Respiratory muscle training for cervical spinal cord injury (Review)

Berlowitz D, Tamplin J

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2013, Issue 7

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Respiratory muscle training for cervical spinal cord injury (Review)
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Respiratory muscle training for cervical spinal cord injury

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Editorial group: Cochrane Injuries Group.
Review content assessed as up-to-date: 28 June 2013.


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ABSTRACT

Background
Cervical spinal cord injury (SCI) severely compromises respiratory function due to paralysis and impairment of the respiratory muscles. Various types of respiratory muscle training (RMT) to improve respiratory function for people with cervical SCI have been described in the literature. A systematic review of this literature is needed to determine the effectiveness of RMT (either inspiratory or expiratory muscle training) on pulmonary function, dyspnoea, respiratory complications, respiratory muscle strength, and quality of life for people with cervical SCI.

Objectives
To evaluate the efficacy of RMT versus standard care or sham treatments in people with cervical SCI.

Search methods
We searched the Cochrane Injuries and Cochrane Neuromuscular Disease Groups’ Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 1), MEDLINE, EMBASE, CINAHL, ISI Web of Science, PubMed, and clinical trials registries (Australian New Zealand Clinical Trials Registry, ClinicalTrials, Controlled Trials metaRegister) on 5 to 8 March 2013. We handsearched reference lists of relevant papers and literature reviews. We applied no date, language, or publication restrictions.

Selection criteria
All randomised controlled trials that involved an intervention described as RMT versus a control group using an alternative intervention, placebo, usual care, or no intervention for people with cervical SCI were considered for inclusion.

Data collection and analysis
Two review authors independently selected articles for inclusion, evaluated the methodological quality of the studies, and extracted data. We sought additional information from the trial authors when necessary. We presented results using mean differences (MD) (using post-test scores) and 95% confidence intervals (CI) for outcomes measured using the same scale or standardised mean differences (SMD) and 95% CI for outcomes measured using different scales.
Main results
We included 11 studies with 212 participants with cervical SCI. The meta-analysis revealed a statistically significant effect of RMT for three outcomes: vital capacity (MD mean end point 0.4 L, 95% CI 0.12 to 0.69), maximal inspiratory pressure (MD mean end point 10.50 cm/H\textsubscript{2}O, 95% CI 3.42 to 17.57), and maximal expiratory pressure (MD mean end point 10.31 cm/H\textsubscript{2}O, 95% CI 2.80 to 17.82). There was no effect on forced expiratory volume in one second or dyspnoea. We could not combine the results from quality of life assessment tools from three studies for meta-analysis. Respiratory complication outcomes were infrequently reported and thus we could not include them in the meta-analysis. Instead, we described the results narratively. We identified no adverse effects as a result of RMT in cervical SCI.

Authors’ conclusions
In spite of the relatively small number of studies included in this review, meta-analysis of the pooled data indicates that RMT is effective for increasing respiratory muscle strength and perhaps also lung volumes for people with cervical SCI. Further research is needed on functional outcomes following RMT, such as dyspnoea, cough efficacy, respiratory complications, hospital admissions, and quality of life. In addition, longer-term studies are needed to ascertain optimal dosage and determine any carryover effects of RMT on respiratory function, quality of life, respiratory morbidity, and mortality.

PLAIN LANGUAGE SUMMARY
Training the muscles used for breathing after a spinal cord injury
After an injury at a high point on the spinal cord (a cervical injury), the muscles responsible for breathing are paralysed or weakened. This weakness reduces the volume of the lungs (lung capacity), the ability to take a deep breath and cough, and puts them at greater risk of lung infection. Just like other muscles of the body, it is possible to train the breathing (respiratory) muscles to be stronger; however, it is not clear if such training is effective for people with a cervical spinal cord injury. This review compared any type of respiratory muscle training with standard care or sham treatments. We reviewed 11 studies (including 212 people with cervical spinal cord injury) and suggested that for people with cervical spinal cord injury there is a small beneficial effect of respiratory muscle training on lung volume and on the strength of the muscles used to take a breath in and to breathe air out and cough. No effect was seen on the maximum amount of air that can be pushed out in one breath, or shortness of breath. An insufficient number of studies had examined the effect of respiratory muscle training on the frequency of lung infections or quality of life, so we could not assess these outcomes in the review. We identified no adverse effects of training the breathing muscles for people with a cervical spinal cord injury.
### Summary of Findings for the Main Comparison

**Respiratory muscle training compared with control for cervical spinal cord injury**

**Patient or population:** cervical spinal cord injury  
**Settings:** hospital and community  
**Intervention:** RMT  
**Comparison:** control

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
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<td><strong>Dyspnoea</strong></td>
<td>The mean dyspnoea in the intervention groups was 0.10 standard deviations lower (1.65 lower to 1.44 higher)</td>
<td>58 (3 studies)</td>
<td>⊕⊕ ○ ○ low1,2</td>
<td>SMD 0.23 (-0.45 to 0.91)</td>
<td></td>
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<tr>
<td><strong>Vital capacity</strong></td>
<td>The mean vital capacity ranged across control groups from 1.4 to 2.7 L</td>
<td>108 (4 studies)</td>
<td>⊕⊕ ○ ○ low1,2,3</td>
<td>SMD 0.97 (0.02 to 1.93)</td>
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<tr>
<td><strong>Maximum inspiratory pressure</strong></td>
<td>The mean maximum inspiratory pressure ranged across control groups from 43 to 102 cm/H₂O</td>
<td>147 (8 studies)</td>
<td>⊕⊕ ○ ○ low1,2</td>
<td>SMD 0.03 (-0.37 to 0.44)</td>
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<tr>
<td><strong>Maximum expiratory pressure</strong></td>
<td>Follow-up: 6-12 weeks</td>
<td>The mean maximum expiratory pressure ranged across control groups from 41 to 91 cm/H2O</td>
<td>The mean maximum expiratory pressure in the intervention groups was 10.31 higher (2.80 to 17.82 higher)</td>
<td>151 (6 studies)</td>
<td>☓ ☓ ☓ low1,2,3</td>
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<td><strong>Forced expiratory volume in 1 second</strong></td>
<td>Follow-up: 6-12 weeks</td>
<td>The mean forced expiratory volume in 1 second ranged across control groups from 1.7 to 2.4 L</td>
<td>The mean forced expiratory volume in 1 second in the intervention groups was 0.05 higher (0.23 lower to 0.34 higher)</td>
<td>97 (4 studies)</td>
<td>☓ ☓ ☓ low1,2,3</td>
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<td><strong>Quality of life</strong></td>
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<td>Not estimable</td>
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<td>See comment</td>
<td>See comment</td>
<td>Not estimable</td>
<td>14 (1 study)</td>
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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RMT: respiratory muscle training; SMD: standardised mean difference

**GRADE Working Group grades of evidence**

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

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

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

**Very low quality:** We are very uncertain about the estimate.

1 High risk of attrition bias.
2 Inconsistency of results + small number of studies with small sample sizes.
3 Blinding and allocation concealment unclear.
BACKGROUND

Spinal cord injury (SCI) is damage to the spinal cord that results in a loss or impairment of function resulting in reduced mobility or sensation. When the spinal cord is injured, muscles below the level of injury become paralysed or impaired. Higher levels of injury cause greater impairment. In addition to paralysis of lower or upper limbs (or both), SCI may also affect respiratory function due to complete or partial paralysis of the respiratory muscles. The extent of the respiratory dysfunction is dependent on both the level of injury and the completeness of the lesion. Typically, paralysis of all muscles involved in respiration occurs with spinal cord lesions above C3. The phrenic nerve receives motor supplies from C3, C4, and C5, and, therefore, injury above C6 may impair diaphragm function.

Respiratory dysfunction resulting from SCI remains a major cause of morbidity, mortality, and economic burden (van den Berg 2010). It is the most common cause of death following SCI and contributes to higher mortality rates for people with SCI than the general population (DeVivo 1999). Alterations in the mechanical properties of the lungs and chest wall (particularly for people with cervical SCIs) results in paradoxical (out of phase) movement of the chest wall, and reduced lung and chest wall compliance (flexibility). This, in turn, leads to reduced breathing efficiency, reduced maximal static respiratory pressures, and reduced lung volumes. Impairment of the muscles of inspiration reduces vital capacity (VC), prevents deep breaths, and may lead to dyspnœa with exertion or collapse of the lungs (atelectasis), or both dyspnœa and collapse of the lungs (Cardozo 2007). Dysfunctional expiratory muscles impair cough and secretion clearance, increase airways resistance, and increase the susceptibility to and persistence of lower respiratory tract infections (Brown 2006). Total lung capacity (TLC) is usually reduced following SCI (due to impaired inspiratory musculature) and residual volume is relatively increased (due to impaired expiratory musculature and subsequent reduced expiratory reserve volume) (Liaw 2000). VC is the difference between TLC and residual volume and is, therefore, reduced following SCI.

Respiratory complications following SCI are common, with a particularly high reported prevalence of mucous retention, atelectasis, pneumonia, and respiratory failure (Fishburn 1990; Reines 1987). Thus, any intervention that improves respiratory function and thereby prevents or alleviates these conditions would be of great benefit to people with SCI.

Description of the condition

Respiratory dysfunction post SCI is characterised by weak or paralysed respiratory muscles, resulting in reduced lung volume, ineffective cough, increased respiratory tract infections, reduced chest wall compliance, and an increased oxygen cost of breathing (Brown 2006; Chen 1990). In particular, paralysis of intercostal and abdominal muscles causes a decrease in inspiratory volume during resting breathing, and the loss of expiratory force during cough (Alvarez 1981). This respiratory inefficiency also increases the risk of respiratory muscle fatigue, particularly when load is imposed on the muscles, as with pneumonia or obstruction of the airways (Fugl-Meyer 1984).

Description of the intervention

Respiratory muscle training (RMT) involves specific training of inspiratory, expiratory, or both, muscles to yield improvements in both strength and endurance. The respiratory muscles can be trained in a similar way to the limb muscles with devices that increase the load on the muscles. A training session typically consists of a certain number of exercise repetitions, or a particular length of time spent exercising. Training intensity is individually set at a percentage of the maximum measured respiratory strength, respiratory pressure, or ventilatory capacity, depending on the chosen technique.

