Respiratory muscle training in neuromuscular disease: a systematic review and meta-analysis

Kathryn Watson¹, Thorlene Egerton², Nicole Sheers ³, Sarah Retica⁵, Rebekah McGaw⁵, Talia Clohessy⁵, Penny Webster ⁶ and David J. Berlowitz ²,³,⁴,⁵

¹Department of Physiotherapy, Fiona Stanley Hospital, Perth, Australia. ²Department of Physiotherapy, The University of Melbourne, Melbourne, Australia. ³Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, Australia. ⁴Institute for Breathing and Sleep, Melbourne, Australia. ⁵Department of Physiotherapy, Austin Hospital, Heidelberg, Australia. ⁶Hunter New England Local Health District, Newcastle, Australia.

Corresponding author: David J. Berlowitz (david.berlowitz@austin.org.au)

Shareable abstract (@ERSpublications)
Respiratory muscle weakness is typical in neuromuscular disease. Respiratory muscles can be trained. Training data comes largely from small, heterogenous trials. Despite these limitations, meta-analysis demonstrates an overall benefit from training. https://bit.ly/3S4N4Hu

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Abstract

Background Neumuscular disease causes a progressive decline in ventilatory function which respiratory muscle training may address. Previous systematic reviews have focussed on single diseases, whereas this study systematically reviewed the collective evidence for respiratory muscle training in children and adults with any neuromuscular disease.

Methods Seven databases were searched for randomised controlled trials. Three reviewers independently reviewed eligibility, extracted characteristics, results, determined risk of bias and combined results using narrative synthesis and meta-analysis.

Results 37 studies (40 publications from 1986–2021, n=951 participants) were included. Respiratory muscle training improved forced vital capacity (standardised mean difference (SMD) 0.40 (95% confidence interval 0.12–0.69)), maximal inspiratory (SMD 0.53 (0.21–0.85)) and maximal expiratory pressure (SMD 0.70 (0.35–1.04)) compared to control (usual care, sham or alternative treatment). No impact on cough, dyspnoea, voice, physical capacity or quality of life was detected. There was high degree of variability between studies.

Discussion Study heterogeneity (children and adults, different diseases, interventions, dosage and comparators) suggests that the results should be interpreted with caution. Including all neuromuscular diseases increased the evidence pool and tested the intervention overall.

Conclusions Respiratory muscle training improves lung volumes and respiratory muscle strength in neuromuscular disease, but confidence is tempered by limitations in the underlying research.

Introduction

Neuromuscular diseases (NMDs) typically result in deteriorating mobility and respiratory function over time with associated impairment, disability and cost to the person living with the NMD, their family and society [1]. Respiratory muscle weakness is associated with reduced chest expansion, vital capacity (VC), shortness of breath (dyspnoea), difficulty communicating, poor cough and impaired airway clearance [2, 3].

Respiratory muscle training (RMT) is any intervention aiming to improve strength or endurance of inspiratory and/or expiratory muscles in order to improve respiratory function. Despite the biological plausibility of RMT as an effective treatment for people with NMD, evidence to guide clinical practice is limited. Most trials lack a control group and the controlled studies typically have very small sample sizes that are limited to a single NMD [4–8]. Similarly, previous systematic reviews have also been limited to a single NMD (e.g., spinal cord injury [5]) or to a specific age group (e.g., children and adolescents [7]).
Further, previous reviews have not investigated markers of cough despite the clear role of coughing in respiratory health [9] and secretion management being a primary patient concern [10]. Therefore, previous systematic reviews have limited generalisability and clinical utility.

This study aimed to systematically review the effect of RMT, compared to usual care, sham training or an alternative intervention on respiratory function in children and adults with any NMD. The primary focus was on lung volumes, inspiratory and expiratory muscle strength, cough metrics and dyspnoea. Secondary aims included the effect of RMT on voice measures, physical capacity, quality of life (QoL) and adverse outcomes.

**Methods**

The review was registered with PROSPERO (Reference CRD42019135178) and reported in accordance with the PRISMA recommendations [11].

