m) was not detectably different from the change in the usual care group (-0.14 m) (mean difference (MD) 9.54 m, 95% confidence interval (CI) -83.04 to 102.12; N = 12). Cardiopulmonary exercise capacity, assessed by the change from baseline to six months' follow-up in peak oxygen uptake (VO_{2max}) was similar in the training group (-0.12 mL/kg/min) and the usual care group (-1.34 mL/kg/min) (MD 1.22 mL/kg/min, 95% CI -2.16 to 4.6; N = 12). A clinically meaningful increase in VO_{2max} is 3.5 mL/kg/min.

The trial assessed function on the Hammersmith Functional Motor Scale - Expanded (HFMSE), which has a range of possible scores from 0 to 66, with an increase of 3 or more points indicating clinically meaningful improvement. The HFMSE score in the training group increased by 2 points from baseline to six months' follow-up, with no change in the usual care group (MD 2.00, 95% CI -2.06 to 6.06; N = 12). The training group showed a slight improvement in muscle strength, expressed as the manual muscle testing (MMT) total score, which ranges from 28 (weakest) to 280 (strongest). The change from baseline in MMT total score was 6.8 in the training group compared to -5.14 in the usual care group (MD 11.94, 95% CI -3.44 to 27.32; N = 12).

The trial stated that training had no statistically significant effects on fatigue and quality of life. The certainty of evidence for all outcomes was very low because of study limitations and imprecision. The study did not assess the effects of physical exercise training on physical activity levels. No study-related serious adverse events or adverse events leading to withdrawal occurred, but we cannot draw wider conclusions from this very low-certainty evidence.

Authors' conclusions

It is uncertain whether combined strength and aerobic exercise training is beneficial or harmful in people with SMA type 3, as the quality of evidence is very low.We need well-

designed and adequately powered studies using protocols thatmeet international standards for the development of training interventions, in order to improve our understanding of the exercise response in people with SMA type 3 and eventually develop exercise guidelines for this condition.

Plain language summary

Physical exercise training for people with spinal muscular atrophy type 3

Review question

In people with spinal muscular atrophy (SMA) type 3, does physical exercise training improve motor function, cardiovascular fitness, muscle strength, fatigue, physical activity levels, or quality of life, and does it have unwanted effects?

Background

Physical exercise training could improve the physical fitness of people with SMA type 3 and protect them from muscle wasting due to inactivity and disease progression. However, we do not know whether physical exercise training is safe or what specific parts of an exercise program might be helpful.We reviewed the evidence about the effect of physical exercise training in people with SMA type 3.

Search date

The evidence is up to date to May 2018.

Study characteristics

We included one trial that studied the effects of a six-month, home-based training program that combined exercises to increase muscle strength with aerobic exercise training (exercise that increases breathing and heart rate). The aerobic exercise training used in the trial was recumbent cycling training (seated cycling, with back support). The study included 14 people with SMA type 3, all of whom were able to walk. The participants were between 10 years and 48 years old and had SMA type 3 of mild-to-moderate severity. The nature of the intervention made it impossible to hide the treatment group from participants or personnel, which is an important limitation when measurements rely on participant assessments or effort.

Study funding sources

The included study was supported by the United States Department of Defense and the SMA Foundation.

Key results and certainty of the evidence

Participants performed strength training as prescribed, but only half of them completed the full aerobic exercise program. The effects of physical exercise training in people with SMA type 3 remain unclear, as the evidence is very uncertain.

Summary of findings for the main comparison

Comparison 1. Combined strength and aerobic exercise training compared to usual care in SMA type 3

Patient or population: children and adults with SMA type 3
Setting: home-based exercise, clinic follow-up
Intervention: combined strength and aerobic exercise training
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with combined strength and aerobic exercise training				
Outcomes from aerobic exercise training						
Walking distance on the 6MWT (m) (a higher score indicates better function) Change from baseline Follow up: 6 months	The mean change in distance walked on the 6MWT in the usual care group was -0.14 m	The mean change in distance walked on the 6MWT in the training group was 9.54 m more (83.04 less to 102.12 more)	-	12 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-
Cardiopulmonary exercise capacity assessed with VO_{2max} mL/kg/min (a higher score indicates better function) Change from baseline Follow up: 6 months	The mean change in VO_{2max} in the usual care group was -1.34 mL/kg/min.	The mean change in VO_{2max} in the training group was 1.22 mL/kg/min more (2.16 less to 4.6 more)	-	12 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-
Outcomes from strength training						
Functional performance assessed with HFMSE Scale from: 0 to 66 (a higher score indicates better function) Change from baseline Follow up: 6 months	The mean change in HFMSE score in the usual care group was 0	The mean change in HFMSE score in the training group was 2 points more (2.06 points less to 6.06 points more)	-	12 (1 RCT)	⊕⊕◯◯ VERY LOW[b,c]	-
Muscle strength (MMT total score) assessed with Medical Research Council total MMT score Scale from: 28 to 280 (a higher score indicates greater muscle strength) Change from baseline Follow up: 6 months	The mean change in MMT total score in the usual care group was -5.14	The mean change in MMT total score was 11.94 more (3.44 less to 27.32 more).	-	12 (1 RCT)	⊕⊕◯◯ VERY LOW[b,c]	-
Outcomes from either type of training						
Fatigue In children, assessed with PedsQLMFS Scale from: 0 to 100 (a higher score indicates less fatigue) In adults, assessed with FSS Scale from: 0 to 7 (a higher score indicates more fatigue) Change from baseline Follow up: 6 months	The trial reported no significant differences between the training group and the usual care group in parent-reported PedsQLMFS score, child-reported PedsQLMFS score, or FFS score in adults, but did not report P values		-	12 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-

Physical activity - change from baseline Follow up: 6 months - not reported	No evidence available on physical activity levels	-	-	-	-
Quality of life In children, assessed with PedsQLNM Scale from: 0 to 100 (a higher score indicates better quality of life) In adults, assessed with SF-36 subdomains Physical Health (SF-36PH) and Mental Health (SF-36MH) Scales from: 0 to 100 (a higher score indicates better quality of life) Change from baseline Follow up: 6 months	The trial reported no significant differences between the training group and the usual care group in child-reported or parent-reported PedsQLNM score, or in SF-36PH and SF-36MH scores, but did not provide P values	-	12 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-
Serious adverse events leading to withdrawal Follow up: 6 months	No study-related serious adverse events or adverse events leading to withdrawal occurred	-	12 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group in the included study and the __relative effect__ of the intervention (and its 95% CI).

6MWT: 6-minute walk test; **CI:** confidence interval; **FSS:** Fatigue Severity Scale; **PedsQLMFS:** Pediatric Quality of Life Inventory Multi Dimensional Fatigue Scale; **PedsQLNM:** Pediatric Quality of Life Inventory Neuromuscular Module; **RR:** risk ratio; **SF-36:** 36-Item Short-Form Health Survey

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

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]We downgraded the certainty of the evidence once for indirectness. Fifty per cent of the training group did not receive the intended volume of aerobic exercise training owing to decreased exercise tolerability.
[b]We downgraded the certainty of the evidence twice for imprecision. There were few participants (training group N = 5, usual care group N = 7) and the wide CI encompassed large effects in either direction.
[c]We downgraded the evidence once for study limitations. No participant blinding was possible, which placed all outcomes at high risk of bias since all were either effort dependent or participant-reported.

Background

Description of the condition

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease caused by a genetic mutation in the survival motor neuron 1 (SMN1) gene (5q11.2-q13.3) (Lefebvre 1995). SMA is characterized by degeneration of spinal cord α-motor neurons, which results in progressive proximal muscle weakness, fatigue, scoliosis, nutritional problems, respiratory complications, and severe functional limitations. SMA has a broad clinical spectrumbut, in general, can be classified into four clinical types based on age of onset and maximum motor function achieved (Mercuri 2012).With an incidence of one in 10,000 live births, SMA type 1 is the leading genetic cause of infant death, accounting for 60% of all cases of SMA (Verhaart 2017). SMA type 1 is characterized by an onset before sixmonths of age and an inability to sit without support. The onset of SMA type 2 is between seven months and 18 months of age and those affected have the ability to sit independently, but not to walk. SMA type 4 is the mildest form, with the onset of weakness in the second or third decade (Lunn 2008; Mercuri 2012). SMA type 3 (Kugelberg-Welander syndrome) is a relatively mild subtype, with symptom onset typically after 18 months of age, but shows large clinical heterogeneity. SMA type 3 can be further classified into type 3a (clinical symptoms before three years of age) and type 3b (clinical symptoms after three years of age) (Zerres 1997). Children generally reach major milestones, including independent walking, but their level of motor performance varies greatly. Some children are hardly able to stand up from sitting and take a few steps unaided, while others walk well, are

able to climb stairs, and mainly experience problems in running and sports (Rudnik-Schöneborn 2001). Long-term followup studies (follow-up time of two to 20 years) in people with SMA type 2 and type 3 suggest a very slow deterioration of muscle strength and motor function that takes years to detect (Deymeer 2008; Kaufmann 2012; Piepers 2008; Wadman 2017; Wadman 2018; Werlauff 2012). Nevertheless, about 50% of people with SMA type 3 will lose independent ambulation during the second decade of life and only a small subgroup will remain ambulatory throughout life (Wadman 2017; Mercuri 2012; Russman 1996). In general, people with SMA type 3b perform better on functional outcome measures, such as the six-minute walk test (6MWT) and the Hammersmith Functional Motor Scale – Expanded (HFMSE), in comparison to people with SMA type 3a (Mazzone 2013; Montes 2010). Nusinersen is the only disease-modifying therapy for people with SMA, but its benefits in the mildest phenotype are not yet fully known, since efficacy was determined in a cohort of patients withmore severemuscle weakness (Mercuri 2018). Current standards of care concentrate on SMA-associated complications, such as impaired mobility, scoliosis, fatigue, respiratory infections, and poor nutritional status (Mercuri 2018b).

Description of the intervention

The intervention under consideration is physical exercise training for children and adults with SMA type 3. Training methods include strength and aerobic exercise training of skeletal muscles. We have not considered respiratory muscle training in people with neuromuscular diseases, as this is the topic of a Cochrane Systematic Review in development (Pedrosa 2015). Types of exercise include, for example, cycling on an ergometer, running on a treadmill, and lifting weights. Physical exercise training aims to increase a person's functional performance, muscle strength, cardiopulmonary exercise capacity and quality of life, and reduce levels of fatigue. These benefits should be achieved without serious adverse events, such as worsening fatigue, pain, or significant increases in levels of biological markers for muscle damage. Suitable comparison interventions are placebo and standard or usual care. The training can be given as monotherapy or in addition to usual practice.

Definitions

- Physical exercise training or physical fitness training: "a planned, structured regimen of regular physical exercise deliberately performed to improve physical fitness. The ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies".
- Physical fitness: "a set of measurable health and skill-related attributes" that includes cardiorespiratory fitness, muscular strength and endurance, body composition, flexibility, balance, agility, reaction time, and power (Caspersen 1985; Garber 2011).
- Strength training: training performed primarily to improve muscle strength and endurance, typically through repeated muscle contractions against resistance (Saunders 2004).
- Aerobic exercise training or cardiorespiratory fitness training: training that consists of an activity or combination of activities using large muscle groups that can be maintained continuously, for example, walking-hiking, running-jogging, cycling-bicycling, or swimming (Pollock 1998).
- Functional performance: performance on functional scores, such as functional strength scores, timed tests, and walking tests.