Resistive training involves breathing through a small diameter hole (resistor), which limits available flow and thus increases ventilatory (training) load. Threshold training involves breathing with sufficient force to overcome a spring-loaded valve and enable airflow. Both resistive and threshold trainers typically involve a one-way valve system such that either the inspiratory or the expiratory muscles are trained selectively.

Normocapnic hyperpnoea is an alternative form of RMT that involves simultaneous training of inspiratory and expiratory muscles. The device used for normocapnic hyperpnoea training consists of a re-breathing bag (at 30% to 40% of the participant’s forced vital capacity) connected to a tube system and mouthpiece. Participants are instructed to fill and empty the bag completely with each breath. To avoid an increase in carbon dioxide, a small hole in the tube permits additional inspiratory and expiratory flow. The training load provided in hyperpnoea training results from high minute ventilation rather than high resistive loads as in resistive training. Singing training may also have positive effects on respiratory function in this population as the act of singing places significant demands on the respiratory system. In particular, singing requires strong and fast inspirations, extended, regulated expirations, and recruitment of accessory respiratory muscles. Therapeutic singing training was thus considered to constitute a form of RMT in this review.

How the intervention might work

For RMT to produce a significant effect, vigorous and forceful efforts within an intensive training regimen are usually needed. Research suggests that people with quadriplegia use accessory respiratory muscles (sternocleidomastoid for inspiration and pectoralis
major and latissimus dorsi for expiration) to improve performance during maximal effort tasks (Fujiwara 1999), and that the strength of these muscles improves with training (Estenne 1989).

The primary mechanisms that influence change of muscle strength during the first four weeks of training are neural adaptations, such as increased motor unit recruitment and synchronisation, and enhanced inter- and intra-muscle co-ordination (Sale 1988). These neural adaptations occur as a result of the ability of the central nervous system to respond to changes in functional demands. Training of other mechanisms beyond four weeks, such as peripheral or structural changes, may be responsible for further improvements in strength.

**Why it is important to do this review**

Respiratory complications are prevalent following SCI due to weakness of the respiratory muscles. It seems feasible that these muscles could be trained to increase in strength or endurance, or both. This review is needed to determine whether such training of the respiratory muscles is effective for people with cervical SCI, and if so, what are the best training techniques and methods to achieve improvements in respiratory function.

Previously, Brooks 2005, Sheel 2008, and Van Houtte 2006 attempted to review research systematically to evaluate the effect of RMT in people with SCI on respiratory muscle strength, endurance, and pulmonary function. These reviews focused on particular types of training, that is, inspiratory muscle training (Brooks 2005; Sheel 2008) and exercise training (Sheel 2008), and used different inclusion criteria, that is, randomised versus non-randomised designs (Brooks 2005). The three reviews reported that the included studies were too variable in terms of research design, participant characteristics, training techniques used, and outcomes measured, thus results could not be pooled for meta-analysis. Van Houtte 2006 concluded that RMT following SCI tended to improve expiratory muscle strength and VC, and decrease residual volume. However, Sheel 2008 excluded expiratory muscle training but reported some evidence for the efficacy of inspiratory muscle training and exercise training.

We believe that a systematic review of all types of RMT is needed in order to synthesise these disparate findings for people living with SCI, clinicians, and clinical researchers working in this area. First, the review will aim to establish the effect of any form of RMT on respiratory function for people with cervical SCI, and second, it will aim to provide methodological recommendations for future clinical research in this area.

**OBJECTIVES**

To assess the effects of RMT on function for people with cervical SCI.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**
We considered all randomised controlled trials (RCT) for inclusion.

**Types of participants**
We included studies involving people with any level of acquired cervical SCI, both acute and chronic. We excluded studies of RMT for people with inherited or congenital neuromuscular disorders, such as muscular dystrophies, congenital and acquired myopathies, and spinal muscular atrophy. We also excluded studies that investigated the effect of RMT on respiratory disorders not caused by SCI (such as chronic obstructive pulmonary disease and asthma).

**Types of interventions**
We considered trials for inclusion if the trial author(s) described an intervention as RMT and compared it with a control group using an alternative intervention, placebo, usual care, or no intervention. RMT may involve inspiratory or expiratory muscle training (including normocapnic hyperpnoea training and singing training), or both.

**Types of outcome measures**
We conducted a survey of 20 people with cervical SCI to identify their needs and determine outcome measures that were patient-focused. Consequently, the primary outcomes included respiratory complications, dyspnoea, and VC. Respiratory complications are defined clinically as when a person sought medical attention for a respiratory symptom and this was ‘confirmed clinically’ as a respiratory complication by objective data as decided by a physician. This is the definition of respiratory complications employed by Van Houtte 2008 and uses the GOLD criteria for acute exacerbations (Rodriguez-Roisin 2009). Secondary outcomes included measures of respiratory muscle strength (maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP)), forced expiratory volume in one second (FEV₁), and quality of life.

**Primary outcomes**

1. Respiratory complications
2. Dyspnoea
3. VC

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Secondary outcomes
1. MIP
2. MEP
3. FEV₁
4. Quality of life

Search methods for identification of studies
We did not restrict searches by date, language, or publication status.

Electronic searches
The Cochrane Injuries Group Trials Search Co-ordinator searched the following:
1. Cochrane Injuries Group's Specialised Register (6 March 2013);
2. CENTRAL (Issue 2, 2013);
3. MEDLINE (Ovid SP) (1946 to February week 3 2013);
4. PubMed (6 March 2013);
5. EMBASE Classic + EMBASE (Ovid SP) (1947 to 5 March 2013);
6. CINAHL Plus (EBSCO) (1937 to 6 March 2013);
7. ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 6 March 2013);
8. ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 6 March 2013).
Appendix 1 lists the search strategies used. Due to the paucity of trials in this area, we did not restrict our search by using a filter for RCTs but sought to identify all types of trials in order to identify those that we may have otherwise missed.

Searching other resources
We also searched the following trials registries:
1. Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/trialSearch.aspx) (8 March 2013);
2. ClinicalTrials (www.clinicaltrials.gov) (8 March 2013);
We sought further, potentially relevant, published and unpublished studies by checking reference lists of relevant papers and literature reviews. We communicated with trial authors to identify ongoing studies.

Data collection and analysis

Selection of studies
One review author (JT) scanned titles and abstracts of each record retrieved by the search and rejected obviously irrelevant references. When a title or abstract could not be rejected with certainty, both review authors obtained the full-text article and independently inspected the article. Both review authors used an inclusion criteria form to assess the trial's eligibility for inclusion. Review authors reported and resolved disagreements by discussion. We noted the reasons for excluding studies.

Data extraction and management
Both review authors independently extracted data using a data collection form (based on recommendations in the Cochrane Handbook for Systematic Reviews of Interventions) (Higgins 2011) and assessed the methodological quality of the selected articles. We resolved disagreement by discussion. Whenever possible, we contacted the author of each included trial to verify the accuracy of the data and, if possible, to obtain further data or information. One review author (JT) entered all trials included in this systematic review into Review Manager 5 (RevMan 2011). Both review authors independently conducted data analysis.

Assessment of risk of bias in included studies
We used The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011). This tool assesses the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. On each domain, the review authors made a judgement of low risk of bias ('Yes'), high risk of bias ('No'), or unclear risk of bias ('Unclear'). Both review authors independently assessed trial quality and agreement between review authors was measured. We assessed risk of bias in these domains as follows:

Sequence generation of the randomisation process
- Yes: using random-number tables, computer random number generation, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, or minimisation.
- No: sequence generation described, but is not one of the randomisation methods under 'Yes' above.
- Unclear: insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

Acceptability of allocation concealment
- Yes: allocation concealment was described, and would not allow either investigators or participants to know or influence treatment group assignment at the time of study entry.
- No: the method of allocation was not concealed (e.g. alternating participants, odd-even day) or one in which the investigators or participants could have been aware of allocation prior to study commencement.
- Unclear: trial either did not describe the method of allocation concealment, or reported an approach that was not clearly adequate.

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Blinding of outcome assessors
- **Yes**: blinding of outcome assessors was clearly maintained.
- **No**: outcome assessors were not blinded to treatment group assignment, or the blinding was incomplete.
- **Unclear**: insufficient information to permit judgement of ‘Yes’ or ‘No’.

Intention-to-treat (ITT) analysis
- **Yes**: specifically reported by the authors that ITT analysis was undertaken, or report that makes it unmistakable that ITT was undertaken, for the primary analysis.
- **No**: lack of ITT was confirmed on study assessment.
- **Unclear**: ITT analysis was mentioned, but it is uncertain from the report whether this was fully carried out.

Completeness of outcome data
- **Yes**: no missing outcome data, reason for missing data unlikely to be related to true outcome, or missing data imputed using appropriate methods.
- **No**: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups, or potentially inappropriate application of simple imputation.
- **Unclear**: insufficient reporting of attrition/exclusions to permit judgement of ‘Yes’ or ‘No’ (e.g. number randomised not stated, no reasons for missing data provided).

Selectiveness of outcome reporting
- **Yes**: the study protocol was available and all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; or the study protocol is not available but it is clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
- **No**: not all of the study’s prespecified primary outcomes were reported, one or more reported primary outcomes were not prespecified, or were reported incompletely so that they could not be included in a meta-analysis.
- **Unclear**: insufficient information to permit judgement of ‘Yes’ or ‘No’. It is likely that the majority of studies will fall into this category.

**Measures of treatment effect**
We anticipated that all outcomes measured in this review would be continuous variables. Thus, we calculated standardised mean differences (SMD) with 95% confidence intervals (CI) for outcome measures using the results from different scales and mean differences (MD) for results using the same scales.

Dealing with missing data
We considered an ITT analysis adequate when the numbers of people who dropped out and the reasons why they dropped out were reported. Where data were missing, we attempted to contact the author(s) of the trial to obtain the missing data. We analysed only the available data (without imputing missing data).

**Assessment of heterogeneity**
We calculated pooled estimates of treatment effect differences using the fixed-effect model (unless there was substantial heterogeneity) and calculated 95% CI for each effect size estimate. Levels of heterogeneity were determined using the I^2 statistic (I^2 greater than 50% was considered substantial heterogeneity) (Higgins 2011). If we found that heterogeneity was present, we used the random-effects model for the meta-analysis and explored and presented possible causes for the heterogeneity. We also used visual inspection of the forest plots to assess heterogeneity.

**Assessment of reporting biases**
We created funnel plots to explore possible publication bias.

**Data synthesis**
For continuous variables, we calculated MD and 95% CIs for each study. We pooled all similar studies using MD and 95% CIs.