**Search strategy**

A search of CINAHL, Medline, Embase, Emcare, Cochrane Database of Systematic Reviews, Cochrane Neuromuscular disease group and the Physiotherapy Evidence Database (PEDro), using pre-specified keywords for specific NMDs and synonyms of RMT, and limited to randomised controlled trials, was completed in February 2021 (Appendix 1) and again in August 2022 [12]. Included study references and clinical trials registries were hand searched. There were no publication date, age or setting restrictions; however, only articles published in English were included.

**Inclusion and exclusion criteria**

Studies on participants with any NMD that can impair respiratory muscle function were eligible, including acquired (e.g., spinal cord injury (SCI), Guillain–Barre syndrome) and congenital (e.g., spinal muscular atrophy and muscular dystrophies) NMDs. Studies were excluded if they involved participants requiring mechanical ventilation. Studies were included if they involved any RMT treatment and provided data on any of the primary or secondary outcome measures.

**Outcome measures**

The primary outcomes were measures of respiratory function: lung volume (vital capacity (VC) or forced VC (FVC)), inspiratory muscle strength (maximal inspiratory pressure (MIP) and sniff nasal inspiratory pressure (SNIP)), expiratory muscle strength (maximal expiratory pressure (MEP)), cough and dyspnoea. Cough assessment was quantified as the maximal expiratory flow achieved during a forced expiration (peak expiratory flow (PEF)) or a cough manoeuvre (peak cough flow (PCF)) or self-reported perceived cough effectiveness using a visual analogue scale (VAS). Dyspnoea was similarly self-rated using the Borg scale or a VAS. Secondary outcomes included measures of physical capacity (e.g., timed walking/mobility tests or self-report questionnaires with a focus on capacity rather than function), voice (e.g., voice quality, phonation or volume), QoL and adverse outcomes.

**Trial selection and data extraction**

Identified references underwent title/abstract and then full-text review by three independent reviewers (K.W., P.W., S.R.). Conflicts were resolved through discussion or with input from a fourth reviewer (D.J.B.). The same reviewers independently extracted study characteristics, risk of bias information and results data. Study characteristics included participant information (number, health condition, age and sex), intervention (experimental and control group intervention description, and intensity, frequency and duration of delivery) and the primary outcome(s) of the study. Risk of bias was assessed using the Cochrane risk of bias assessment tool version 2 (ROB2) [13]. Results data were extracted for baseline, immediately post intervention and the final study time point. Mean and standard deviations (SD) of within- and between-group differences, confidence intervals (CIs) and effect sizes were extracted as available.

**Data synthesis**

Meta-analyses were planned when comparable and single-construct outcome measures were available from a minimum of three studies. Meta-analysis heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic, with an $I^2$ of $>50\%$ considered significantly heterogeneous. The variables of interest were all continuous and, as such, data were combined using random effects models and standardised mean differences (SMD) with 95% confidence interval (CI) to account for differing measurement methods and variances using post-test scores (RevMan software version 5.3 [12]). The Grading of Recommendations, Assessment, Development and Evaluations tool (GRADE) [14] was used to determine the confidence in the results and to guide recommendations.
Sensitivity and secondary analyses assessed the influence of excluding lower-quality studies for meta-analyses that included at least one study with “high” risk of bias and at least three remaining studies. To assist with clinical interpretation of results, meta-analyses were repeated using change scores in the subset of studies when available to express the effect of RMT in the original units of measurement. Subgroup analyses for diagnoses were undertaken if at least three studies of similar neuromuscular presentation could be grouped for meta-analyses. Similarly, subgroup analyses by intervention (inspiratory muscle training (IMT), expiratory muscle training (EMT), or combined muscle training (IMT+EMT)) were conducted where possible. The last subgroup analysis was not specified in the original protocol but was considered important post hoc. Where meta-analysis was not possible, results were summarised using narrative synthesis taking into consideration magnitude and direction of effects.

Results
The search identified 2806 articles, with 1872 remaining once duplicates were removed. After 1833 articles were excluded, 39 articles remained for the synthesis (figure 1) [2, 3, 15–51]. Three pairs of articles [18, 25, 26, 31, 35, 36] reported data from a single study. Henceforth only the first is cited. A repeat search was performed prior to publication in August 2022 which identified a further single article meeting the inclusion criteria [52].