For physically stronger people with SMA type 3b, physical training is a potentially easily accessible and affordable intervention, which could be provided through exercise groups or personal trainers working together with health practitioners. Those who have significant difficulty with transfers, uneven surfaces, and stairs are more vulnerable to injury and require specialized supervision.

How the intervention might work

The loss of α-motor neurons in the spinal cord leads to denervation of skeletal muscles, atrophy, and muscle weakness (Mercuri 2012). Functional performance, especially ambulation, deteriorates in most people with SMA type 3, which may lead to inactivity and deconditioning (Wadman 2017). The slow progression of the disease, the relatively preserved residual strength, and a sedentary lifestyle make people with SMA type 3 a promising target population for physical training programs. Training may improve functional performance, muscle strength, and exercise capacity by optimizing resources and metabolic function in available muscle tissue and counteracting further muscle deterioration that occurs with inactivity (Abresch 2012). The effect is likely to depend on the type of training. Strengthening training may increase muscle strength and, as a secondary effect, improve functional performance of anti-gravity activities, such as rising from lying or sitting positions, jumping, and stair climbing. Aerobic exercise training will enhance exercise capacity and improve walking distance and endurance.

Exercise might also have a neuroprotective effect, which could be explained by a relationship between the maturation state of the motor unit and resistance to neuronal cell death. Preclinical studies in SMA mouse models report positive effects of exercise on postnatal maturation of motor units; delayed motor neuron death; and improved motor function and survival (Biondi 2008; Grondard 2005). Biondi 2008 performed a progressive running-wheel training program in SMA type 2-like mice and showed an exercise-induced acceleration ofmotor-unitmaturation at the level of the motor neuron, neuromuscular junction, and muscle fiber, and a delay in motor neuron death. In addition, Grondard 2005 reported a positive effect of exercise on muscle performance measured with a forelimb grip strength-endurance test and physical activity measured with an open-field ambulatory behavior test.

Why it is important to do this review

Physical exercise training has emerged as a potential intervention for people with inherited neuromuscular disorders for which no curative treatment is as yet available, including people with SMA. Skeletalmuscle training may partly counteract disease progression and secondary deconditioning by improvement of functional performance (Voet 2013). At a time when some people with SMA are benefiting from the first approved disease-modifying compound aimed at splicing the SMN2 gene, and other compounds that directly target skeletal muscle are in development, understanding the effects of conservative treatments remains important. There is currently limited evidence available on physical exercise training in people with SMA type 3. The potential for combination therapies may be better exploited if we first understand the role of exercise therapy when used alone.

Objectives

To assess the effects of physical exercise training on functional performance in people with spinal muscular atrophy type 3, and to identify any adverse effects.

Methods

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi- RCTs. Quasi-RCTs are studies that use a quasi-random method to allocate participants to groups, such as alternation, date of birth, or case record number (Higgins 2011). In the 'Discussion' section, we described relevant cross-over studies, case control studies and multi- and single-case reports that fulfilled the same standards as eligible

RCTs regarding diagnostic criteria, description of intervention, and outcome measures. We considered trials available in any language, whether available as full-text articles, abstracts, or unpublished data only.

Types of participants

We included studies in children from the age of five years and adults with a diagnosis of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander syndrome) who fulfilled the clinical criteria and had a deletion or mutation of the survival motor neuron 1 (SMN1) gene (5q11.2-13.2) confirmed by genetic analysis (Lefebvre 1995). Studies of mixed populations, e.g. studies that include mixed neuromuscular diseases or mixed SMA types, were only eligible for inclusion in the review if they reported results for SMA type 3 separately.

Types of interventions

We included trials that used any form of physical exercise training of skeletal muscles, including aerobic exercise and strength training, carried out for a period of at least 12 weeks, compared with placebo, standard or usual care, or another type of non-physical intervention. We included trials that provided co-interventions to each group equally. We excluded studies of respiratory muscle training or that used a non-exercised limb as a control. We included trials that used training programs standardized on frequency, intensity, time, and type of training, with an incremental exercise protocol.

Types of outcome measures

We included studies that reported outcomes at baseline and at the end of training. We would have reported longer-term outcomes if they had been available.

Primary outcomes

- Walking distance on the six-minute walk test (6MWT;Dunaway 2016; Montes 2010).
- Functional performance, measured with the Hammersmith Functional Motor Scale - Expanded (HFMSE; O'Hagen 2007), Motor Function Measure (MFM; Vuillerot 2013), and timed tests (10-meter walk/run test (10MWT), Gower's time, or Timed Up and Go Test (TUG; Dunaway 2014)).

Secondary outcomes

- Cardiopulmonary exercise capacity, assessed with validated cycle ergometry (W, mL/kg/min) or treadmill testing (mL/min, time to limitation) (Bartels 2015).
- Muscle strength, including maximal isometric and isokinetic voluntary contraction, measured with validated dynamometry (Newton/N*M) and validated Manual Muscle Testing (MMT; an ordinal scale).
- Fatigue, assessed in adults with the Fatigue Severity Scale (FSS; Werlauff 2014) and in children with the Pediatric Quality of Life Inventory Multi Dimensional Fatigue Score (PedsQLMFS; Varni 2004).
- Physical activity, assessed with questionnaires or accelerometry.
- Quality of life, assessed in adults with the 36-Item Short-Form Health Survey (SF-36; Kruitwagen-Van Reenen 2016) questionnaire and in children with the Pediatric Quality of Life Inventory Neuromuscular Module (PedsQLNM; Iannaccone 2009).
- Serious adverse events leading to withdrawal, such as debilitating fatigue, medical treatment, and hospitalization.

- We reported continuous outcomes as changes from baseline.

Search methods for identification of studies

Electronic searches

The Cochrane Neuromuscular Information Specialist searched the following databases.

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; 8 May 2018; Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the CRS-Web (8 May 2018; Appendix 2).
- MEDLINE (1946 to 8 May 2018; Appendix 3).
- Embase (1980 to 8 May 2018; Appendix 4).
- CINAHL Plus (1937 to 8 May 2018; Appendix 5).
- AMED (1985 to 8 May 2018; Appendix 6).
- LILACS (1982 to 8 May 2018; Appendix 7).

The review authors searched the following databases.

- US National Institutes for Health Clinical Trials Registry (www.ClinicalTrials.gov; 25 April 2018; Appendix 8).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/; 25 April 2018; Appendix 9).
- NHS Economic Evaluation Database (NHSEED; https://www.crd.york.ac.uk/CRDWeb/; 25 April 2018 (updates until 31 March 2015); Appendix 10).
- Database of Abstracts of Reviews of Effects (DARE; https://www.crd.york.ac.uk/CRDWeb/; 25 April 2018 (updates until March 2015); Appendix 11).

We searched all databases from inception to the present, and did not impose any restriction on language of publication.

Searching other resources

We searched reference lists of review articles and of the included trial for additional references. We also searched for errata or retractions of the included trial.

Data collection and analysis

Selection of studies

Two review authors (BB and JM) independently screened titles and abstracts of all references identified as a result of the literature searches.We coded the articles as either 'retrieve' (eligible, potentially eligible, or unclear), or 'do not retrieve'.We retrieved the fulltext study reports and publications coded as 'retrieve'. Two review authors (BB and JM) independently screened the full-text articles, identified trials for inclusion, and identified and recorded reasons for exclusion of ineligible studies. The review authors resolved any disagreements through discussion or, if required, they consulted a third review author (JdG).We identified and excluded duplicates, and collated multiple reports of the same trial so that each trial rather than each report was the unit of interest in the Cochrane Systematic Review. We completed a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

We used a data extraction form to initially pilot one trial included in the reviewto collect study characteristics and outcome data.One review author (BB) extracted the following study characteristics.

- Methods: study design, total duration of study, details of any 'run in' period, number of study centers and location, study setting, withdrawals, and date of study.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, concomitant treatments, and excluded treatments.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

A review author (JM) authored the included trial. Therefore, BB and JdG independently extracted outcome data from this trial. We noted in the 'Characteristics of included studies' table if the trial did not report outcome data in a usable way.We resolved any disagreements by consensus. One review author (BB) transferred data into ReviewManager (RevMan) 5 (RevMan 2014). A second review author (JM) checked the outcome data entries. The same reviewauthor (JM) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (BB and JdG) independently performed 'Risk of bias' assessments for the included trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).We resolved any disagreements by discussion.We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

The review authors graded each study as at high, low, or unclear risk of bias and provided a quote from the study report together with a justification for the judgment in the 'Risk of bias' table.We did not consider it necessary to consider blinding separately for subjective and objective outcomes, as the outcomes in the review were either effort dependent or subjective, and were therefore all at a high risk of bias from a lack of participant blinding.We noted in the 'Risk of bias' table when we based a 'Risk of bias' assessment on unpublished data or correspondence with a trial author. When considering treatment effects, we only took into account the risk of bias that contributed to that outcome.

Assesment of bias in conducting the systematic review

We conducted the Cochrane Systematic Review according to the published protocol (Bartels 2016).We described any protocol deviations in the Differences between protocol and review section.

Measures of treatment effect

We analyzed continuous data as mean differences (MDs) with corresponding 95% confidence intervals (CIs).

Dealing with missing data

We planned to contact trial authors or trial sponsors to verify key study characteristics and,where possible, obtainmissing numerical outcome data (e.g. when a trial was available as an abstract only or when SMA subgroup data were not reported separately). We obtained additional information on

random sequence generation and allocation concealment from the authors of the included trial (Montes 2015).
We used RevMan to obtain missing standard deviations fromP values for the differences between means in the two groups (RevMan 2014).

Data synthesis
See Appendix 12 for methods of data synthesis described in the protocol (Bartels 2016).

'Summary of findings' tables
We planned to create separate 'Summary of findings' tables for aerobic exercise training and strength training. However, we presented findings from the included study, which combined both types of training, in a single table.

- Outcomes from aerobic exercise training
  - Walking distance on the 6MWT
  - Cardiopulmonary exercise capacity
- Outcomes from strength training
  - Functional performance
  - Muscle strength
- Outcomes from either type of training
  - Fatigue
  - Physical activity
  - Quality of life
  - Serious adverse events leading to withdrawal

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence (studies that contribute data for the prespecified outcomes). We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and constructed 'Summary of findings' tables using GRADEpro Guideline Development Tool software (GRADEpro GDT 2015).We provided footnotes to justify our decisions to downgrade or upgrade the quality of the evidence, and we commented where necessary to aid the reader's understanding of the Cochrane Systematic Review.

Subgroup analysis and investigation of heterogeneity
The included trial, which had 12 participants, was too small to perform subgroup analyses.

Reaching conclusions
We based our conclusions on findings from the quantitative and narrative review of the included trial. We avoided making recommendations for practice. Our Implications for research section suggests priorities for future research and outlines the remaining uncertainties in the area.

Results

Description of studies

Results of the search
The search retrieved 513 records. After removal of duplicates, we screened the titles and abstracts of 444 records. We identified 10 studies for full-text review, of which we excluded 9 because they were

not randomized controlled trials (RCTs). We included one study (Montes 2015). See Figure 1 for a PRISMA flow-chart illustrating the study selection process.