**Subgroup analysis and investigation of heterogeneity**
Due to the anticipated small number of trials available for systematic review, we planned only one a priori subgroup analysis, which was for acute (less than one year) versus chronic cervical SCI participants. We conducted dose-response analyses where possible to determine any relationship between treatment intensity or duration and an intervention effect.

**Sensitivity analysis**
We performed sensitivity analyses based on the methodological quality of the included studies. The analyses examined the effect of excluding studies that either failed to report or did not include evidence of concealed allocation, blinding of outcome assessments, and analyses performed on an ITT basis.

**R E S U L T S**
**Description of studies**
See: Characteristics of included studies; Characteristics of excluded studies.
Results of the search

The database searches identified 843 citations. After duplicates and animal studies were removed, 747 citations remained. We screened the abstracts of these 747 citations and retrieved 40 full-text references for possible inclusion based on titles and abstracts. In several cases, we contacted chief investigators to obtain additional information on study details and data. We examined the reference lists of these 40 papers for possible additional studies to include. This generated a further six studies. Three of the 40 studies were not written in English. A native speaker of the language that the paper was written in screened these three studies against the inclusion criteria. As none of these met the inclusion criteria, we deemed that full-text translations were unnecessary.

Following full-text review of the remaining 37 studies, we excluded a further 25 studies. Reasons for exclusion are detailed in the Characteristics of excluded studies table. Initial disagreement between authors occurred with three studies and this was resolved through discussion and consensus. Twelve publications of 11 studies met all the inclusion criteria and were included in the review. Figure 1 shows a study flow diagram.
Figure 1. Flow diagram.

843 records identified through database searching
6 records identified through other sources

799 records after duplicates removed

747 records after animal studies removed

747 records screened
708 records excluded

28 articles excluded:
- 3 not randomised trials;
- 3 ineligible populations;
- 4 not respiratory muscle training intervention

40 full-text articles assessed for eligibility

Included: 12 reports of 11 studies (2 with multiple comparison groups)
- 6 RMT vs. standard care
- 3 RMT vs. sham treatment
- 3 RMT vs. other treatment

Number of trials per outcome
- 1 Respiratory complications
- 4 Dyspnoea
- 6 Vital capacity
- 8 Maximal inspiratory pressure
- 7 Maximal expiratory pressure
- 5 Forced expiratory volume in 1 second
- 4 Quality of life

9 studies included in meta-analysis
Reasons for exclusion: raw data from 2 studies was not able to be obtained for meta-analysis
Included studies

We included 11 studies with 212 participants in this review. These studies examined the effects of RMT on physiological and psychological outcomes in people with cervical SCI. The majority of participants were male (82%). Four studies were from the USA (Derrickson 1992; Litchke 2008; Litchke 2010; Roth 2010), with one each from Canada (Loveridge 1989), Australia (Tamplin 2013), Belgium (Van Houtte 2008), Switzerland (Mueller 2013), Taiwan (Liaw 2000), Slovenia (Zupan 1997), and South Africa (Gounden 1990). Not all studies measured every outcome identified for this review. Two studies utilised a three-way comparison between two different RMT interventions and control condition (Litchke 2010; Mueller 2013). To enable both training interventions to be included in the meta-analysis, these have been listed as Mueller 2013 (A) and (B) and Litchke 2010 (A) and (B) in the data analysis. Completed details of all included studies are provided in the Characteristics of included studies table. Below is a brief summary of the 11 included studies.

Design

All studies had an RCT design. One study had a cross-over design (Zupan 1997), and in the remaining 10 studies there were four comparisons between RMT and an alternative intervention and seven comparisons between RMT and a control condition (three sham treatments and four ‘usual care’). Studies were conducted in hospital (N = 6) and community (N = 4) settings (and one study recruited from both). Sample sizes ranged from nine to 40 participants with injury levels ranging from C4 to C8. Two studies also included participants with thoracic level injuries (Roth 2010; Van Houtte 2008) and two with non-traumatic SCI (Litchke 2008; Litchke 2010). Testing position was not consistent across the included studies. Two studies tested participants in the supine position (Derrickson 1992; Liaw 2000), six studies tested participants when sitting upright (Litchke 2008; Litchke 2010; Mueller 2013; Roth 2010; Tamplin 2013; Van Houtte 2008), two studies tested in both positions (Gounden 1990; Zupan 1997), and testing position was not able to be determined for one study (Loveridge 1989) (see Table 1). Testing with an abdominal binder has been reported to deliver a similar result as testing in the supine position for people with cervical SCI (Estenne 1987). Of the six studies that tested participants in a seated position, only two confirmed that an abdominal binder was not used (Mueller 2013; Tamplin 2013).

Interventions

Two of the included studies compared two RMT interventions with a control condition (Litchke 2010; Mueller 2013). Mueller 2013 compared inspiratory resistance training and isocapnic hyperpnoea training versus a placebo condition (incentive spirometry). To enable clear comparison of interventions, the inspiratory resistance training comparison is referred to as Mueller 2013 (A) and the isocapnic hyperpnoea comparison is referred to as Mueller 2013 (B). Litchke 2010 compared concurrent flow resistance training and concurrent pressure threshold resistance training to a usual care control condition. The concurrent flow resistance training comparison is thus referred to as Litchke 2010 (A) and concurrent pressure threshold resistance training as Litchke 2010 (B). Five studies used an inspiratory muscle resistance training intervention (Derrickson 1992; Liaw 2000; Loveridge 1989; Mueller 2013 (A); Zupan 1997) and three studies used an expiratory muscle resistance training intervention (Gounden 1990; Roth 2010; Zupan 1997). In these studies, resistive muscle training devices were used. Five studies used an intervention described as simultaneous training of both inspiratory and expiratory muscle function (Litchke 2008; Litchke 2010; Mueller 2013 (B); Tamplin 2013; Van Houtte 2008). Van Houtte 2008 and Mueller 2013 (B) used normocapnic or isocapnic hyperpnoea and Tamplin 2013 used singing training. Training intensity ranged from 10 to 60 minutes per day, three to seven days per week, and the training length ranged from four to 12 weeks (mean eight weeks).

We could not pool the data of two studies with the other studies because outcomes were presented as percentages of predicted normal values rather than raw scores (Loveridge 1989; Zupan 1997). In addition, there were no common outcomes between these two studies that could enable comparison of percentage of predicted scores. We were unable to contact the authors of these studies to obtain raw data. Thus, we only included the data from these studies in narrative form in this review.

Excluded studies

We excluded 25 studies because they were not RCTs. Of these 25 studies, three did not use a RMT intervention, and three did not recruit only participants with cervical SCI. The reasons for exclusion are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

Figure 2 and Figure 3 show a summary of risk of bias judgements for all included studies. Risk of bias is detailed for each study in the risk of bias tables included with the Characteristics of included studies table.
Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
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<th>Selective reporting (reporting bias)</th>
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<td>?</td>
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<td>?</td>
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<tr>
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</table>
Allocation
Only two studies (18%) described adequate allocation concealment (Tamplin 2013; Van Houtte 2008).

Blinding
Only four studies (36%) described blinding of participants and assessors (Mueller 2013; Roth 2010; Tamplin 2013; Van Houtte 2008).

Incomplete outcome data
We classified six of the included studies (55%) as having a high risk of incomplete outcome data (Derrickson 1992; Liaw 2000; Litchke 2008; Litchke 2010; Mueller 2013; Roth 2010). This risk was attributable to a failure to report outcome data for participants who were recruited but did not complete the study. The dropout rate was 0% for five of the trials and between 8% and 73% for the remaining six trials.

Selective reporting
We classified only one study (9%) as selectively reporting results (Gounden 1990). In this study, MIP was measured at baseline, but no post assessment measures of MIP were presented.

Other potential sources of bias
We identified no other potential sources of bias.

Effects of interventions
See: Summary of findings for the main comparison Respiratory muscle training compared with control for cervical spinal cord injury
See: Summary of findings for the main comparison for the main comparison of RMT versus control.

Primary outcomes
Although most outcomes were reported using the same measures or scales, most studies did not provide change score standard deviations. Thus, we conducted the meta-analysis using mean post-test scores for control and intervention groups. Although this meant that we could not account for baseline scores between groups and between studies, random allocation should account for any baseline differences.

Respiratory complications
Only one study reported on respiratory complications that occurred during the trial (Van Houtte 2008). In this study, 14 episodes of respiratory complications were reported for the control group and one episode for the RMT group.

Dyspnoea
Three studies reported dyspnoea outcomes (Liaw 2000; Mueller 2013; Van Houtte 2008). Two studies used different versions of the Borg scale (the original Borg scale has 15 points whereas the modified has only 10 points) (Liaw 2000; Van Houtte 2008), and one study used a 10-point visual analogue scale (Mueller 2013). Thus, we used SMDs to compare dyspnoea outcomes. On each scale, a higher score equated to worse dyspnoea. The pooled estimate of the four data sets from these three studies found no significant effect of RMT on reported dyspnoea (SMD -0.10, 95% CI -1.65 to 1.44, P value = 0.89). A random-effects model was applied due to the high level of heterogeneity between the three studies ($I^2 = 81\%$) (Analysis 1.1).

Vital capacity
The pooled estimate of four studies examining five data sets (Gounden 1990; Liaw 2000; Mueller 2013 (A); Mueller 2013 (B); Tamplin 2013) indicated that RMT significantly increased VC (MD mean end point 0.4 L, 95% CI 0.12 to 0.69, P value = 0.006; $I^2 = 0\%$) (Analysis 1.2). In the included studies, the mean control VC ranged from 1.4 to 2.7 L. As such, an improvement of 0.40 L represents approximately a 15% to 30% improvement.