Included studies
The 37 included studies (n=951 participants) were randomised controlled parallel or crossover designs (table 1), published between 1986 and 2021. NMDs represented were SCI (n=15), multiple sclerosis (n=5),...
| Citation, setting, country | Diagnosis, sample size (IG/CG), IG age, CG age, gender | Intervention (dosage) | Comparator | Study primary outcomes |
|---------------------------|--------------------------------------------------------|-----------------------|------------|------------------------|
| **Aslan et al. [2], outpatient clinic, Turkey** | Slowly progressive neuromuscular disease, n=24 (14/10), IG: 31.6±12.3 years, CG: 26.5±8.6 years, 42% male | Inspiratory+expiratory training (30% of MIP/MEP, 15 min, twice daily, 5 days-week⁻¹, 8 weeks) | Sham training 9 cmH₂O, same protocol | Spirometry, PCF, MIP/MEP, SNIP |
| **Boswell-Ruys et al. [48], community, Australia** | Spinal cord injury, n=60 (30/32), IG: 51.5±14.3, CG: 55.7±14.9, 94% male | Inspiratory+expiratory training (30% P<sub>Imax</sub>, increased by 10% each week to a max of 80%, 3–5 sets, 12 breaths, twice daily, five times per week, 6 weeks) | Sham training, no resistance, same protocol | Spirometry, PCF, P<sub>Emax</sub>, dyspnoea, QoL |
| **Cheah et al. [15], tertiary hospital, Australia** | Amyotrophic lateral sclerosis, n=19 (9/10), IG: 54.9±9.8 years, CG: 53.4±9.5 years, 63% male | Inspiratory training (15% of SNIP, increased by 15% of SNIP each week until 4 weeks, 10 min, three times daily, 7 days-week⁻¹, 12 weeks) | Sham training, same protocol, no resistance | Spirometry, MIP/MEP, SNIP |
| **Derrickson et al. [16], rehabilitation hospital, USA** | Spinal cord injury, n=11 (6/5, IG: 28.5±5.6 years, CG: 27.0±10.7 years, 82% male | Inspiratory training (minimal resistance, resistance increased when able to complete three consecutive sessions, 2×15 min, 5 days-week⁻¹, 7 weeks) | Abdominal muscle weight training | Spirometry, P<sub>max</sub> |
| **Fregonez et al. [17], outpatient clinic, Spain** | Myasthenia gravis, n=27 (14/13), IG: 67±10 years, CG: 61±12 years, 41% male | Inspiratory training (20% P<sub>max</sub> and increased by 15% every 2 weeks, 10 min active, 5 min rest, 45 min, three times weekly, 8 weeks) | Single breathing retraining and education session | Spirometry, P<sub>max</sub>/P<sub>Emax</sub>, thoracic mobility |
| **Fri et al. [18], community, USA** | Multiple sclerosis, n=41 (20/21), IG: 50.9±9.1 years, CG: 46.1±9.4 years, 17% male | Inspiratory training (30% of MIP and adjusted weekly depending on Borg RPE, three sets of 15 reps, daily, 10 weeks) | Standard care | Spirometry, MIP/MEP, functional measures |
| **Gosseink et al. [19], rehabilitation hospital, Belgium** | Multiple sclerosis, n=18 (9/9), IG: 54±13 years, CG: 59±14 years, 50% male | Expiratory training (60% of P<sub>Emax</sub>, three sets, 15 reps, twice every three days, 3 months) | Breathing exercises | Spirometry, P<sub>max</sub>/P<sub>Emax</sub>, functional measures |
| **Gouden et al. [20], inpatients, South Africa** | Spinal cord injury, n=40 (20/20), IG: 27.8 years, CG: 30.6 years, 80% male | Expiratory training (60% of P<sub>Emax</sub> 5 min sessions, five times a day, 6 days-week⁻¹, 8 weeks) | Usual care, low intensity physiotherapy two to three times per week | Spirometry, P<sub>Emax</sub> |
| **Gozal et al. [3], home-based programme, France** | Children with neuromuscular disease, n=21 (11/10), IG: 12.7±2.2 years, CG: 13.2±2.6 years, 62% male | Inspiratory+expiratory training (30% of P<sub>Imax</sub>/P<sub>Emax</sub>, twice daily, 6 months) | Sham training | Spirometry, P<sub>Emax</sub>/P<sub>Emax</sub>, load perception |
| **Inzeldi et al. [21], outpatient clinic, Israel** | Parkinson’s disease, n=20 (10/10), IG: 59.4±2.4 years, CG: 65±3.6 years, 60% male | Inspiratory training (15% of P<sub>Imax</sub>, increasing by 5–10% after week 1 to reach 60% by end of first month, 30 mins day⁻¹, six times per week, 3 months) | Sham training 7 cmH₂O, same protocol | Spirometry, P<sub>Emax</sub> dyspnoea, QoL |
| **Jones et al. [47], home-based programme, USA** | Late-onset Pompe disease, n=22 (12/10), IG: 53.2±12.7, CG: 46.6±13.9, 41% male | Inspiratory+expiratory training (70% MIP/MEP, 75 repetitions, five times per week, 12 weeks) | Sham training, 15% MIP/MEP, same protocol | Spirometry, MIP, MEP, PCF, functional capacity |
| **Kim et al. [22], rehabilitation hospital, Republic of Korea** | Spinal cord injury, n=37 (12/12 – data not extracted for other intervention group), IG: 41.5±10.0 years, CG: 40.1±8.7 years, 63% male | Inspiratory training (maximal inspiration held for 4 s, 10 reps, five sets, three times per week, 8 weeks) | Standard care | Spirometry |
| **Klevebro et al. [23], outpatient clinic, Sweden** | Multiple sclerosis, n=15 (7/8), IG: 46 years, CG: 52.5 years, 60% male | Inspiratory training (40–60% P<sub>max</sub>, twice every second day, three sets, 10 reps, 10 weeks) | Standard care | Spirometry, P<sub>max</sub>/P<sub>Emax</sub>, subjective reporting |