[Figure 1]

Included studies

Montes 2015 was an evaluator-blinded RCT that studied the effects of a home-based, combined muscle strength and recumbent cycle ergometry training program in 14 participants with spinal muscular atrophy (SMA) type 3, who were ambulatory and ranged in age from 10 years to 48 years. Three participants had SMA subtype 3a and 11 had subtype 3b. Participants had SMA of mild to-moderate severity; mean baseline scores on the Hammersmith Functional Motor Scale - Expanded (HFMSE) were 53.4 (standard deviation (SD) 8.9) in the exercise group and 54.0 (SD 8.2) in the usual care group. The investigators randomly allocated participants to exercise or usual care groups after a one-month lead-in period. During months two to seven, the intervention group received training,while the control group continued their usual care. The muscle strength training consisted of a three-times-weekly program of three sets of five-to-six concentric, isometric, or gravity- eliminated exercises, performed at an intensity of 60% to 80% of one repetition maximum. Most participants reported that they performed the strength training program as prescribed, but the trial authors did not mention specific percentages of compliance. The aerobic training consisted of a five-times-weekly program of 30-minute recumbent cycling sessions, performed at an exercise intensity of 5 to 7 on theOMNI Scale of Perceived Exertion.Only one participant after three months and 50% of participants after sixmonths achieved the target exercise volume of 150 minutes per week. The exercise volume of the other participants ranged from 24 minutes to 91 minutes per week at the same time points. After month seven, both groups received the exercise intervention for a further 12 months. Twelve participants completed the first seven months and nine participants completed all 19months of the trial. The two participants who dropped out during the controlled period were in the training group. The trial authors analyzed the results from the controlled period (months two to seven). They monitored compliance with a heart monitor, participant diary, teleconference and videoconference calls, and via text, phone, and email communications. Program compliance was enhanced by the use of customized illustrated instructional exercise sheets. The investigators asked participants about adverse events, including falls, excessive fatigue, muscle soreness, illness, and other health-related events at every contact, whether in person or by videoconference. The Characteristics of included studies table includes additional information on participants and study design.

Excluded studies

We excluded nine studies that were not RCTs (see Characteristics of excluded studies). The interventions were strength training alone in four studies (Basoglu 2006; Lewelt 2015; McCartney 1988;Milner-Brown 1988), aerobic exercise training alone in one study (Madsen 2015), aquatic therapy incorporated in a comprehensive rehabilitation programin three studies (Cunha 1996;Dahl 2004; Salem 2010), and a combination of functional strengthening exercises and whole body vibration in one study (Vry 2014). Strength training consisted of concentric resistance training either alone (in McCartney 1988 and Milner-Brown 1988) or in combination with gravity-eliminated movements (in Basoglu 2006 and Lewelt 2015). The duration of the interventions varied between eight weeks and 24 months. The target frequencies ranged from two to seven times per week, with durations of 18 minutes to 60 minutes. The target frequency was fully achieved in one study (Vry 2014), partly achieved in two studies (Lewelt 2015; Madsen 2015), and not reported in six studies (Basoglu 2006; Cunha 1996; Dahl 2004;McCartney 1988;Milner-Brown 1988; Salem 2010). Descriptions of training parameters were incomplete: in four studies with regards to intensity

(Basoglu 2006; Cunha 1996; Dahl 2004; Salem 2010), and in three studies with regards to time (Basoglu 2006; McCartney 1988; Milner-Brown 1988). Four studies reported on the occurrence of adverse events (Lewelt 2015; Madsen 2015; McCartney 1988; Vry 2014). Four studies included participants with other neuromuscular diseases, such as muscular dystrophies, polyneuropathies, and myopathies (Dahl 2004; McCartney 1988; Milner-Brown 1988; Vry 2014). Four studies used home-based exercise programs (Basoglu 2006; Lewelt 2015; Madsen 2015; Vry 2014), in four studies participants exercised at an outpatient clinic or university (Cunha 1996; Dahl 2004; McCartney 1988; Salem 2010), and one study did not specify the setting (Milner-Brown 1988). Most studies were limited by inadequate research design: one was a non-randomized controlled clinical trial (Madsen 2015), seven were multiple-case studies (Basoglu 2006; Cunha 1996; Dahl 2004; Lewelt 2015; McCartney 1988;Milner-Brown 1988; Vry 2014), and one was a single-case study (Salem 2010). Two non-RCTs fulfilled the standards regarding diagnostic criteria, description of intervention, and outcome measures (Lewelt 2015; Madsen 2015).

Lewelt 2015 investigated the effect of a home-based supervised strength training program in a pilot study of nine children with SMA type 2 (N = 6) and SMA type 3 (N = 3), aged 10.4 (SD 3.8) years, during a 12-week period. Training sessions lasted 45 minutes to 60 minutes (including a 5-minute warm-up and cool down). Participants exercised three times weekly on non-consecutive days and performed two sets of 15 repetitions, with a recovery period of at least 5 minutes between sets. All participants performed concentric and gravity-eliminated exercises of shoulder and elbow flexion and extension. Ambulatory participants also exercised hip flexion, hip extension, and knee extension. Resistance was achieved using ankle and wrist weights, body weight, and variation in level of assistance. Each exercise was increased by 0.08 kg increments until the participant scored between 6 and 8 on the Children's OMNI Resistance Exercise Scale of Perceived Exertion (where 0 = extremely easy and 10 = extremely hard; Robertson 2005). Treatment fidelity, percentage of people with SMA willing to participate, progression of exerciseworkload, reported pain, and perceived exertion were used to determine feasibility and safety. The study included extremity composite scores of Manual Muscle Testing (MMT), quantitative myometry, and the HFMSE as outcome measures for strength and motor function.

Madsen 2015 studied the effect of a 12-week, home-based aerobic exercise training program in a clinical controlled trial of six participants with SMA and nine healthy controls, aged 19 to 58 years. Participants trained on a cycle ergometer, performing 30-minute training sessions (including 3 to 5 minutes of warm-up) at target heart rate, corresponding to an oxygen uptake (VO_2) of 60% to 75% of maximal (VO_{2max}). The number of sessions per week was gradually increased from two to four, aiming to reach a total of 42 sessions in 12 weeks. The trialists monitored compliance using weekly calls or emails, a training diary, and by downloading exercise data from pulse watches. Outcome measures were VO_{2max} , measured with an incremental exercise test; activities of daily living (ADL) functioning, assessed with a questionnaire; hand-held myometry of four muscle groups; body composition; and functional tests, including the six-minute walk test (6MWT), six-step stair test, the Timed Up and Go (TUG) test, and the five-timessit-to-stand test. Creatine kinase was measured three times during the training period as a marker for muscle damage.

Risk of bias in included studies

See the 'Risk of bias' summary figure for a representation of the review authors' 'Risk of bias' assessments (Figure 2).

[Figure 2]

Allocation

Montes 2015 randomly assigned participants to the training or usual care group. There was no published information on the method of randomization or allocation concealment, but the first author reported that the trialists created 14 envelopes containing either exercise or usual care allocations. After consent was obtained, a designated research coordinator blindly selected a group assignment slip for each participant from a bin and placed it in an envelope labeled with the subject identification code inside a locked cabinet.We judged the randomization and allocation concealment procedures at low risk of bias.

Blinding

Blinding of personnel and participants was not possible because of the nature of the intervention. As all outcomeswere to some degree effort-dependent or subjective, we considered themall at high risk of performance bias.Tomaintain outcome assessor blinding, study personnel, participants, and families were instructed not to discuss study design, group assignment, or the exercise program with the blinded primary evaluator.We judged the blinding procedure for the outcome assessor at low risk of bias.

Incomplete outcome data

Two participants in the training group did not complete the training period of six months because they found the travel distance of more than 1000 miles too burdensome. The trial authors did not perform intention-to-treat analysis. The trial author informed us, however, that differences in baseline values between the participants that completed the study and those that dropped out were not significant. We therefore concluded that the dropout of these two participants was probably not related to the true outcome at six month

Selective reporting

We found no evidence of selective reporting. The trial authors reported results showing significant and non-significant differences, in accordance with the protocol.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: Summary of findings for the main comparison Combined strength and aerobic exercise training compared to usual care in SMA type 3
All primary and secondary outcomes were from one study (Montes 2015).

Combined strength and aerobic exercise training versus usual care in SMA type 3

Montes 2015 studied a combined strength and aerobic exercise training program (see Summary of findings for the main comparison). The trial reported outcomes after six months of training.

Primary outcome measure: walking distance on the sixminute walk test

The minimal detectable change on the 6MWT is 24.0 m (Dunaway 2016).
The change frombaseline inmean distance walked on the 6MWT (m) was not detectably different in the exercise group than in the usual care group (mean difference (MD) 9.54, 95% confidence interval (CI) -83.04 to 102.12, N = 12; very low-certainty evidence; Analysis 1.1).We downgraded the evidence to very low: twice for imprecision, as the sample size was small (there were five participants in the

training group) and CIs encompassed large effects in either direction, and once for indirectness, as 50% of the training group did not achieve the intended volume of aerobic exercise training, owing to decreased exercise tolerability. Additionally, the lack of participant blinding represented a study limitation.

Secondary outcome measures

Functional performance
The trial assessed the change in functional performance from baseline to six months' follow-up, using the HFMSE, 10MWT, and TUG test. The HFMSE scores revealed no clinicallymeaningful difference in functional performance between the training group and the usual care group (MD 2.00, 95% CI -2.06 to 6.06; N = 12; Analysis 1.2). The range of possible scores on the HFMSE is 0 to 66 and a clinically meaningful improvement is an increase of 3 points or more (Mercuri 2018).
The change in 10MWT time (s) revealed no clear difference between the training group and usual care group (MD -0.65, 95% CI -1.84 to 0.54; N = 12; Analysis 1.3). Performance on the TUG test (s) was worse in the training group than in the usual care group (MD 4.28, 95% CI -3.43 to 11.99; N = 12; Analysis 1.4).
We considered the evidence for all functional performance scores of very low certainty, downgrading twice for imprecision, as the sample size was small (there were five participants in the training group), and CIs encompassed moderate effects in either direction, and once for study limitations, as participants could not be blinded to the intervention.

Secondary outcome measures

Cardiopulmonary exercise capacity
A clinically meaningful increase in VO_{2max} is 3.5 mL/kg/min (Myers 2002).
There was no clear difference in the change from baseline in VO_{2max} (mL/kg/min) between the training group and the usual care group (MD 1.22, 95% CI -2.16 to 4.6; Analysis 1.5). We considered the evidence of very low certainty, downgrading three times: twice for imprecision, as the sample size was small (there were five participants in the training group) and CIs encompassed moderate effects in either direction, and once for indirectness, because 50% of the training group did not achieve the intended volume of aerobic exercise training owing to decreased exercise tolerability. Additionally, the lack of participant blinding represented a study limitation.