Secondary outcomes
Maximal inspiratory pressure
MIP was measured in nine trials (11 data sets; Derrickson 1992; Liaw 2000; Litchke 2008; Litchke 2010 (A); Litchke 2010 (B); Loveridge 1989; Mueller 2013 (A); Mueller 2013 (B); Roth 2010; Tamplin 2013; Van Houtte 2008). All respiratory pressures are expressed as absolute values (e.g. MIP is positive not negative). As discussed previously, the data from Loveridge 1989 could not be included in the meta-analysis because raw scores were not presented. The pooled estimate of the 11 data sets included in the meta-analysis indicated a significant effect of RMT on MIP (MD mean end point 10.66 cm/H$_2$O, 95% CI 3.59 to 17.72, P value = 0.003; $I^2 = 0\%$) (Analysis 1.3). In the included studies, the mean control MIP ranged from 43 to -102 cm/H$_2$O. As such, an improvement of 10 cm/H$_2$O represents approximately a 10%
to 25% improvement. The Derrickson 1992 study used another form of inspiratory muscle training (abdominal weights training) as a control condition rather than standard care, no intervention, or sham training. As such, this could represent a potential bias for the meta-analysis. A post-hoc sensitivity analysis excluding the data from this study did not significantly alter the result (MD mean end point 9.47 cm/H$_2$O, 95% CI 8.28 to 59.72, P value = 0.02; $I^2$ = 6%). Loveridge 1989 also reported greater improvements in MIP for the RMT group versus control; however, these improvements did not achieve statistical significance.

Maximal expiratory pressure
Six studies (seven data sets) examined the effect of RMT on MEP (Gounden 1990; Liaw 2000; Mueller 2013 (A); Mueller 2013 (B); Roth 2010; Tamplin 2013; Van Houtte 2008). The pooled estimate of these studies indicated a significant intervention effect (MD mean end point 10.31 cm/H$_2$O, 95% CI 2.80 to 17.82, P value = 0.007; $I^2$ = 42%). In the included studies, the mean control MEP ranged from 41 to 91 cm/H$_2$O. As such, an improvement of 10 cm/H$_2$O represents approximately a 10% to 25% improvement.

Forced expiratory volume in one second
The pooled estimate of four studies examining FEV$_1$ indicated no strong effect of RMT (MD mean end point 0.05 L, 95% CI -0.23 to 0.34, P value = 0.70; $I^2$ = 0%) (five data sets: Liaw 2000; Mueller 2013 (A); Mueller 2013 (B); Roth 2010; Tamplin 2013).

Quality of life
Quality of life outcomes were reported for four studies (Litchke 2010; Mueller 2013; Tamplin 2013; Van Houtte 2008). However, different instruments were used for each of these studies. Litchke 2010 found that RMT improved some aspects of health-related quality of life for wheelchair rugby athletes with cervical SCI. Specifically, they found perceived increases on the vitality domain of the SF-36v2 and decreases on the bodily pain domain. We found no significant differences for the remaining six domains: physical functioning, role physical, role emotional, social functioning, general mental health, and general health perceptions. Mueller 2013 found no statistically significant changes in quality of life outcomes after inspiratory resistance training compared with sham training; however, they demonstrated high positive effect sizes for the physical component of the generic SF-12 assessment (but not for the mental component). Tamplin 2013 found no significant changes in quality of life as measured by the generic Assessment of Quality of Life tool following a therapeutic singing intervention. Van Houtte 2008 found a significant improvement in disorder-specific Index of Pulmonary Dysfunction for the experimental group (P value = 0.03). It was not possible to conduct a meta-analysis of the quality of life outcome data because of the diversity of instruments and subscales used between studies.

Sensitivity analyses
We conducted sensitivity analyses based on the methodological quality of the included studies. The analyses examined the effect of excluding studies that either did not report or did not include evidence of concealed allocation, blinding of outcome assessments, and analyses performed on an ITT basis. In some cases, this meant that we removed all but one study from the analysis and, therefore, meta-analysis was impossible. After removing the two studies with a high risk of attrition bias (Liaw 2000; Roth 2010), a stronger effect was found for both MIP (MD mean end point 14.17 cm/H$_2$O, 95% CI 5.85 to 22.49, P value = 0.0008) and MEP (MD mean end point 17.35 cm/H$_2$O, 95% CI 7.42 to 27.27, P value = 0.0006).

Subgroup analyses
We conducted subgroup analyses only on outcomes that had data from more than three trials (MIP and MEP). When we included studies with only acute (less than one year) participants in the analysis (Derrickson 1992; Liaw 2000; Mueller 2013 (A); Mueller 2013 (B); Roth 2010; Van Houtte 2008), the effect on MEP was minimal but the studies were more heterogeneous (MD mean end point 9.99 cm/H$_2$O, 95% CI 1.79 to 18.28, P value = 0.02; $I^2$ = 43%). There was no significant effect on MEP for studies with only acute participants (MD mean end point 5.95 cm/H$_2$O, 95% CI -3.39 to 15.28, P value = 0.21; $I^2$ = 33%). It was difficult to conduct dose-response analyses due to the small number of studies in the meta-analysis for each outcome. We confirmed no relationship between treatment intensity and an intervention effect. We conducted subgroup analyses on MIP and MEP outcomes to determine any relationship between treatment duration (greater than eight weeks) and an intervention effect. When we included only studies with a duration of less than eight weeks in the meta-analysis of MIP and MEP, there was no longer a significant effect of RMT. However, this is probably because only two or three studies were included (Derrickson 1992; Liaw 2000; Roth 2010), thus increasing heterogeneity.

DISCUSSION
The results of the meta-analyses indicate that RMT may increase VC and maximal respiratory pressures (MIP and MEP) for people with cervical SCI. The findings overall are conservative due to the small number of included studies in the meta-analysis (N = 9), and the small sample sizes in these studies (n = nine to 40). The inability to use change scores makes the meta-analyses sensitive to baseline differences. Although in theory, randomisation should
adequately deal with baseline differences, it may not when there are so few studies with small sample sizes. In addition, the measures themselves are variable. There was a high co-efficient of variation for MIP, MEP, and VC in the able-bodied and even more so in the cervical SCI population with a range of injury levels and severity (ATS/ERS 2002; ATS/ERS 2005). This increased ‘measure-specific’ variability and the consequent larger standard deviation of summary effect estimates reduced the power of smaller studies to find statistically significant treatment effects. Further, the inclusion of a range of different training mechanisms in this review should be acknowledged. Subgroup analyses according to training type were not feasible due to the small number of included studies. Despite these limitations, the current meta-analysis revealed a significant treatment effect for these outcomes (MIP, MEP, and VC), suggesting that training improves measures of respiratory function after cervical SCI.

Summary of main results

The meta-analyses indicated an effect of RMT on VC and respiratory muscle strength (MIP and MEP). However, the small number of studies (with limited sample sizes) (Goudenhooi 1990; Liaw 2000; Mueller 2013; Tamplin 2013), that reported VC data warrant cautious interpretation of the findings in this variable and further research is needed. The respiratory muscle strength (MIP and MEP) results are more reliable due to the greater number of included studies reporting these outcomes. The meta-analysis did not provide evidence for the effect of RMT on FEV₁ (P value = 0.69).

Of the two studies assessing dyspnoea that could be combined for the meta-analysis, one found an SMD favouring the intervention group (Van Houtte 2008), and the other found no difference between groups (Liaw 2000). However, the raw data from the Van Houtte 2008 study indicated minimal change in dyspnoea scores over time for either group, whereas the data from the Liaw 2000 study indicated a significant difference between groups in improvement on dyspnoea scores. Mueller 2013 found a high effect size on dyspnoea following isocapnic hyperpnoea training. Mueller 2013 also found an improvement in quality of life as measured by the physical component of the SF-12, and Van Houtte 2008 found a significant improvement on the Index of Pulmonary Dysfunction for the experimental group (P value = 0.03). Litchke 2010 found increases in vitality and decreases in bodily pain. In contrast, Tamplin 2013 observed no significant changes in quality of life by using the Assessment of Quality of Life. The study that captured data on respiratory complications (Van Houtte 2008), reported a much lower incidence of respiratory complications in the group that received RMT in comparison to a control group. The limited number of studies with small sample sizes makes it difficult to draw any strong conclusions about the effect of RMT on these more functional outcomes (dyspnoea, quality of life, and respiratory complications).

Overall completeness and applicability of evidence

This review included 11 studies with 212 participants. In addition, we checked reference lists of relevant papers and literature reviews. We contacted trial authors to request additional data and study information where necessary. Overall, the quality of reporting risk of bias was poor. Only four studies reported the method of randomisation (Derrickson 1992; Mueller 2013; Roth 2010; Tamplin 2013), and four studies provided details regarding allocation concealment or blinding, or both (Mueller 2013; Roth 2010; Tamplin 2013; Van Houtte 2008). We had to contact most study authors to gain additional methodological and statistical information.

It is important to note that we deliberately included a number of different types of RMT in this review. These included: inspiratory muscle training, expiratory muscle training, and techniques that trained both expiratory and inspiratory muscles, including isocapnic hyperpnoea and therapeutic singing. In addition, the ‘control’ conditions to which these interventions were compared included: no training, usual care, sham training, and alternate interventions. Interestingly, the Mueller 2013 study data have provided support for their hypothesis that low training volumes at higher intensities can improve respiratory muscle strength. Further research is needed on this type of RMT as it has great potential to affect motivation and training compliance positively.

Quality of the evidence

All included studies explicitly stated that randomisation was used, but allocation concealment was unclear in eight of the 11 studies and blinding was unclear in seven studies. Further, six of the included studies had a high risk of attrition bias. We conducted sensitivity analyses to determine the effect when these high-risk studies were excluded. We found a stronger effect for MIP and MEP as a result of these sensitivity analyses.

Potential biases in the review process

Lack of available data on the standard deviations of the change scores made it difficult to account for baseline differences. This may have altered the estimate of the overall effect size for the intervention. In cervical SCI, respiratory function measures may be substantially affected by both the position in which the tests are performed and the presence or not of an abdominal binder. For example, an increase in VC is observed in cervical SCI when changing from the seated to the supine posture. This is the opposite to that which is observed in able-bodied people and, moreover, this postural dependence can be ameliorated when the abdomen is tightly supported by elastic straps or a binder (Hart 2005). The position in which respiratory function and strength was measured varied...
across the 11 studies and while likely, it was uncertain whether testing position and abdominal binder use was standardised within each study (Table 1). Data for meta-analysis was restricted to end scores (rather than change) and, as such, there was a risk of bias attributable to position in the estimates of the magnitude of treatment effects that may not have been accounted for in our analyses. Sensitivity analyses examining position were not selected a priori in this review and are also not reported due to an insufficient number of studies per outcome.