Continued
| Citation, setting, country | Diagnosis, sample size (IG/CG), IG age, CG age, gender | Intervention (dosage) | Comparator | Study primary outcomes |
|-----------------------------|----------------------------------------------------|----------------------|------------|-----------------------|
| LIAW et al. [24], rehabilitation hospital, Taiwan | Spinal cord injury, n=20 (10/10), IG: 30.9±11.6 years, CG: 36.5±11.5 years, 80% male | Inspiratory training (7 mm resistance increased when tolerated for 3 days, 20 min sessions, twice daily, 6 weeks) | Standard care | Spirometry, MIP/MEP, dyspnoea |
| LITCHKE et al. [27], community, USA | Spinal cord injury n=9 (4/5), IG: 30.3±7.7 years, CG: 30.6±10.8 years, 100% male | Inspiratory training (unclear resistance, one set, twice/thrice daily, 10 weeks) | Standard care | VO₂ peak, MIP |
| LITCHKE et al. [25], community, USA | Spinal cord injury, n=16 (4/5/7), no data, 100% male | Inspiratory+expiratory training (group 1 pressure resistance, three sets of 10 cycles, three times daily, 9 weeks; group 2 flow resistance, long inspiration with 5 s breath hold and prolonged expiration, 10 reps, three times daily, 9 weeks) | Standard care | Spirometry, aerobic capacity |
| LOVERIDGE et al. [28], outpatient clinic, Canada | Spinal cord injury, n=12 (6/6), IG: 31±4.4 years, CG: 35±12 years, unknown sex | Inspiratory training (85% of sustained inspiratory pressure 15 min, twice daily, five times per week, 8 weeks) | Standard care | Spirometry, MIP |
| MARTIN et al. [29], outpatient clinic, Australia* | Duchenne’s muscular dystrophy, n=18 (9/9), IG: 14.1 years, CG 14.2 years, 100% male | Inspiratory and expiratory training (maximum static manoeuvres sustained for 3–5 s for 30 min, and ventilation to exhaustion at variable resistance for 30 min/day⁻¹, five times per week, 8 weeks) | Delayed training with washout period (participants acted as own controls) | Spirometry, MIP/MEP |
| MOHAMED et al. [52], Outpatient clinic, Egypt | Down syndrome, n=30 (15/15), IG: 11.06±0.84 years, CG: 11.3±0.92 years, 47% male | Inspiratory training (40% MIP, 20 min, once daily, 5 days-week⁻¹, 12 weeks) | Usual care (aerobic exercise) | MIP, MEP, VC, PEF, 6MWT |
| MUßLER et al. [30], rehabilitation hospital, Netherlands | Spinal cord injury, n=24 (8/8/8), IG (group 1): 33.5±11.7 years, IG (group 2): 35.2±12.7 years, CG: 41.6±17 years, 75% male | Group 1: inspiratory training (maximal inspirations for 90 repetitions); group 2: isocapnic hyperpnoea (40–50% of MVV 4×10 min·week⁻¹, 8 weeks) | Incentive spirometry, 16 breaths with 30–40 s rest, 4×10 min·week⁻¹, 8 weeks | Spirometry, voice, thorax mobility, QoL |
| PINTO et al. [32], outpatient clinic, Portugal* | Amyotrophic lateral sclerosis, n=20 (11/9), IG: 57.14±9.3 years, CG: 56.8±8.7 years, 69% male | Inspiratory training (30–40% of MIP, twice daily, 10 min, 8 months) | Sham training, 9 cmH₂O, same protocol | Spirometry, MIP/MEP |
| PLOWMAN et al. [33], home-based programme, USA | Amyotrophic lateral sclerosis, n=48 (23/23), IG: 63.1±10.0 years, 60% male | Expiratory training (50% of MEP reassessed weekly, 5×5 reps, five times per week) | Sham training, same protocol | MEP, PCF, spirometry |
| POSTMA et al. [34], rehabilitation hospital, Netherlands | Spinal cord injury, n=40 (19/21), IG: 47.1±14.1 years, CG: 46.6±14.9 years, 87.5% male | Inspiratory training (60% MIP, seven sets of 2 min, five times per week, 8 weeks) | Standard care | Spirometry, MIP/MEP, perceived respiratory function |
| Reyes et al. [37], home-based programme, Chile | Huntington’s disease, n=18 (9/9), IG: 56±10.2 years, CG: 50±9.2 years, 61% male | Inspiratory+expiratory training (30% of MIP/MEP gradually increased to 70%, five sets, five reps, six times per week, 16 weeks) | Sham training, same protocol | Spirometry, MIP/MEP, functional capacity, water swallowing test, swallow QoL |
| Reyes et al. [35], home-based programme, Chile | Parkinson’s disease, n=31 (11/10/10), inspiratory group: 70.5±8.2 years, expiratory group: 70.4±6.8 years, 55% male | Inspiratory+expiratory training (50% of MIP/MEP gradually increased to 75%, five sets, five reps, six times per week, 8 weeks) | Sham training, same protocol | Spirometry, MIP/MEP |