Muscle strength

Manual muscle testing
Muscle strength was assessed by the change frombaseline inMMT score (the Medical Research Council (MRC) 10-point grading scale, expressed as total MMT score (which is the total scores of 28 arm and leg muscle groups, maximal score 280), arm MMT score (score of 12 arm muscle groups, maximal score 120), and leg MMT score (score of 16 leg muscle groups, maximal score 160). The total MMT score (MD 11.94, 95% CI -3.44 to 27.32; Analysis 1.6), armMMT score (MD7.51, 95%CI -0.05 to 15.07; Analysis 1.7), and leg MMT score (MD 4.43, 95% CI -5.64 to 14.50; Analysis 1.8) improved more in the training group than in the usual care group. We graded the certainty of the evidence for muscle strength, expressed as total MMT score, as low, downgrading twice for imprecision, as the sample size was small (there were five participants in the training group) and CIs encompassed moderate effects in either direction, and once for study limitations,as participants could not be blinded to the intervention.

Hand-held dynamometry

The trial also assessed the change frombaseline in muscle strength of individual muscles using hand-held dynamometry. There were no clear differences in muscle strength (kg) between the training group and the usual care group for knee extension (MD -0.73, 95% CI -3.10 to 1.64; Analysis 1.9), knee flexion (MD -0.79, 95%CI -16.24 to 14.66; Analysis 1.10), shoulder abduction (MD -0.40, 95% CI -0.92 to 0.12; Analysis 1.11), elbow flexion (MD 0.29, 95% CI -0.49 to 1.07; Analysis 1.12), or elbow extension (MD -0.34, 95% CI -2.12 to 1.44; Analysis 1.13).

Fatigue

We could not report CIs for fatigue, as the trial authors did not report P values and the subgroup sample sizes were very small (between four and eight participants). Instead, we provided the raw mean scores for the changes from baseline.

Children

The Pediatric Quality of Life Inventory Multi-Dimensional Fatigue Scale (PedsQLMFS) is a scale from: 0 to 100 (a higher score indicates less fatigue). The mean PedsQLMFS score in the training group (N = 1) increased by 2 points from a baseline of 88 (child report) and by 6 points from a baseline of 51 (parent report). In the usual care group (N = 3), PedsQLMFS scores increased by 3.5 froma baseline of 81.7 (child report) and by 7.3 from a baseline of 75.9 (parent report).

Adults

The Fatigue Severity Scale (FSS) has a range from 0 to 7 (a higher score indicates more fatigue).
The mean FFS score at baseline was 4.6 in the training group (N = 4) at baseline, and did not change following training. In the usual care group (N = 4), the FSS score increased by 0.4 from a baseline of 5.0. The trial authors stated that the differences were not significant but did not report P values.
We considered the evidence of very low certainty, downgrading twice for imprecision, as the sample size was small (training group N = 5) and CIs encompassed large effects in either direction, and once for indirectness, as 50%of the training group did not achieve the intended volume of aerobic exercise training owing to decreased exercise tolerability. Additionally, the lack of participant blinding represented a study limitation.

Physical activity

The included study did not measure physical activity levels.

Quality of life

We could not report CIs for quality of life, as the trial authors did not report P values and the subgroup sample sizes were very small (between four and eight participants). Instead, we provided the raw mean scores for the changes from baseline.

Children

The Pediatric Quality of Life Inventory Neuromuscular Module (PedsQLNM) is a scale from: 0 to 100 (a higher score indicates better quality of life).
The trial reported no significant changes in quality of life either from baseline or between the exercise and control groups over the six-month trial, according to child and parent scores on the PedsQLNM. Mean changes in PedsQLNM score in the training group (N = 1) were a 1-point decrease from a baseline of 90 (child report) and a 5-point increase from a baseline of 68 points (parent report). In the usual care group (N = 3), there was a 0.1-point increase from a baseline of 85.3 points (child report) and a 2.7- point increase from a baseline of 83.0 points (parent report).

Adults

The 36-Item Short-Form Health Survey (SF-36) questionnaire subdomains Physical Health (SF-36PH) and Mental Health (SF-36MH) range from: 0 to 100 (a higher score indicates better quality of life). The mean change in SF-36PH score in the training group (N = 4) was an increase of 0.5 points from a baseline of 35.6 points. In the usual care group (N = 2), there was a decrease of 1.6 points from a baseline of 39.4 points.

The mean change in the SF-36MH score in the training group (N = 4) was an increase of 0.2 points from a baseline of 60.3 points. In the usual care group (N = 2), there was an increase of 0.8 points from a baseline of 54.2 points.

The trial authors stated that differences were not significant, but did not report P values. We considered the evidence of very low certainty, downgrading twice for imprecision, as the sample size was small andCIs encompassed large effects in either direction, and once for indirectness, because 50% of the training group did not achieve the intended volume of aerobic exercise training owing to decreased exercise tolerability. Additionally, the lack of participant blinding represented a study limitation.

Discussion

Summary of main results

We identified one trial for inclusion in this review. Montes 2015 was a single-blind, randomized, controlled clinical trial that studied the effects of a 6-month, home-based combined cycle ergometry and strength training program in 12 participants with spinal muscular atrophy (SMA) type 3. The comparison group received usual care. The evidence was too uncertain to draw conclusions about the effects of exercise training on walking distance on the six-minutewalk test (6MWT), cardiopulmonary exercise capacity, fatigue, quality of life, functional performance (on the Hammersmith Functional Motor Scale - Expanded (HFMSE)), or muscle strength. No study-related serious adverse events occurred in either the training or usual care group; however, the certainty of this evidence was also too low for any conclusions to be drawn.

Overall completeness and applicability of evidence

This review does not provide sufficient evidence for or against aerobic training or strength training in people with SMA type 3. There is a lack of well-designed studies, as most studies are characterized by small sample sizes, a high risk of bias, and inadequate training prescriptions. The striking difference in efficacy and feasibility findings between the randomized trial included in this review (Montes 2015), and a non-randomized controlled trial reported in the discussion section (Madsen 2015), could arise from multiple factors, including differences in study design, training program, and participant population. The paucity of evidence and variability in study designs make it impossible to conclude whether or not physical exercise training is beneficial for people with SMA type 3.

Quality of the evidence

Training program

Guidelines recommend that training programs are standardized on the 'Frequency', 'Intensity', 'Time' and 'Type' (FITT) principle and use an incremental exercise protocol (ACSM2010;Ganley 2011). In Montes 2015, aerobic training consisted of recumbent cycle ergometry (T), five times weekly (F) for 30 minutes (T) at an intensity level of a 5 to 7 on a perceived exertion scale with a range of 10 (I). Workload was increased every two weeks, when perceived exertion would drop below a score of 5. The use of a subjective score to determine the exercise intensity level in the trial was not in accordance with the initial protocol (Montes 2014), in which the trial authors stated that moderate

intensity would be objectively based on peak oxygen uptake (VO_{2max}) during amaximal exercise test. The trial author explained that the workload of the recumbent bicycles used by participants at home could only be adjusted on an ascending scale, but not in Watts. Instead, the trial used a perceived exertion scale to guide workload increase. Strength training consisted of five or six concentric, isometric, or gravity-eliminated exercises of hip, ankle, and all shoulder muscles, as well as core muscles (T). Target muscles were individually selected based on the most weakened muscles. Strength training was performed three times weekly (F): three sets each of 8 to 12 repetitions during 30 minutes (T), at an intensity level of 60% to 80% of 1 repetition maximum (I).Workload was increased every two weeks when perceived exertion would drop below a score of 5. The trial authors did not report specific data on individual participants and muscles, which makes it difficult to determine the variability in individual strengthening programs.

Diagnostic criteria

In Montes 2015, all participants had genetically confirmed SMA with a clinical type 3. We therefore considered the quality of the diagnostic criteria to be adequate.

Outcomes

Our overall certainty in the results according to GRADE criteria was very low for all outcomes, which means that further research is very likely to have an important impact on the estimate of effect. Imprecision (a small study sample and wide confidence intervals), indirectness (suboptimal aerobic exercise dosing), and study limitations (lack of participant blinding) were the reasons for the judgement of very low certainty. We need larger, well-controlled studies with optimal exercise dosing to improve the body of evidence

Potential biases in the review process

Although it is possible that we missed studies from databases not covered by our searches, the extent of our search and the paucity of exercise studies in SMA make it very unlikely that we overlooked eligible studies.
The involvement of JM who was an author of the one included trial was a potential bias in the review process. We used a third reviewer (JdG) to substitute for JMin extraction of outcome data and 'Risk of bias' assessment for this trial (Montes 2015).

Agreements and disagreements with other studies or reviews

Aerobic exercise training in SMA

There were both agreements and disagreements between the one included trial by Montes and colleagues and the controlled study by Madsen and colleagues (Madsen 2015; Montes 2015). Neither trial reached optimal training frequency within the predetermined dosing period, for different reasons. In Montes 2015, the investigators aimed to gradually increase the number of sessions to five per week. However, only one participant managed to accomplish this training frequency at three months. At six months, 50% reached a frequency of five sessions per week, while the other 50% reached a frequency of one to three sessions per week. There were no dropouts for adverse events and the protocol was well tolerated. In Madsen 2015, the aim was to gradually increase the number of sessions from two to four per week, but the program had to be modified in two out of eight participants with SMA, owing to fatigue. Two participants experienced adverse events (fall incidents and joint pain) and two participants dropped out of the study due to excessive fatigue.The remaining participants eventually reached a frequency range of 1.7 to 2.6 sessions per week, in comparison to three sessions per week in healthy controls. The training effect between the studies was significantly different. Whereas Montes 2015 found no significant improvement in VO_{2max} in the training group

versus the usual care group, Madsen 2015 reported a significant and clinically relevant improvement in VO_{2max} in participants with SMA (from 17 mL/kg/min to 21 mL/kg/min, which was an increase of 27% (standard error (SE) 3%); P < 0.001). The two studies were both small, subject to imprecision, and had several differences in study design that could explain the differences in outcomes. Madsen 2015 was at risk of selection from bias from use of a non-randomized sample of eight adults with SMA and matched healthy sedentary control participants. Training type and intensity also differed, as Montes 2015 used a recumbent bicycle and set the intensity at a score of 5 to 7 on a subjective rating scale, while Madsen 2015 used an upright bicycle and an exercise intensity set at 60% to 75% of VO_{2max} . The two strategies (’subjective fatigue’ and ’oxygen uptake’) used to determine exercise intensityin these studies might represent different physiological limitations (peripheral versus cardiopulmonary limitations), and it is difficult to determine whether the training intensities were similar. The studies agree on the fact that people with SMA are vulnerable to exercise-induced fatigue and overexertion, and that optimal titration of exercise dosing has still to be determined. Although not formally tested, there did not seem to be a large difference in baseline disease severity in the intervention groups between Montes 2015 and Madsen 2015 to explain differences in exercise response: the mean (SD) baseline distances walked in the 6MWT (m) were 389.9 (SD 111.3) in Montes 2015 and 330 (SE 67) in Madsen 2015. The mean ages of participants at baseline were 27 years (SD 14.6) in Montes 2015 and 32.5 years (SE 16.5) inMadsen 2015).

Strength training in SMA

The findings of Montes 2015 were to a large extent in agreement with themulti-case study by Lewelt and colleagues (Lewelt 2015). Participants in both studies tolerated strength training well, as reflected by high completion rates (of 90% to 100%), without an increase in adverse events. Both Montes 2015 and Lewelt 2015 found that theremay be improvement in both strength (expressed as total and armmanualmuscle testing scores) andmotor function (the HFMSE score). Lewelt 2015, however, had several methodological flaws that necessitate caution when interpreting the results. Physical therapists delivering the intervention and often the evaluator were not blinded, which introduced potential performance and detection bias. It is unclear whether the results were entirely representative of people with SMA type 3, because the paper did not report findings in participants with SMA type 2 and SMA type 3 separately. There was also a difference in the mean age at baseline between Montes 2015 and Lewelt 2015 (27 years versus 10.4 years), which makes comparisons between the studies difficult.