Agreements and disagreements with other studies or reviews
Similar to reports from previous reviews (Brooks 2005; Sheel 2008; Van Houtte 2006), this review provided no conclusive findings for a number of reasons. Although this topic of RMT has received considerable interest in the research literature, few publications met the standards of methodological rigour for inclusion in this review. Furthermore, the small number of studies that were included were heterogeneous in terms of research design, participant characteristics, training techniques, and comparison conditions used. The systematic review by Van Houtte 2006 found trends towards improvement following RMT on VC and MEP (which were supported by this Cochrane review), but insufficient support for the effect of MIP, quality of life, and respiratory complications in SCI. The systematic review by Sheel 2008 indicated some evidence that inspiratory muscle training could improve respiratory function and decrease dyspnoea. The current review provides further support for the effect of RMT on respiratory function (MIP, MEP, and VC).

AUTHORS’ CONCLUSIONS

Implications for practice
The results of this review suggest that respiratory muscle training (RMT) can improve vital capacity and respiratory muscle strength (maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)) for people with cervical spinal cord injury (SCI). However, the effect size for all three outcomes was small and there was no evidence of carryover beyond the training period. It is interesting that despite the significant and often reported effect of respiratory dysfunction on health-related quality of life for people with cervical SCI, few studies have examined the effect of RMT on functional outcomes such as dyspnoea, cough efficacy, respiratory complications, hospital admissions, or quality of life.

Implications for research
More large-scale studies are needed to examine the effect of RMT on respiratory and quality of life outcomes for people with cervical SCI further. In particular, the effects of RMT on dyspnoea, incidence of respiratory complications, and quality of life were not often reported and need to be assessed in future studies. Also, the effect of RMT on standard respiratory function outcomes also needs further study as results of our meta-analysis are currently conservative. In addition, more studies are needed to ascertain a dosage effect and longer-term follow-up studies will assist in determining any carryover effects of training. Without long-term studies, it is impossible to determine effects of RMT on quality of life, respiratory morbidity, and mortality.

ACKNOWLEDGEMENTS
The authors would like to thank the following people for valuable help with the translation of trial reports:

- Dr Charlotta Karner, systematic reviewer, Cochrane Airways Group;
- Prof Ian Roberts, Professor of Epidemiology & Public Health, Cochrane Injuries Group;
- Dr Vasilii V. Vlassov, President, Society for Evidence Based Medicine, Russia.

REFERENCES

References to studies included in this review
Derrickson 1992  [published data only]

Gounden 1990  [published data only]

Liaw 2000  [published data only]

Litchke 2008  [published data only]
Litchke LG, Russian CJ, Lloyd KL, Schmidt EA, Price L, Walker JL. Effects of respiratory resistance training with a concurrent flow device on wheelchair athletes. Journal of
Litchke 2010 [published data only]

Mueller 2013 [published data only]

Roth 2010 [published data only]
Roth EJ, Stenson KW, Powley S, Oken J, Primack S, Crane 1994 [published data only]

Ehrlich 1999 [published data only]

Epifanov 1987 [published data only]

Estrup 1986 [published data only]

Fugl-Meyer 1972 [published data only]

Goosey-Tolfrey 2010 [published data only]

Gross 1980 [published data only]

Hornstein 1986 [published data only]

Imamura 1997 [published data only]

Lee 2012 [published data only]

Lerman 1987 [published data only]
Lin 1999 (published data only)

Lin 2001 (published data only)

Metcalf 1966 (published data only)

Moreno 2012 (published data only)

Moreno 2013 (published data only)

Nygren-Bonnier 2009 (published data only)

Rutchik 1998 (published data only)

Sapienza 2006 (published data only)

Sutbeyaz 2005 (published data only)

Uijl 1999 (published data only)

Valent 2009 (published data only)

Walker 1987 (published data only)

Wang 2002 (published data only)

Additional references

ATS/ERS 2002

ATS/ERS 2005

Brooks 2005

Brown 2006

Cardozo 2007

Chen 1990

DeVivo 1999

Estenne 1987

Estenne 1989
**Fishburn 1990**

**Fugl-Meyer 1984**

**Fujiwara 1999**

**Hart 2005**

**Higgins 2011**

**Reines 1987**

**RevMan 2011**

**Rodriguez-Roisin 2009**

**Sale 1988**

**Sheel 2008**

**van den Berg 2010**

**Van Houtte 2006**

* Indicates the major publication for the study
**CHARACTERISTICS OF STUDIES**

**Characteristics of included studies [ordered by study ID]**

**Derrickson 1992**

| Methods          | RCT  
|------------------|-----  
|                  | Randomisation method: table of random numbers |  

| Participants     | 11 acute inpatients with C4-C7 complete quadriplegia (9 males, 2 females), aged 16-41 years, USA |  

| Interventions    | **Inspiratory resistance muscle training** (continuous for 15 min/day) vs. **abdominal weights training** (10 breaths x 4). The inspiratory resistance group initially trained with least amount of resistance. Resistance increased when participant was able to complete 3 consecutive sessions of continuous breathing for 15 min. Abdominal weights training used the maximum weight that did not alter IC and required 4 x 10 maximal inspirations, holding each breath for several seconds. **Training intensity**: 2 x daily (5 days/week) for 7 weeks |  

| Outcomes         | FVC, MVV, PEFR, PI$_{max}$ (also known as MIP), and IC were measured pre and post intervention |  

| Notes            | No 'control' group, likely post randomisation withdrawal not reported |  

**Risk of bias**

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<th>Bias</th>
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<th>Support for judgement</th>
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<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>40 participants met admission criteria, but only 11 full sets of data reported (dropout rate of 73%)</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
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</table>
### Gounden 1990

**Methods**

RCT

Randomisation method: not specified

**Participants**

40 inpatients and outpatients with C5-C7 quadriplegia (32 males, 8 females), aged 16-64 years, South Africa

**Interventions**

**Expiratory muscle training** (progressive resistive loading) vs. **no training**. Experimental group trained using the PFLEX Inspiratory Muscle Trainer® and expired against a resistance set at 60% of maximal expiratory mouth pressure

Training intensity: 5-8 min x 5 daily (6 days/week) for 8 weeks

**Outcomes**

MEP, VC

**Notes**


### Risk of bias

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### Liaw 2000

**Methods**

RCT

Randomisation method: not specified

**Participants**

20 inpatients with C4-C7 complete quadriplegia at least 6 months post injury (16 males, 4 females), aged 16-52 years, Taiwan

**Interventions**

**Resistive inspiratory muscle training** vs. **usual care**. Initially trained with at lowest resistance setting. Resistance level increased when participant able to complete 3 consecutive sessions of continuous breathing

Training intensity: 15-20 min x 2 daily (12-16 breaths/min) for 6 weeks

**Outcomes**

FVC, FEV₁, PEFR, VC, TLC, RV, RV/TLC, FRC, VE, MIP, MEP, and dyspnœa (Borg scale) were measured pre and post intervention
### Liaw 2000  *(Continued)*

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</tr>
<tr>
<td><strong>Bias</strong></td>
<td><strong>Authors’ judgement</strong></td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Litchke 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT with block randomisation (matched by lesion level or track rating, or both)  Randomisation method: not specified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>9 wheelchair athletes with C5-T12 SCI (1 neuro disorder, 1 postpolio). All males aged 21-49 years, USA</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Respiratory resistance training (inspiratory and expiratory) + usual exercise vs. usual exercise only.</strong> Participants instructed to inhale slowly and deeply through the concurrent flow resistance device, hold their breath for 2 seconds, exhale until almost out of air, then forcefully blow out as much of the remaining residual air as possible. This sequence was repeated up to 10 times with 10-20 seconds of rest between each sequence. Respiratory resistance was increased by 1 level when able to complete 1 set of 10 without experiencing respiratory fatigue, dizziness, or light-headedness  <strong>Training intensity:</strong> (set of 10) 3 x daily for 10 weeks</td>
</tr>
<tr>
<td>Outcomes</td>
<td>MIP, MVV, and VO$_2$ peak were measured pre and post intervention</td>
</tr>
<tr>
<td>Notes</td>
<td>Only 5 of 9 subjects fit inclusion criteria for this review</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th><strong>Bias</strong></th>
<th><strong>Authors’ judgement</strong></th>
<th><strong>Support for judgement</strong></th>
</tr>
</thead>
</table>
### Litchke 2008

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Data not reported for 1 participant who withdrew from the study (dropout rate of 11%)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>

### Litchke 2010

#### Methods
- **RCT**
- Randomisation method: not specified

#### Participants
- 16 wheelchair athletes with C5-C7 quadriplegia (11 complete, 11 incomplete, 1 spastic cerebral palsy, 1 congenital deformities). All male, aged 18-50 years, USA

#### Interventions
- **Concurrent flow resistance** (1 set of 10 breaths) vs. **concurrent pressure threshold resistance** (3 sets of 10 breaths) vs. **no training**. The flow resistance training consisted of inhaling slowly and deeply through the concurrent flow resistance device, holding breath for 2-5 seconds, exhaling until almost out of air, then forcefully blowing out as much of the remaining residual air as possible. This sequence was repeated up to 10 times with 10-20 seconds of rest between each sequence.
- The pressure resistance training consisted of inhaling fully and forcefully through the concurrent pressure resistance device for 3 seconds (completely filling the lungs), holding breath for 1-2 seconds, exhaling fully and forcefully through the device (completely emptying the lungs), and pausing for 1-2 seconds. For both conditions, respiratory resistance was increased by 1 level when able to complete 1 set of 10 without experiencing respiratory fatigue, dizziness, or light-headedness.
- **Training intensity**: 3 times daily for 9 weeks

#### Outcomes
- MVV, MIP, and 1-mile time trial performance were measured pre and post intervention

#### Notes
- **Risk of bias**
### Litchke 2010 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Data reported only for 16 participants who completed the study (24 were initially recruited) - dropout rate of 33%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>

### Loveridge 1989

**Methods**

RCT  
Randomisation method: not specified

**Participants**

12 outpatients with C6-C7 complete quadriplegia, aged 22-49 years, Canada

**Interventions**

**Inspiratory resistance training vs. no treatment.** Participants trained with an inspiratory resistance device at 85% of their SIP at normal resting flow rates  
**Training intensity:** 15 min twice daily (5 days/week) for 8 weeks

**Outcomes**

MIP, SIP, TLC, RV, FRC, IC, FVC, and breathing frequency were measured every 2 weeks from baseline

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>
### Methods

RCT

### Participants

24 participants with C5-C8 complete quadriplegia, aged 22-58 years, Switzerland

### Interventions

- **Inspiratory resistance training vs. isocapnic hyperpnoea vs. placebo (incentive spirometry).** Inspiratory resistance training utilised an electronic inspiratory threshold device with visual feedback of achieved resistance. Participants were instructed to inhale with maximal inspiratory power during each of the 90 repetitions. Inhalations with less than 80% of the individual maximal inspiratory power had to be repeated. Isocapnic hyperpnoea utilised a device allowing intensive hyperventilation by partial re-breathing of ventilated air, supported by visual and acoustic feedback of breathing volume and frequency. Participants had to hyperventilate for 10 min continuously at 40-50% of their individual MVV. Intensity was increased by increasing breathing frequency by 1 breath/min every second or third training session. Placebo involved ‘volume training’ with an incentive spirometer, inhaling 16 times from RV to TLC with 30-40 seconds of rest in between repetitions.