Physical training in other neuromuscular diseases

No other systematic reviews on the effects of physical exercise training in people with SMA have been published to date, although there are reviews of exercise for other neuromuscular conditions. Voet and colleagues published a Cochrane Systematic Review on the effects of strength and aerobic exercise training for muscle disease, which at the time of writing is being updated (Voet 2013). Voet 2013 included five studies: two in myotonic dystrophy, one in myositis, one in facioscapulohumeral dystrophy, and one in mitochondrial myopathy. Voet 2013 concluded that moderateintensity strength training and aerobic exercise training seem feasible but that there was not enough evidence to determine efficacy. Also in 2013, Dal Bello-Haas and colleagues performed a Cochrane systematic review on the effects of progressive resistance or strengthening exercise and endurance or aerobic exercise in people with amyotrophic lateral sclerosis (ALS)/motor neuron disease, which included two studies (Dal Bello-Haas 2013). The review found a significant increase on the ALS Functional Rating Scale when combining the data from one study of undefined endurance exercise and one resistance exercise program. The certainty of evidence in the review was limited by small sample sizes and a high risk of bias in one of the studies. The findings of both reviews are consistent with those of our review.

Authors' conclusions

Implications for practice

It is uncertain whether combined strength and aerobic exercise training is beneficial or harmful in people with spinal muscular atrophy (SMA) type 3 in terms of walking distance, cardiopulmonary exercise capacity, fatigue, quality of life, functional performance, muscle strength, and adverse effects, as the quality of evidence is very low. Implications for research We need more evidence, of greater certainty to be able to develop exercise guidelines for people with SMA type 3. National or international multicenter studies should be developed, which include sufficient participants and meet requirements for statistical power. The balance between feasibility and optimal dosing seems pivotal in the design of effective training programs for people with SMA type 3, especiallywith regards to aerobic exercise training.We need studies to determine the optimal dose of exercise, both for people with mild weakness and for those who are more severely affected, and when used as monotherapy or in combination with a drug. Training protocols should be clearly described with regards to the FITT-factors (Frequency, Intensity, Time, and Type). Blinding of outcome assessors is important and achievable, but adequate blinding of participants and personnel is rarely possible in exercise trials. Knowledge of group assignment can affect participant behaviour, but use of objective outcome measures, with monitoring of participant effort where this can influence outcome measurement, may improve the certainty of findings.

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We based the Methods section of the protocol on a template developed by Cochrane Neuromuscular from an original created by the Cochrane Airways Group. The Information Specialist for Cochrane Neuromuscular, Angela Gunn, developed the search strategy in consultation with the protocol authors.

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∗ *Indicates the major publication for the study*l

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Montes 2015

Methods	Single-blind, randomized, controlled clinical trial
Participants	**Inclusion criteria** Genetic confirmation of SMA diagnosis SMA type 3 Aged between 8 and 50 years Able to walk at least 25 m without assistance Able to pedal the stationary cycle ergometer In good health, based on the findings of a physical examination and the judgment of the clinical investigator at the time of screening assessment **Exclusion criteria** Use of investigational medications intended for the treatment of SMA A contraindication to exercise according to American College of Sports Medicine (ACSM) criteria Pregnancy Breastfeeding **Study sample** "At baseline, all participants had normal pulmonary function and substantially attenuated exercise capacity. On average, the exercise capacity was 35.3% of predicted for age and gender. Both groups were insufficiently active, spending on average 83.5% of waking hours in sedentary activities **Intervention group (N = 7)** Age in years (SD): 27.0 (14.6), range 10 to 43 Sex (male/female): 6/1 SMA subtype: 3a (N = 0); 3b (N = 7) Severity of illness (HFMSE score): 53.4 (8.9) **Control (usual care) group (N = 7)** Age in years (SD): 26.7 (17.7), range 10 to 48 Sex (male/female): 5/2 SMA subtype: 3a (N = 3); 3b (N = 4) Severity of illness (HFMSE score): 54.0 (8.2)
Interventions	Combined strength and aerobic exercise training or no training **Aerobic exercise training** *Frequency:* 5 times weekly *Intensity* Moderate intensity (a score of 5 to 7 on the OMNI Scale of Perceived Exertion) Participants were allowed to increase their workload once every 2 weeks, provided they maintained a submaximal level of intensity, as measured on the OMNI Scale of Perceived Exertion *Time* Session: 30 minutes Program: 6 months

Montes 2015 (Continued)

	Type Recumbent cycle ergometry **Strength training** *Frequency* 3 times weekly *Intensity* 60% to 80% of 1 repetition maximum 3 sets, each of 8 to 12 repetitions 2 to 3 minutes break between each set *Time* 30 minutes *Type* 5 to 6 exercises, concentric, isometric, or modified in a gravity-eliminated position for weaker muscles Muscle groups: hip, ankle, and all shoulder muscles, and core muscles. Target muscles were individually selected based on most weakened muscles
Outcomes	**Primary outcome** 6-minute walk test (6-minute walking distance) HFMSE **Secondary outcomes** Cardiopulmonary exercise capacity (VO_{2max}) 10-meter walk/run Timed Up and Go Test Muscle strength (manual muscle testing sum scores, hand-held dynamometry (kg)) Fatigue (questionnaire) Quality of life (questionnaire) Number of serious adverse events
Conflicts of interest among principal investigators	The authors report no conflict of interests.
Funding	Department of Defense; USAMRAA Grant/Cooperative award number: 09131005 (W81XWH-10-1-0127), and the Spinal Muscular Atrophy Foundation. "The sponsors had no role in the conduct of this study."
Notes	ClinicalTrials.gov id: NCT01166022 Start date: December 2010, completion date August 2014 Location: USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized to control and exercise cohorts." Comment: The author (Montes) informed us that a designated research coordinator blindly selected a group assignment slip (exercise or control) from a bin and placed it in an envelope labeled with the participant identification code. The envelopes were kept in a locked cabinet

Montes (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomized to control and exercise cohorts." Comment: The author (Montes) informed us that a designated research coordinator blindly selected a group assignment slip (exercise or control) from a bin and placed it in an envelope labeled with the participant identification code. The envelopes were kept in a locked cabinet
Blinding of participants and personnel (performance bias) All outcomes	High risk	The primary evaluator was blinded but other study personnel and participants were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To maintain the blind, study personnel as well as patients and families will be instructed not to discuss study design, group assignment, or exercise program with the primary evaluator." Comments: The primary evaluator was blinded. Other study personnel and participants were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The two participants who dropped out during the first 7 months of the study lived more than 1000 miles from the study site and found the travel too burdensome." Comment: 2/14 participants (both in the training group) did not complete the controlled period of 6 months Reasons for missing outcome data unlikely to be related to true outcome at six months (N = 2) because of random missing data (travel reasons)
Selective reporting (reporting bias)	Low risk	No evidence found for selective reporting Report of both significant and non-significant differences in accordance with protocol (Montes 2014)
Other bias	Low risk	No risk of bias from other sources detected

HFMSE: Hammersmith Functional Motor Scale - Expanded; SD: standard deviation; SMA: spinal muscular atrophy;

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Basoglu 2006	Not a RCT (multi-case study) and insufficient description of the intervention
Cunha 1996	Not a RCT (multi-case study) and insufficient description of the intervention
Dahl 2004	Insufficient description of the intervention and participants
Lewelt 2015	Not a RCT (multi-case study). Included in the Discussion
Madsen 2015	Not a RCT (controlled trial in people with SMA versus healthy controls). Included in the Discussion
McCartney 1988	Not a RCT (multi-case study) and inadequate exercise protocol
Milner-Brown 1988	Not a RCT, and insufficient description of participants and the intervention
Salem 2010	Not a RCT (case study) and insufficient description of the intervention
Vry 2014	Not a RCT (multi-case study) and inadequate exercise protocol

RCT: randomized controlled trial

Data and analyses

Comparison 1. Combined strength and aerobic exercise training versus usual care in SMA type 3

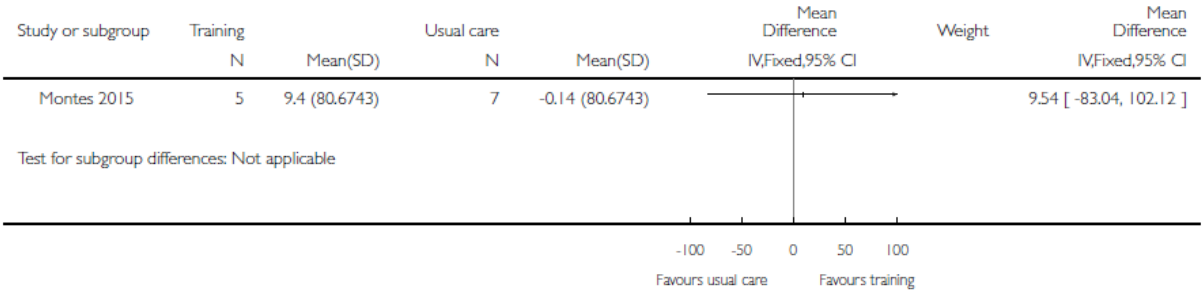
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Walking distance: 6-minute walk test (m)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2 Functional performance: Hammersmith Functional Motor Scale Expanded	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Functional performance: 10-meter walk test (s)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Functional performance: Timed Up and Go test (s)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5 Cardiopulmonary exercise capacity: VO_{2max} (mL/kg/min)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6 Muscle strength: total manual muscle testing score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Muscle strength: arm manual muscle testing score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8 Muscle strength: leg manual muscle testing score	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9 Muscle strength: hand-held dynamometry - knee extension (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10 Muscle strength: hand-held dynamometry - knee flexion (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
11 Muscle strength: hand-held dynamometry - shoulder abduction (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12 Muscle strength: hand-held dynamometry - elbow extension (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
13 Muscle strength: hand-held dynamometry - elbow flexion (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 1 Walking distance: 6-minute walk test (m).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 1 Walking distance: 6-minute walk test (m)

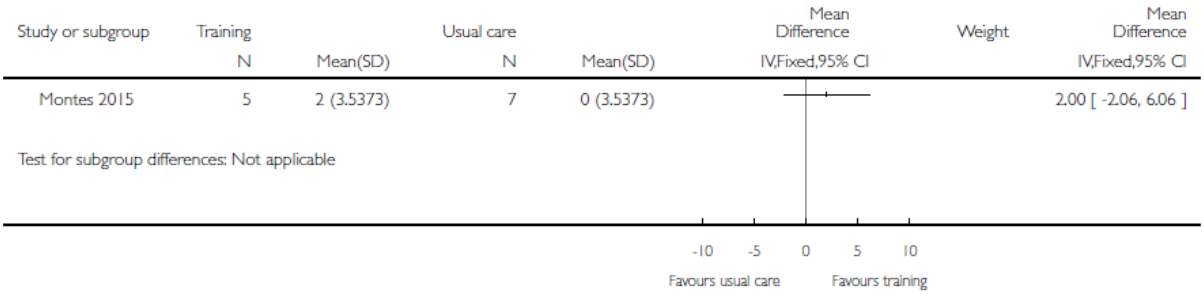


Analysis 1.2. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 2 Functional performance: Hammersmith Functional Motor Scale Expanded.

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 2 Functional performance: Hammersmith Functional Motor Scale Expanded

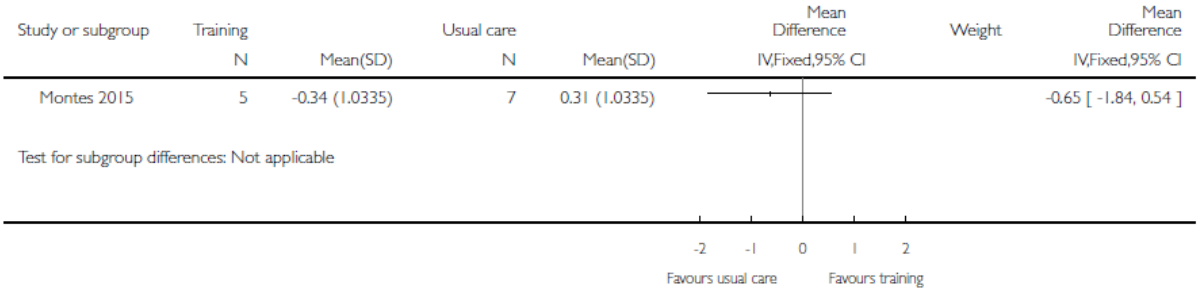


Analysis 1.3. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 3 Functional performance: 10-meter walk test (s).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 3 Functional performance: 10-meter walk test (s)

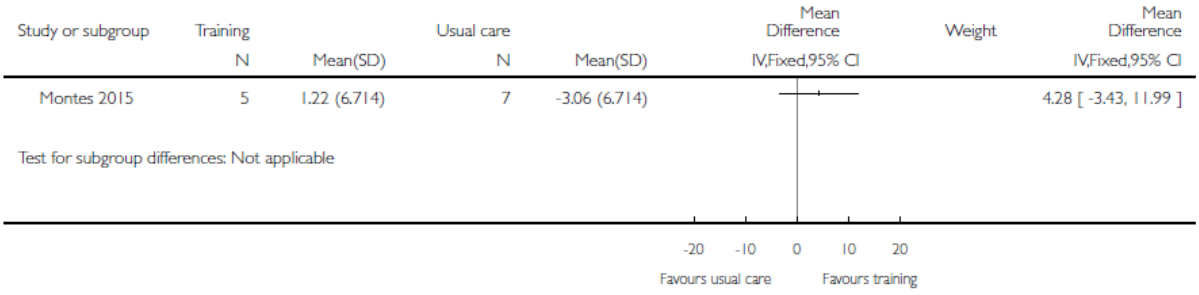


Analysis 1.4. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 4 Functional performance: Timed Up and Go test (s).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 4 Functional performance: Timed Up and Go test (s)

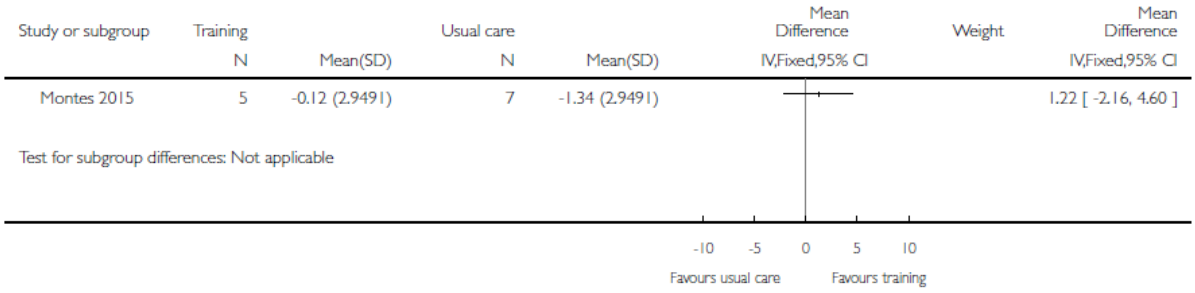


Analysis 1.5. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 5 Cardiopulmonary exercise capacity: VO_{2max} (mL/kg/min).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 5 Cardiopulmonary exercise capacity: VO_{2max} (mL/kg/min)

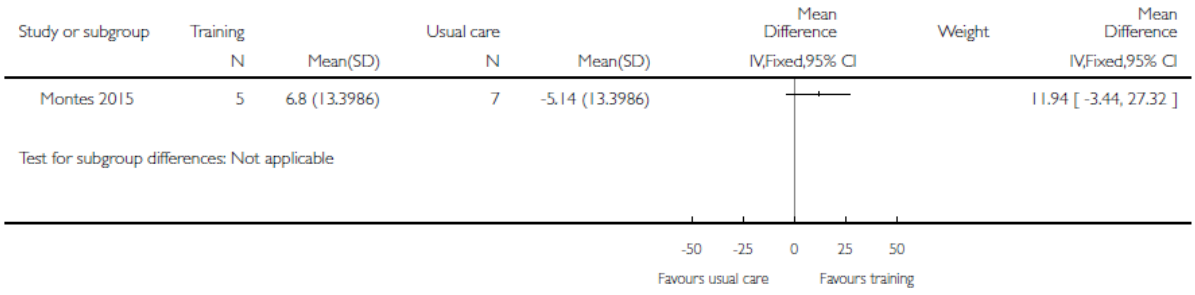


Analysis 1.6. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 6 Muscle strength: total manual muscle testing score.

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 6 Muscle strength: total manual muscle testing score



Analysis 1.7. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 7 Muscle strength: arm manual muscle testing score.

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 7 Muscle strength: arm manual muscle testing score

Study or subgroup	Training N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Montes 2015	5	4.8 (6.5837)	7	-2.71 (6.5837)			7.51 [-0.05, 15.07]

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 8 Muscle strength: leg manual muscle testing score.

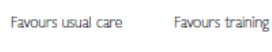
Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 8 Muscle strength: leg manual muscle testing score

Study or subgroup	Training N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Montes 2015	5	2 (8.7789)	7	-2.43 (8.7789)			4.43 [-5.64, 14.50]

Test for subgroup differences: Not applicable

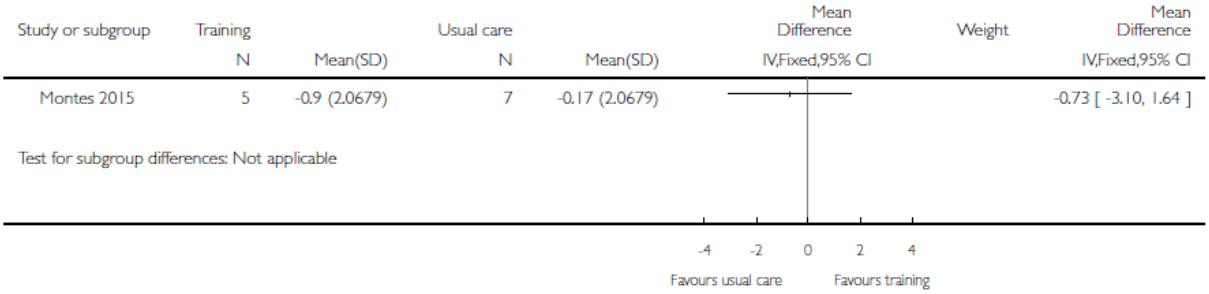


Analysis 1.9. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 9 Muscle strength: hand-held dynamometry - knee extension (kg).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 9 Muscle strength: hand-held dynamometry - knee extension (kg)

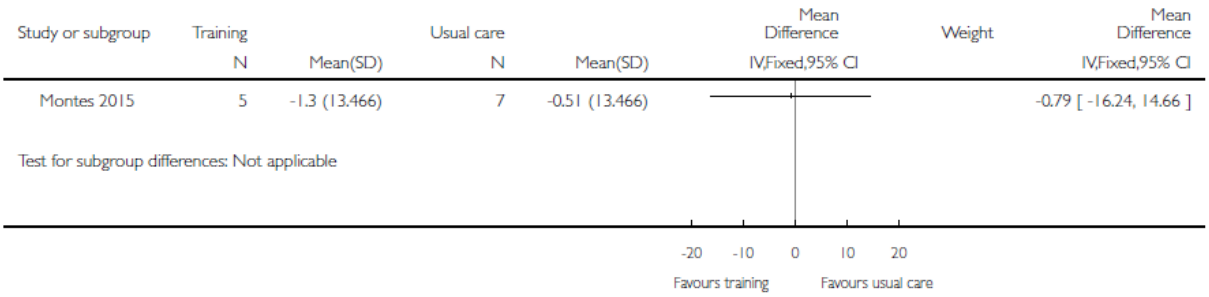


Analysis 1.10. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 10 Muscle strength: hand-held dynamometry - knee flexion (kg).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 10 Muscle strength: hand-held dynamometry - knee flexion (kg)

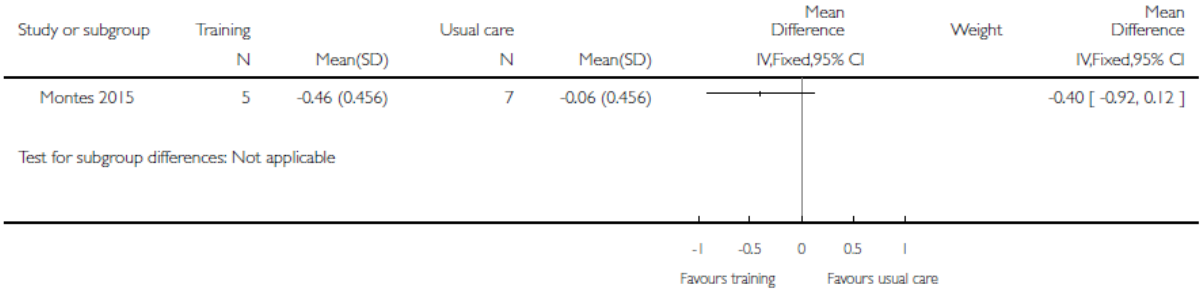


Analysis 1.11. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 11 Muscle strength: hand-held dynamometry - shoulder abduction (kg).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 11 Muscle strength: hand-held dynamometry - shoulder abduction (kg)

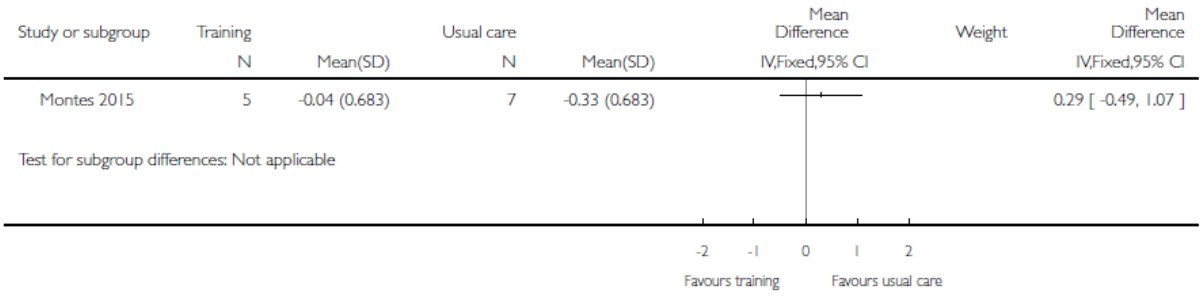


Analysis 1.12. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 12 Muscle strength: hand-held dynamometry - elbow extension (kg).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 12 Muscle strength: hand-held dynamometry - elbow extension (kg)

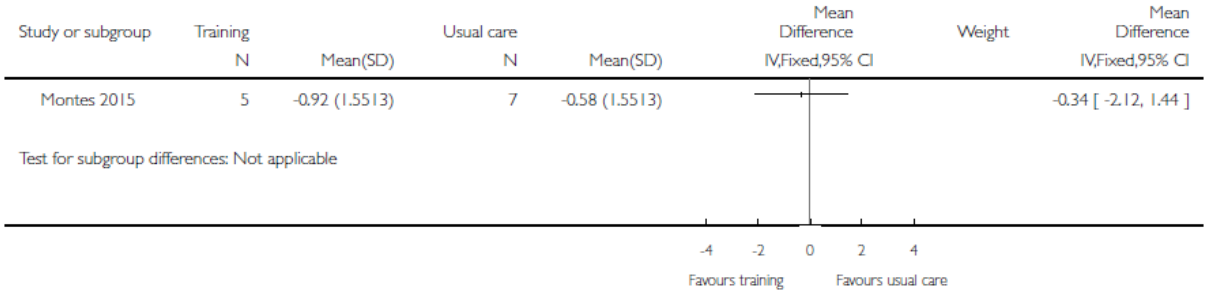


Analysis 1.13. Comparison 1 Combined strength and aerobic exercise training versus usual care in SMA type 3, Outcome 13 Muscle strength: hand-held dynamometry - elbow flexion (kg).