**Training intensity:** 4 x 10 min/week for 8 weeks

### Outcomes

TLC, RV, ERV, FEV₁, PEF, MVV, PImax (also known as MIP), PEMax (also known as MEP), voice loudness and sustain time, subjective ability to cough, clear secretions, blow one’s nose, and breathlessness during exercise, as well as physical and mental quality of life were measured pre and post intervention.

### Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>Sham treatment used for control group. Assessors blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>2 dropouts reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>
### Methods

RCT  
Randomisation method: based on medical record number

### Participants

29 acute inpatients with C4-T1 complete SCI < 6 months post injury (22 males, 7 females), aged 16-60 years, USA

### Interventions

**Expiratory muscle resistance training** vs. **sham**. The training group exhaled quickly and forcefully through a high-pressure gauge providing resistance to expiration. The sham group exhaled forcefully through the same device but with no pressure gauge and thus no resistance. Each participant performed 10 repetitions without resting between breaths  
**Training intensity**: 2 x 10 repetitions daily (5 days/week) for 6 weeks

### Outcomes

FVC, FEV\textsubscript{1}, MEP, MIP, IC, ERV, TLC, FRC, and RV were measured pre and post intervention

### Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>The randomisation allocations were made by an investigator who had no contact with any of the subjects and who had no knowledge of the any of the subjects’ demographic or injury characteristics</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Sham treatment used for control group. Assessors blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Data reported only for 29 participants who completed the study (52 were initially recruited) - dropout rate of 42%</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>
### Tamplin 2013

| Methods | RCT with block randomisation (matched by history of tracheostomy)  
Randomisation method: computer-generated table of random numbers |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>24 participants with C4-C8 quadriplegia (ASIA A or B), aged 27-70 years, Australia</td>
</tr>
</tbody>
</table>
| Interventions | **Singing training** vs. **music appreciation**. Singing training included oral motor and respiratory exercises, vocal warm-ups, and singing familiar songs. Music appreciation included song sharing and discussion, musical games, and music-assisted relaxation  
**Training intensity**: 1 hour daily (3 days/week) for 12 weeks |
| Outcomes | FVC, FEV\(_1\), FEV\(_1\)/FVC, MEP, MIP, SNIP, IC, TLC, FRC, RV, voice loudness and sustain time, mood and quality of life were measured pre and post intervention |
| Notes | |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Computer-generated randomisation sequence</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Randomised sequence concealed in sealed, opaque envelopes</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Low risk</td>
<td>Participants blinded to which intervention was the experimental condition. Assessors blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>No dropouts reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>

### Van Houtte 2008

| Methods | RCT with block randomisation (match by lesion level)  
Randomisation method: not specified |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>14 acute inpatients with C4-T1 SCI (ASIA A, B, or C) at least 6 weeks, but &lt; 6 months post injury (12 males, 2 females), aged 17-66 years, Belgium</td>
</tr>
<tr>
<td>Interventions</td>
<td><strong>Normocapnic hyperpnoea training</strong> vs. <strong>sham</strong>. Normocapnic hyperpnoea training utilised a re-breathing bag device set at 30-40% of FVC, filling and emptying the bag completely with each breath at 30-45 breaths/min. Pace or volume (or both) were increased if the participant sustained these targets for 25 min. Sham training breathed at a constant ventilation of 15% MVV at 15-25 breaths/min</td>
</tr>
</tbody>
</table>
Van Houtte 2008  (Continued)

<table>
<thead>
<tr>
<th>Training intensity</th>
<th>30 min daily (4 days/week) for 8 weeks</th>
</tr>
</thead>
</table>

Outcomes

- FVC, MVV, $P_{I_{\text{max}}}$ (also known as MIP), $P_{E_{\text{max}}}$ (also known as MEP), and respiratory endurance time were measured pre, mid (4 weeks), post (8 weeks), and at follow-up (16 weeks).

Notes

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Both participants and assessors blinded to group allocation</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Low risk</td>
<td>Sham treatment used for control group. Assessors blinded to group allocation</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>

Zupan 1997

**Methods**

- RCT (cross-over design)
- Randomisation method: not specified

**Participants**

- 13 inpatients with C4- C7 quadriplegia (10 complete, 3 incomplete) (11 males, 2 females), aged 17-46 years, Slovenia

**Interventions**

- Inspiratory muscle training (incentive spirometry) vs. expiratory muscle training + electrical stimulation vs. control (no training). For inspiratory muscle training the participants were instructed to inhale slowly to maximum value on the incentive spirometer and attempt to hold the breath at 75% of this value for as long as possible. For expiratory muscle training the participants were instructed to inhale slowly, hold the breath, and then attempt to achieve maximal expiration on a peak flow meter (twice without electrical stimulation of the abdominal muscles and 8 times with electrical stimulation) and blow bubbles through a thin straw for 3 min
- Training intensity: 7 exercises x 10 sets twice daily (6 days/week) for 4 weeks

**Outcomes**

- FVC and $FEV_1$ (sitting and lying) were measured at baseline and monthly for 3 months. FVC and $FEV_1$ were measured under 4 conditions: unassisted, manual assistance, elec-
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Random group assignment</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No dropouts reported</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Results presented for all original variables recorded</td>
</tr>
</tbody>
</table>

ASIA: American Spinal Injury Association; ERV: expiratory reserve volume; FEV\textsubscript{1}: forced expiratory volume in one second; FRC: functional residual capacity; FVC: forced vital capacity; IC: inspiratory capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MVV: maximal voluntary ventilation; PE\textsubscript{max} (also known as MEP): maximum expiratory pressure; PEF: peak expiratory flow; PEFR: peak expiratory flow rate; PI\textsubscript{max} (also known as MIP): maximum inspiratory pressure; RCT: randomised controlled trial; RV: residual volume; SCI: spinal cord injury; SIP: sustainable inspiratory pressure; SNIP: sniff nasal inspiratory pressure; TLC: total lung capacity; VC: vital capacity; V\textsubscript{E}: volume of expired gas; VO\textsubscript{2}: oxygen consumption.

### Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez 1981</td>
<td>Not an RCT, no RMT intervention</td>
</tr>
<tr>
<td>Biering-Sorensen 1991</td>
<td>Not an RCT, no control group, pre-post study</td>
</tr>
<tr>
<td>Crane 1994</td>
<td>Not an RCT, exercise training with retrospective sample</td>
</tr>
<tr>
<td>Ehrlich 1999</td>
<td>Not an RCT, case study</td>
</tr>
<tr>
<td>Epifanov 1987</td>
<td>Not an RCT, not quadriplegia</td>
</tr>
<tr>
<td>Author</td>
<td>Type of Study</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Estrup 1986</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Fugl-Meyer 1972</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Gallego 1993</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Goosey-Tolfrey 2010</td>
<td>Not an RCT, not quadriplegia</td>
</tr>
<tr>
<td>Gross 1980</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Hornstein 1986</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Imamura 1967</td>
<td>Not an RCT</td>
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<tr>
<td>Lee 2012</td>
<td>Poor description of the expiratory muscle training makes it is difficult to understand if it would have added to the effect of the mechanical in-exsufflation (which would be expected to be large). Randomisation order was determined by hospital admission, therefore, no allocation concealment and high potential for bias. Also, no indication of when the lung volume measures were made</td>
</tr>
<tr>
<td>Lerman 1987</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Lin 1999</td>
<td>Not an RMT, no training intervention</td>
</tr>
<tr>
<td>Lin 2001</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Metcalf 1966</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Moreno 2012</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Moreno 2013</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Nygren-Bonnier 2009</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Rutchik 1998</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Sapienza 2006</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Sutbeyaz 2005</td>
<td>Not an RCT, not quadriplegia</td>
</tr>
<tr>
<td>Uijl 1999</td>
<td>Not an RCT, cross-over design, but not randomised</td>
</tr>
<tr>
<td>Valent 2009</td>
<td>Not an RCT, no control group, pre-post study, not RMT intervention</td>
</tr>
<tr>
<td>Walker 1987</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Wang 2002</td>
<td>Not an RCT</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; RMT: respiratory muscle training.
## DATA AND ANALYSES

### Comparison 1. Respiratory muscle training versus control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dyspnoea</td>
<td>3</td>
<td>58</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.10 [-1.65, 1.44]</td>
</tr>
<tr>
<td>2 Vital capacity (L)</td>
<td>4</td>
<td>108</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.40 [0.12, 0.69]</td>
</tr>
<tr>
<td>3 Maximal inspiratory pressure (cmH₂O)</td>
<td>8</td>
<td>147</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>10.66 [3.59, 17.72]</td>
</tr>
<tr>
<td>4 Maximal expiratory pressure (cmH₂O)</td>
<td>6</td>
<td>151</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>10.31 [2.80, 17.82]</td>
</tr>
<tr>
<td>5 Forced expiratory volume in 1 second (L)</td>
<td>4</td>
<td>97</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.05 [-0.23, 0.34]</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Respiratory muscle training versus control, Outcome 1 Dyspnoea.**

Review: Respiratory muscle training for cervical spinal cord injury

Comparison: 1 Respiratory muscle training versus control

Outcome: 1 Dyspnoea

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw 2000</td>
<td></td>
<td>10</td>
<td>10.4 (0.7)</td>
<td>10</td>
<td>12 (1.2)</td>
<td>-1.56 [-2.59, -0.53]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (1)</td>
<td></td>
<td>8</td>
<td>8.5 (1.5)</td>
<td>4</td>
<td>7.3 (2.8)</td>
<td>0.56 [-0.67, 1.79]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (2)</td>
<td></td>
<td>8</td>
<td>9 (1.5)</td>
<td>4</td>
<td>7.3 (2.8)</td>
<td>0.79 [-0.47, 2.05]</td>
<td></td>
</tr>
<tr>
<td>Van Houtte 2008</td>
<td></td>
<td>7</td>
<td>0 (0)</td>
<td>7</td>
<td>0.7 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>33</td>
<td></td>
<td>25</td>
<td></td>
<td>-0.10 [-1.65, 1.44]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.51; Chi² = 10.50, df = 2 (P = 0.001); I² =81%

Test for overall effect: Z = 0.13 (P = 0.89)

Test for subgroup differences: Not applicable

-2 -1 0 1 2

Favours intervention  Favours control

Respiratory muscle training for cervical spinal cord injury (Review)

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### Analysis 1.2. Comparison 1 Respiratory muscle training versus control, Outcome 2 Vital capacity (L).