Review: Physical exercise training for type 3 spinal muscular atrophy

Comparison: 1 Combined strength and aerobic exercise training versus usual care in SMA type 3

Outcome: 13 Muscle strength: hand-held dynamometry - elbow flexion (kg)



Appendices

Appendix 1. Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web) search strategy

#1 MeSH DESCRIPTOR Muscular Atrophy, Spinal Explode All AND INSEGMENT
#2 MeSH DESCRIPTOR Muscular Disorders, Atrophic AND INSEGMENT
#3 “spinal muscular” NEXT atroph* AND INSEGMENT
#4 Kugelberg next Welander AND INSEGMENT
#5 #1 or #2 or #3 or #4 AND INSEGMENT
#6 (aerobic or endurance or physical or strength or strengthening) NEAR5 (exercise or program or programme or training) AND INSEGMENT
#7 (aerobic or anaerobic) NEAR5 conditioning AND INSEGMENT
#8 (aquatic or functional or kinesio*) NEAR5 therapy AND INSEGMENT
#9 (cardio or excessive or exercise or muscle or power) NEAR5 training AND INSEGMENT
#10 (home or therapeutic) NEAR5 (exercise* or program or programme) AND INSEGMENT
#11 (home or therapeutic) NEAR5 (exercise or exercises or program or programme) AND INSEGMENT
#12 (isokinetic or isometric or muscle or resistance) NEAR5 strength training AND INSEGMENT
#13 (muscle or resistance or resistive) NEAR5 exercise AND INSEGMENT
#14 “cycle ergometer” or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill AND INSEGMENT
#15 weight NEAR5 (training or lifting) AND INSEGMENT
#16 “whole body vibration” AND INSEGMENT
#17 (strengthen or strengthening) NEAR5 therap* AND INSEGMENT
#18 “resistance training” AND INSEGMENT
#19 MeSH DESCRIPTOR Exercise Explode All AND INSEGMENT
#20 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 AND INSEGMENT
#21 #5 and #20 AND INSEGMENT
#22 (#5 and #20) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Registerof Studies (CRS-Web) search strategy

#1 MeSH DESCRIPTOR Muscular Atrophy, Spinal Explode All AND CENTRAL:TARGET
#2 MeSH DESCRIPTOR Muscular Disorders, Atrophic AND CENTRAL:TARGET
#3 “spinal muscular” NEXT atroph* AND CENTRAL:TARGET
#4 Kugelberg next Welander AND CENTRAL:TARGET
#5 #1 or #2 or #3 or #4 AND CENTRAL:TARGET
#6 (aerobic or endurance or physical or strength or strengthening) NEAR5 (exercise or program or programme or training) AND CENTRAL:TARGET
#7 (aerobic or anaerobic) NEAR5 conditioning AND CENTRAL:TARGET
#8 (aquatic or functional or kinesio*) NEAR5 therapy AND CENTRAL:TARGET
#9 (cardio or excessive or exercise or muscle or power) NEAR5 training AND CENTRAL:TARGET
#10 (home or therapeutic) NEAR5 (exercise* or program or programme) AND CENTRAL:TARGET
#11 (home or therapeutic) NEAR5 (exercise or exercises or program or programme) AND CENTRAL:TARGET
#12 (isokinetic or isometric or muscle or resistance) NEAR5 strength training AND CENTRAL:TARGET
#13 (muscle or resistance or resistive) NEAR5 exercise AND CENTRAL:TARGET
#14 “cycle ergometer” or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill AND CENTRAL: TARGET
#15 weight NEAR5 (training or lifting) AND CENTRAL:TARGET
#16 “whole body vibration” AND CENTRAL:TARGET
#17 (strengthen or strengthening) NEAR5 therap* AND CENTRAL:TARGET
#18 “resistance training” AND CENTRAL:TARGET
#19 MeSH DESCRIPTOR Exercise Explode All AND CENTRAL:TARGET
#20 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 AND CENTRAL:TARGET
#21 #5 and #20 AND CENTRAL:TARGET

Appendix 3. MEDLINE (OvidSP) search strategy

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

1 exp Muscular Atrophy, Spinal/ (4341)
2 muscular disorders, atrophic/ (384)
3 spinal muscular atroph$.mp. (4667)
4 (Kugelberg adj Welander).mp. (188)
5 or/1-4 (6445)
6 ((aerobic or endurance or physical or strength or strengthening) adj5 (exercise or program or programme or training)).mp. (67577)
7 ((aerobic or anaerobic) adj5 conditioning).mp. (330)
8 ((aquatic or functional or kinesio*) adj5 therapy).mp. (7534)
9 ((cardio or excessive or exercise or muscle or power) adj5 training).mp. (26497)
10 (exercise adj5 (program or programme or therap*)).mp. (48627)
11 ((home or therapeutic) adj5 (exercise*1 or program or programme)).mp. (12383)
12 ((isokinetic or isometric or muscle or resistance) adj5 strength training).mp. (917)
13 ((muscle or resistance or resistive) adj5 exercise).mp. (18926)

14 (cycle ergometer or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill).mp. (239978)
15 (weight adj5 (training or lifting)).mp. (7398)
16 whole body vibration.mp. (1712)
17 (strengthen*3 adj5 therap*).mp. (857)
18 resistance training.mp. (10076)
19 exp exercise/ (164910)
20 exp physical therapy modalities/ (135332)
21 or/6-20 (511331)
22 5 and 21 (173)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1980 to 2018 Week 19>
Search Strategy:

1 crossover-procedure.sh. (55236)
2 double-blind procedure.sh. (146675)
3 single-blind procedure.sh. (31247)
4 randomized controlled trial.sh. (498269)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1490626)
6 trial.ti. (242915)
7 controlled clinical trial/ (461290)
8 or/1-7 (1796736)
9 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (25511522)
10 human/ or human cell/ or human tissue/ or normal human/ (19524508)
11 9 not 10 (6016210)
12 8 not 11 (1598869)
13 limit 12 to embase (1020963)
14 spinal muscular atrophy/ or hereditary spinal muscular atrophy/ (6543)
15 (Kugelberg adj Welander).mp. (295)
16 spinal muscul$ atroph$.mp. (7651)
17 or/14-16 (7759)
18 13 and 17 (131)
19 ((aerobic or endurance or physical or strength or strengthening) adj5 (exercise or program or programme or training)).mp. (87125)
20 ((aerobic or anaerobic) adj5 conditioning).mp. (489)
21 ((aquatic or functional or kinesio*) adj5 therapy).mp. (12914)
22 ((cardio or excessive or exercise or muscle or power) adj5 training).mp. (44433)
23 (exercise adj5 (program or programme or therap*)).mp. (33822)
24 ((home or therapeutic) adj5 (exercise*1 or program or programme)).mp. (18400)
25 ((isokinetic or isometric or muscle or resistance) adj5 strength training).mp. (1170)
26 ((muscle or resistance or resistive) adj5 exercise).mp. (29343)
27 (cycle ergometer or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill).mp. (271055)
28 (weight adj5 (training or lifting)).mp. (8885)
29 whole body vibration.mp. (2265)
30 (strengthen*3 adj5 therap*).mp. (1261)
31 resistance training.mp. (15862)

32 exp exercise/ (289998)
33 exp physiotherapy/ (77976)
34 or/19-33 (628599)
35 17 and 34 (277)
36 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (25511522)
37 human/ or human cell/ or human tissue/ or normal human/ (19524508)
38 36 not 37 (6016210)
39 35 not 38 (264)
40 limit 39 to (conference abstracts or embase) (249)

Appendix 5. CINAHL Plus (EBSCOhost) search strategy

Tuesday, May 08, 2018 5:56:32 PM

S21 S20 Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase 15
S20 S4 and S19 48
S19 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 192,873
S18 (MH “Exercise+”) 89,224
S17 resistance training 6,123
S16 strengthen* N5 therap* 428
S15 whole body vibration 922
S14 weight N5 (training or lifting) 4,398
S13 cycle ergometer or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill 82,987
S12 (muscle or resistance or resistive) N5 exercise 8,700
S11 (isokinetic or isometric or muscle or resistance) N5 strength training 1,697
S10 (home or therapeutic) N5 (exercise or exercising or program or programme) 26,578
S9 exercise N5 (program or programme or therap*) 27,847
S8 (cardio or excessive or exercise or muscle or power) N5 training 11,860
S7 (aquatic or functional or kinesio*) N5 therapy 3,209
S6 (aerobic or anaerobic) N5 conditioning 145
S5 ((aerobic or endurance or physical or strength or strengthening) N5 (exercise or program or programme or training) 33,805
S4 S1 OR S2 OR S3 796
S3 Kugelberg n1 Welander 5
S2 muscular disorders n1 atrophic 93
S1 muscular atrophy N1 spinal 723

Appendix 6. AMED (OvidSP) search strategy

Database: AMED (Allied and Complementary Medicine) <1985 to May 2018>
Search Strategy:

1 spinal muscular atrophy.mp. (79)
2 “Muscular atrophy spinal”.et. (6)
3 muscular atrophy/ and spinal.mp. (66)
4 (Kugelberg adj Welander).mp. (1)
5 or/1-4 (99)