Review: Respiratory muscle training for cervical spinal cord injury

Comparison: 1 Respiratory muscle training versus control

Outcome: 2 Vital capacity (L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Gauden 1990</td>
<td>20</td>
<td>1.97 (0.54)</td>
<td>20</td>
<td>1.41 (0.79)</td>
<td>46.5 %</td>
</tr>
<tr>
<td>Liaw 2000</td>
<td>10</td>
<td>2.0 (0.5)</td>
<td>10</td>
<td>1.9 (0.9)</td>
<td>20.1 %</td>
</tr>
<tr>
<td>Mueller 2013 (1)</td>
<td>8</td>
<td>2.7 (0.6)</td>
<td>4</td>
<td>2.7 (0.8)</td>
<td>10.4 %</td>
</tr>
<tr>
<td>Mueller 2013 (2)</td>
<td>8</td>
<td>3.4 (1.1)</td>
<td>4</td>
<td>2.7 (0.8)</td>
<td>6.8 %</td>
</tr>
<tr>
<td>Tamplin 2013</td>
<td>12</td>
<td>2.96 (0.89)</td>
<td>12</td>
<td>2.49 (0.89)</td>
<td>16.1 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>58</strong></td>
<td></td>
<td></td>
<td><strong>50</strong></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.51, df = 4 (P = 0.64); I² =0.0%
Test for overall effect: Z = 2.77 (P = 0.0056)
Test for subgroup differences: Not applicable

(1) Mueller B
(2) Mueller A
### Analysis 1.3. Comparison 1 Respiratory muscle training versus control, Outcome 3 Maximal inspiratory pressure (cmH₂O).

**Review:** Respiratory muscle training for cervical spinal cord injury  
**Comparison:** 1 Respiratory muscle training versus control  
**Outcome:** 3 Maximal inspiratory pressure (cmH₂O)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV, Fixed, 95% CI</td>
<td></td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Derrickson 1992</td>
<td>6 58.17 (12)</td>
<td>5 43.4 (13)</td>
<td>22.5 %</td>
<td>14.77 [ -0.13, 29.67 ]</td>
<td></td>
</tr>
<tr>
<td>Liaw 2000</td>
<td>10 58.6 (16.7)</td>
<td>10 63.1 (17.9)</td>
<td>21.7 %</td>
<td>-4.50 [ -19.67, 10.67 ]</td>
<td></td>
</tr>
<tr>
<td>Litchke 2008</td>
<td>4 107.5 (21.2)</td>
<td>5 102.4 (18.5)</td>
<td>7.2 %</td>
<td>5.10 [ -21.25, 31.45 ]</td>
<td></td>
</tr>
<tr>
<td>Litchke 2010 (1)</td>
<td>4 94.5 (26.1)</td>
<td>3 88.29 (24)</td>
<td>3.6 %</td>
<td>6.21 [ -31.10, 43.52 ]</td>
<td></td>
</tr>
<tr>
<td>Litchke 2010 (2)</td>
<td>5 106 (16.09)</td>
<td>4 88.29 (24)</td>
<td>6.6 %</td>
<td>17.71 [ -9.71, 45.13 ]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (3)</td>
<td>8 76.4 (24.4)</td>
<td>4 78.3 (30.5)</td>
<td>4.2 %</td>
<td>-1.90 [ -36.24, 32.44 ]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (4)</td>
<td>8 101.5 (38.2)</td>
<td>4 78.3 (30.5)</td>
<td>3.1 %</td>
<td>23.20 [ -16.73, 63.13 ]</td>
<td></td>
</tr>
<tr>
<td>Roth 2010</td>
<td>16 71 (32)</td>
<td>13 56 (30)</td>
<td>9.7 %</td>
<td>15.00 [ -7.62, 37.62 ]</td>
<td></td>
</tr>
<tr>
<td>Tampin 2013</td>
<td>12 88.9 (20.4)</td>
<td>12 75.3 (26.7)</td>
<td>13.8 %</td>
<td>13.60 [ -5.41, 32.61 ]</td>
<td></td>
</tr>
<tr>
<td>Van Houtte 2008</td>
<td>7 95 (26)</td>
<td>7 61 (23)</td>
<td>7.5 %</td>
<td>34.00 [ 8.28, 59.72 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>80</strong></td>
<td><strong>67</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>10.66 [ 3.59, 17.72 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.90, df = 9 (P = 0.45)$; $I^2 = 0.0$
Test for overall effect: $Z = 2.96 (P = 0.0031)$
Test for subgroup differences: Not applicable

(1) Litchke B  
(2) Litchke A  
(3) Mueller A  
(4) Mueller B
### Analysis 1.4. Comparison 1 Respiratory muscle training versus control, Outcome 4 Maximal expiratory pressure (cmH$_2$O).

**Review:** Respiratory muscle training for cervical spinal cord injury

**Comparison:** 1 Respiratory muscle training versus control

**Outcome:** 4 Maximal expiratory pressure (cmH$_2$O)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Gounden 1990</td>
<td>20</td>
<td>68.05 (23.28)</td>
<td>20</td>
<td>46.45 (19.91)</td>
<td>31.3 %</td>
</tr>
<tr>
<td>Liaw 2000</td>
<td>10</td>
<td>39.7 (18.8)</td>
<td>10</td>
<td>40.9 (8.9)</td>
<td>34.0 %</td>
</tr>
<tr>
<td>Mueller 2013 (1)</td>
<td>8</td>
<td>67.3 (35.9)</td>
<td>4</td>
<td>65 (40.1)</td>
<td>2.6 %</td>
</tr>
<tr>
<td>Mueller 2013 (2)</td>
<td>8</td>
<td>63 (38.6)</td>
<td>4</td>
<td>65 (40.1)</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Roth 2010</td>
<td>16</td>
<td>98 (35)</td>
<td>13</td>
<td>91.2 (26)</td>
<td>11.4 %</td>
</tr>
<tr>
<td>Tamplin 2013</td>
<td>12</td>
<td>86.6 (37.96)</td>
<td>12</td>
<td>91.2 (35.04)</td>
<td>6.6 %</td>
</tr>
<tr>
<td>Van Houtte 2008</td>
<td>7</td>
<td>64 (23)</td>
<td>7</td>
<td>34 (19)</td>
<td>11.6 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>81</strong></td>
<td></td>
<td><strong>70</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 10.30, df = 6 (P = 0.11); I$^2$ =42%

Test for overall effect: Z = 2.69 (P = 0.0072)

Test for subgroup differences: Not applicable

(1) Mueller A

(2) Mueller B
Analysis 1.5. Comparison 1 Respiratory muscle training versus control, Outcome 5 Forced expiratory volume in 1 second (L).

Review: Respiratory muscle training for cervical spinal cord injury

Comparison: 1 Respiratory muscle training versus control

Outcome: 5 Forced expiratory volume in 1 second (L)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Control</th>
<th>N</th>
<th>Mean(SD)</th>
<th>Mean Difference W eight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liaw 2000</td>
<td></td>
<td>10</td>
<td>1.6 (0.4)</td>
<td>10</td>
<td>1.7 (0.8)</td>
<td>25.8 %</td>
<td>-0.10 [-0.65, 0.45]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (1)</td>
<td></td>
<td>8</td>
<td>2.8 (0.9)</td>
<td>4</td>
<td>2.4 (0.6)</td>
<td>10.8 %</td>
<td>0.40 [-0.46, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Mueller 2013 (2)</td>
<td></td>
<td>8</td>
<td>2.3 (0.6)</td>
<td>4</td>
<td>2.4 (0.6)</td>
<td>15.3 %</td>
<td>-0.10 [-0.82, 0.62]</td>
<td></td>
</tr>
<tr>
<td>Roth 2010</td>
<td></td>
<td>16</td>
<td>2 (0.62)</td>
<td>13</td>
<td>2.03 (0.81)</td>
<td>27.7 %</td>
<td>-0.03 [-0.56, 0.50]</td>
<td></td>
</tr>
<tr>
<td>Tamplin 2013</td>
<td></td>
<td>12</td>
<td>2.57 (0.64)</td>
<td>12</td>
<td>2.27 (0.9)</td>
<td>20.3 %</td>
<td>0.30 [-0.32, 0.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td>54</td>
<td></td>
<td>43</td>
<td></td>
<td>100.0 %</td>
<td>0.05 [-0.23, 0.34]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.79, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.70)
Test for subgroup differences: Not applicable

(1) Mueller A

(2) Mueller B

ADDITIONAL TABLES

Table 1. Body position in which respiratory outcomes were measured

<table>
<thead>
<tr>
<th>Study</th>
<th>Test position</th>
<th>Binder</th>
<th>Vital capacity</th>
<th>MIP</th>
<th>MEP</th>
<th>FEV₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derrickson 1992</td>
<td>Supine</td>
<td>n/a</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gounden 1990</td>
<td>Supine and sitting</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liaw 2000</td>
<td>Supine</td>
<td>n/a</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Litchke 2008</td>
<td>Sitting</td>
<td>?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Litchke 2010</td>
<td>Sitting</td>
<td>?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loveridge 1989</td>
<td>Sitting</td>
<td>?</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Body position in which respiratory outcomes were measured (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Position</th>
<th>Measure</th>
<th>Yes</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mueller 2013</td>
<td>Sitting</td>
<td>no</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Roth 2010</td>
<td>Sitting</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tamplin 2013</td>
<td>Sitting</td>
<td>no</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Van Houtte 2008</td>
<td>Sitting</td>
<td>?</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zupan 1997</td>
<td>Supine and sitting</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Gounden 1990 included the 'best' measure obtained during testing. It was not stated whether data were standardised within participant for both pre- and post-test measures.

FEV<sub>1</sub>: forced expiratory volume in one second; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure.

**APPENDICES**

**Appendix 1. Search strategies**

**Cochrane Injuries Group Specialised Register**

myelopathy and (traumatic or post-traumatic) OR ((spine or spinal)) and (fracture* or wound* or trauma* or injur* or damage*) OR ("spinal cord") and (contusion or laceration or transaction or trauma or ischemia or syndrome)) OR SCI AND (Breath* or respirat*) and (muscle* or exercise*)) OR (Breath* or respirat*) and (train* or "exercise therap*" or endurance or strength* or resist*)) OR (normocapnic or hyperpnoea) and train*) OR ((inspiratory or respiratory or breath*) and (endurance or train* or exercis* or resist* or strength*)) OR RMT

**Cochrane Central Register of Controlled Trials (The Cochrane Library)**

#1 MeSH descriptor: [Spinal Cord Injuries] explode all trees
#2 MeSH descriptor: [Spinal Cord Ischemia] explode all trees
#3 MeSH descriptor: [Central Cord Syndrome] explode all trees
#4 myelopathy near/3 (traumatic or post-traumatic):ti,ab,kw (Word variations have been searched)
#5 (spine or spinal) near/3 (fracture* or wound* or trauma* or injur* or damag*):ti,ab,kw (Word variations have been searched)
#6 spinal cord near/3 (contusion* or laceration* or transaction* or trauma* or ischemia*):ti,ab,kw (Word variations have been searched)
#7 "central cord injury syndrome":ti,ab,kw (Word variations have been searched)
#8 "central spinal cord syndrome":ti,ab,kw (Word variations have been searched)
#9 MeSH descriptor: [Cervical Vertebrae] explode all trees and with qualifiers: [Injuries - IN]
#10 MeSH descriptor: [Spinal Cord] explode all trees
#11 MeSH descriptor: [Paraplegia] explode all trees
#12 MeSH descriptor: [Quadriplegia] explode all trees
#13 SCL:ti,ab,kw (Word variations have been searched)
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 MeSH descriptor: [Breathing Exercises] explode all trees
#16 MeSH descriptor: [Exercise Therapy] explode all trees

Respiratory muscle training for cervical spinal cord injury (Review)

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#17 train* or exercis* or endurance or strength* or resistive:ti,ab,kw (Word variations have been searched)
#18 (#15 or #16 or #17)
#19 MeSH descriptor: [Respiratory Muscles] explode all trees
#20 #18 and #19
#21 normocapnic hyperpnoea training:ti,ab,kw (Word variations have been searched)
#22 (inspiratory or respiratory or breath*) near/5 (endurance or train* or exercis* or resist* or strength*):ti,ab,kw (Word variations have been searched)
#23 RMT:ti,ab,kw (Word variations have been searched)
#24 (#15 or #20 or #21 or #22 or #23)
#25 (#14 and #24)

MEDLINE (Ovid SP)
1. exp Spinal Cord Injuries/
2. exp Spinal Cord Ischemia/
3. exp Central Cord Syndrome/
4. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
5. ((spine or spinal) adj3 (fracture$ or wound$ or trauma$ or injur$ or damag$)).ab,ti.
6. (spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
7. central cord injury syndrome.ab,ti.
8. central spinal cord syndrome.ab,ti.
9. exp Cervical Vertebrae/in [Injuries]
10. exp Spinal Cord/
11. SCI.ab,ti.
12. exp Paraplegia/
13. exp Quadriplegia/
14. (paraplegia* or quadriplegia* or tetraplegia*).ab,ti.
15. or/1-14
16. exp Breathing Exercises/
17. exp Respiratory Muscles/
18. exp exercise therapy/
19. (train* or exercis* or endurance or strength* or resistive).ab,ti.
20.18 or 19
21.17 and 20
22. normocapnic hyperpnoea training.ab,ti.
23. ((inspiratory or respiratory or breath*) adj5 (endurance or train* or exercis* or resist* or strength*)).ab,ti.
24. RMT.ab,ti.
25. 16 or 21 or 22 or 23 or 24
26. 15 and 25

EMBASE (Ovid SP)
1. exp Spinal Cord Injuries/
2. exp Spinal Cord Ischemia/
3. exp Central Cord Syndrome/
4. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
5. ((spine or spinal) adj3 (fracture$ or wound$ or trauma$ or injur$ or damag$)).ab,ti.
6. (spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
7. central cord injury syndrome.ab,ti.
8. central spinal cord syndrome.ab,ti.
9. exp cervical spine/
10. exp Spinal Cord/
11. SCI.ab,ti.
12. exp Paraplegia/
13. exp Quadriplegia/
14. (paraplegia* or quadriplegia* or tetraplegia*).ab,ti.
15. or/1-14
16. exp Breathing Exercises/
17. exp Respiratory Muscles/
18. exp exercise therapy/
19. (train* or exercis* or endurance or strength* or resistive).ab,ti.
20. 18 or 19
21. 17 and 20
22. normocapnic hyperpnoea training.ab,ti.
23. ((inspiratory or respiratory or breath*) adj5 (endurance or train* or exercis* or resist* or strength*)).ab,ti.
24. RMT.ab,ti.
25. 16 or 21 or 22 or 23 or 24
26. 15 and 25
27. limit 26 to exclude MEDLINE journals

PubMed

(((publisher[SB])) AND (((((((paraplegi*[title/abstract] OR quadriplegi*[title/abstract] OR tetraplegi*[title/abstract]) OR (SCI[Title/Abstract])) OR ((("Cervical Vertebrae/injuries"[Mesh]) OR "Spinal Cord"[Mesh]) OR "Paraplegia"[Mesh]) OR "Quadriplegia"[Mesh])) OR (central cord injury syndrome[Title/Abstract] OR "central spinal cord syndrome"[Title/Abstract])) OR (((((contusion*[Title/Abstract]) OR laceration*[Title/Abstract]) OR transaction*[Title/Abstract]) OR trauma*[Title/Abstract]) OR ischemia*[Title/Abstract])) AND (spinal cord[Title/Abstract]))) OR (((((fracture*[Title/Abstract]) OR wound*[Title/Abstract]) OR trauma*[Title/Abstract]) OR (injury*[Title/Abstract]) OR damage*[Title/Abstract])) AND ((spine[Title/Abstract]) OR spinal[Title/Abstract]))) OR (((post-traumatic[Title/Abstract] OR traumatic[Title/Abstract])) AND (myelopathy[Title/Abstract]))) OR (((Spinal Cord Injuries[Mesh:noexp]) OR "Central Cord Syndrome"[Mesh]) OR "Spinal Cord Ischemia"[Mesh]))) AND ((("Respiratory Muscles"[Mesh]) AND ((("Breathing Exercises"[Mesh]) OR "Exerci se Therapy"[Mesh]) OR (train*[title/abstract] OR exercis*[title/abstract] OR endurance[title/abstract] OR strength*[title/abstract] OR resistive[title/abstract]))) OR (normocapnic hyperpnoea training[Title/Abstract]) OR (RMT[Title/Abstract])) OR (((inspiratory[title/abstract] OR respiratory[title/abstract] OR breath*[title/abstract]) AND (endurance[title/abstract] OR train*[title/abstract] OR exercis*[title/abstract] OR resist*[title/abstract] OR strength*[title/abstract])))

CINahl (EBSCO)

S21 S9 and S20 (Limiters - Exclude MEDLINE records)
S20 S11 or S12 or S16 or S17 or S18 or S19
S19 TX RMT
S18 TX (inspiratory or respiratory or breath*) and (endurance or train* or exercis* or resist* or strength*)
S17 TX normocapnic hyperpnoea training
S16 S10 and S15
S15 S11 or S12 or S13 or S14
S14 TX train* or exercis* or endurance or strength* or resistive
S13 (MH "Therapeutic Exercise")
S12 (MH "Buteyko Method")
S11 (MH "Breathing Exercises")
S10 (MH "Respiratory Muscles")
S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8
S8 TX paraplegi* or quadriplegi* or tetraplegi* or SCI
S7 (MH "Cervical Vertebrae/IN")
S6 TI spinal cord and (contusion or laceration or transaction or trauma or ischemia)
S5 TI (spine or spinal) AND (fracture* or wound* or trauma* or injur* or damage)
S4 TX myelopathy N5 post-traumatic
S3 TX myelopathy N5 traumatic
S2 (MH "Spinal Cord Injury Nursing")
S1 (MH "Spinal Cord Injuries")

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED)

ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S)

1. TS=(myelopathy and (traumatic or post-traumatic)) OR TS=((spine or spinal) same (fracture* or wound* or trauma* or injur* or damage*)) OR TS=("spinal cord" same (contusion or laceration or transaction or trauma or ischemia or syndrome)) OR TS=(SCI)
2. TS=(Respiratory Muscle* same (train* or exercis* or endurance or strength* or resistive or Therap*)) OR TS=(normocapnic hyperpnoea training) OR TS=((inspiratory or respiratory or breath*) same (endurance or train* or exercis* or resist* or strength*)) OR TS=(RMT)

3. 1 and 2

**Australian New Zealand Clinical Trials Registry**

spinal injury

**ClinicalTrials.gov**

spinal injury AND respiratory

**Current Controlled Trials**

spinal injury AND respiratory

**CONTRIBUTIONS OF AUTHORS**

Jeanette Tamplin drafted the protocol and replied to comment of the peer reviewer. David Berlowitz reviewed the draft and approved the final version.

For the review:

Jeanette Tamplin:

- Assisting with design of search strategies, undertaking and screening searches, organising retrieval of papers;
- Screening retrieved papers against eligibility criteria, appraising quality of papers, developing a data collection form, and extracting data from papers;
- Inter-rater reliability (trial selection);
- Writing to authors of papers for additional information;
- Providing additional data about papers, obtaining and screening data on unpublished studies;
- Entering data into RevMan;
- Analysis and interpretation of data;
- Writing the review.

David Berlowitz:

- Screening retrieved papers against eligibility criteria, appraising quality of papers, and extracting data from papers;
- Providing additional data about papers, obtaining and screening data on unpublished studies;
- Analysis and interpretation of data;
- Assisting with writing the review.
DECLARATIONS OF INTEREST

The review authors are currently involved in a research study, which, on completion, may be eligible for inclusion in this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Victorian Neurotrauma Initiative, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.