6 ((aerobic or endurance or physical or strength or strengthening) adj5 (exercise or program or programme or training)).mp. (6723)
7 ((aerobic or anaerobic) adj5 conditioning).mp. (38)
8 ((aquatic or functional or kinesio*) adj5 therapy).mp. (756)
9 ((cardio or excessive or exercise or muscle or power) adj5 training).mp. (3262)
10 (exercise adj5 (program or programme or therap*)).mp. (9032)
11 ((home or therapeutic) adj5 (exercise*1 or program or programme)).mp. (1657)
12 ((isokinetic or isometric or muscle or resistance) adj5 strength training).mp. (247)
13 ((muscle or resistance or resistive) adj5 exercise).mp. (2469)
14 (cycle ergometer or cycling or exercising or exercise or hydrotherapy or running or sports or swimming or treadmill).mp. (30322)
15 (weight adj5 (training or lifting)).mp. (625)
16 whole body vibration.mp. (220)
17 (strengthen*3 adj5 therap*).mp. (148)
18 resistance training.mp. (1261)
19 or/6-18 (33458)
20 5 and 19 (12)

Appendix 7. LILACS (IAHx) search strategy

("Muscular Atrophy, Spinal" or "spinal muscular atrophy" or "AtrofiaMuscular Espinal" or (Kugelberg AND Welander)) AND (aerobic or anaerobic or endurance or physical or strength or strengthening or training or exercise or "cycle ergometer" or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill or lifting or "body vibration") AND ((PT:"Randomized Controlled Trial" or "Randomized Controlled trial" or "Ensayo Clínico Controlado Aleatorio" or "Ensaio Clínico Controlado Aleatório" or PT: "Controlled Clinical Trial" or "Ensayo Clínico Controlado" or "Ensaio Clínico Controlado" or "Random allocation" or "Distribución Aleatoria" or "Distribuição Aleatória" or randon$ or Randomized or randomly or "double blind" or "duplo-cego" or "duplo-cego" or "single blind" or "simples-cego" or "simples cego" or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

Appendix 8. ClinicalTrials.gov search strategy

Advanced Search; Condition or Disease:Spinal Muscular Atrophy; Study type: Interventional studies (Clinical Trials); Study results: All studies

Appendix 9.World Health Organization (WHO) International Clinical Trials Registry Platform search strategy

Advanced search; in the Title: Spinal Muscular Atrophy; Recruitment status is: All

Appendix 10. NHS Economic Evaluation Database (NHSEED) search strategy

https://www.crd.york.ac.uk/CRDWeb/: Advanced search; any field: Spinal Muscular Atrophy

Appendix 11. Database of Abstracts of Reviews of Effects (DARE) search strategy

https://www.crd.york.ac.uk/CRDWeb/ : Advanced search; any field: Spinal Muscular Atrophy

Appendix 12. Additional methods specified in the protocol

We were unable to implement the following methods described in our protocol (Bartels 2016).

Data extraction and management

When reports require translation, the translator will extract data directly, using a data extraction form, or we will extract data from the translation provided. Where possible, a review author will check numerical data in the translation against the study report.
To minimize bias in the review process, the review authors will not screen studies for inclusion, extract data, or assess the risk of bias if they are also an author of the study. In such circumstances, we will involve a third review author (JdG).

Measures of treatment effect

We will report dichotomous data as risk ratios and continuous data as mean differences, or as standardized mean differences (SMDs) for outcomes that are conceptually the same but measured in different ways in different studies. We will report corresponding 95% confidence intervals (CIs).
When different trials use comparable but different scales to measure the same outcome, we will report pooled results using SMD with 95% CI, ensuring that data from scales are pooled with a consistent direction of effect.We will convert scores on cycle ergometry and treadmill testing, fatigue, and quality of life to percentage scores or Z-scores for pooling. For disability and impairment measures, we will consider an SMD 0.4 to 0.7 (moderate change) clinically significant, whereas in quality of life and fatigue measures, we will consider an SMD less than 0.4 but greater than 0.2 clinically significant.
We will undertake meta-analyses only when this is meaningful, that is, if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We did not plan to combine scores on dynamometry and MMT, or scores on questionnaires and accelerometry, but to report these different measurements separately. We will narratively describe skewed data reported as medians and interquartile ranges.

Dealing with missing data

If we are unable to obtain missing outcome data by contact with trial authors or sponsors, and we consider the methods used to deal with missing data to have introduced serious bias, we will explore the impact of inclusion of such trials in the overall assessment of results by a sensitivity analysis.

Unit of analysis issues

Where multiple trial arms are reported in a single trial, we will include only the eligible arms. If two eligible comparisons (e.g. drug A versus placebo and drug B versus the same placebo group) are combined in the same meta-analysis, we will avoid double-counting by creating a single pair-wise comparison as recommended in the CochraneHandbook for Systematic Reviews of Interventions or, alternatively, halve the control group (Higgins 2011).

Assessment of heterogeneity

We will use the I^2 statistic tomeasure heterogeneity among the trials in each analysis. If we identify substantial unexplained heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.We will use the rough guide to interpretation as outlined in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions, as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will avoid the use of absolute cut-off values, but interpret I^2 in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the Chi-squared test, or CI for I^2) (Deeks 2011).
If we identify substantial unexplained heterogeneity (e.g. over 50%), we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting bias

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases.

Data synthesis

We expect heterogeneity among trials and we will use a random-effects model.We will perform a sensitivity analysis with a fixed-effect model.
If the review includes more than one comparison that cannot be included in the same analysis, we will report the results for each comparison separately.

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses.

- SMA type 3a and SMA type 3b.
- Children (aged <18 years) and adults.

We will use primary and secondary outcome measures in all subgroup analyses.
We will use the formal test for subgroup interactions in RevMan (RevMan 2014).

Sensitivity analysis

We plan to undertake the following sensitivity analyses.

- Repeat the analysis by excluding unpublished studies (if there are any).
- Repeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, and outcome assessment).
- If there are one or more very large trials, we will repeat the analysis by excluding these large trials to examine how much they dominate the results.

Contributions of authors

Each of the review authors contributed to the design and development of this Cochrane Systematic Review. BB wrote the first draft and the other co-authors contributed to subsequent revisions.

Declarations of interest

BB: no known conflicts of interest.
WLvP: obtained research grants from Prinses Beatrix Spierfonds and Stichting Spieren voor Spieren, both non-profit foundations. His employer receives fees for SMA-related (ad hoc) consultancy activities.
JFdG: no known conflicts of interest.
JM: was an investigator in the completed trial on the effect of exercise training in ambulatory patients with SMA (Montes 2015).
The United States Department of Defense funded the trial. However, since the completion of the trial, JM has not received funding for the study (NCT01166022). JM receives research support from Eunice Kennedy Shriver Institute for Child Health and Human Development (NICHD) and the Muscular Dystrophy Association (MDA) and has no other conflicts of interest.

Sources of support

Internal sources
• University Medical Center Utrecht, Netherlands.

External sources
• None, Other

Differences between protocol and review

We changed the title from that of the protocol, 'Skeletalmuscle training for spinal muscular atrophy type 3' (Bartels 2016), to 'Physical exercise training for spinal muscular atrophy type 3', to better reflect the review topic.
To minimize bias in the review process, JdG substituted for JMin extracting data and performing 'Risk of bias' assessments for Montes 2015.
We did not report data from the questionnaires on fatigue and quality of life as MDs but as separate raw scores for children and adults
because of the small subgroup sample sizes for adults (N = 8) and children (N = 4).
We did not assess performance bias separately for subjective outcomes (e.g. questionnaires and visual analogue scales) and objective outcomes (e.g. physiological outcomes), as the distinction was not important in the included trial.

Subgroup analyses by subtype and age were not possible. We moved sections of the protocol that were not applicable in practice to Appendix 12. We also updated the planned approach to heterogeneity, based on current Cochrane guidance.
We reported that we used the RevMan calculator tool to obtain missing standard deviations from P values for the differences between means in the two groups (RevMan 2014).

Figures

Figure 1. Study flow diagram

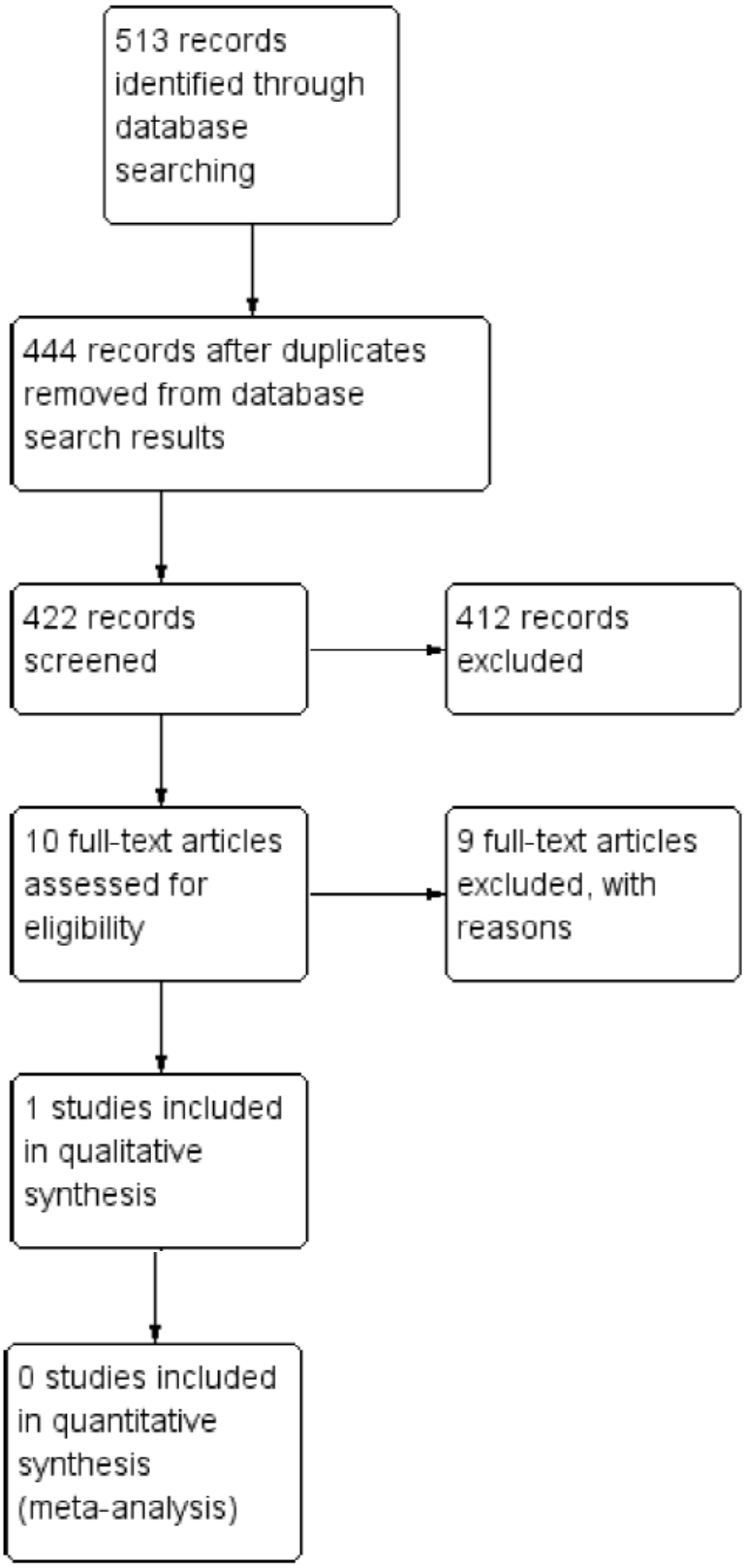


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for the oneincluded study. Green (+) = low risk of bias; red (-) = high risk of bias.