Continued
| Citation, setting, country | Diagnosis, sample size (IG/CG), IG age, CG age, gender | Intervention (dosage) | Comparator | Study primary outcomes |
|---------------------------|--------------------------------------------------------|----------------------|------------|------------------------|
| **Spinal cord injury**    |                                                        |                      |            |                        |
| *Roth et al.* [38], rehabilitation hospital, USA | Spinal cord injury, n=29 (16/13), IG: 31.1±12.4 years, CG: 28.9±9.6 years, 76% male | Expiratory training (maximal expiratory force, 10 reps, twice daily, five times per week, 6 weeks) | Sham training, no resistance, same protocol | Spirometry, MEP, MIP |
| *Sapienza et al.* [39], outpatient clinic, USA | Parkinson’s disease, n=60 (30/30), IG: 66.7±8.9 years, CG: 68.5±10.3 years, 78% male | Expiratory training (75% MEP, five sets, five reps, five times per week, 4 weeks) | Sham training, same protocol | Spirometry, MEP |
| *Smeltzer et al.* [40], home-based programme, USA | Multiple sclerosis, n=15 (10/5), no age data, 47% male | Expiratory training (unclear resistance, three sets, 15 reps, twice daily, 12 weeks) | Sham training, low resistance with focus on inspiration | Spirometry, $P_{\text{Imax}}$, $P_{\text{Emax}}$ |
| **Parkinson’s disease**  |                                                        |                      |            |                        |
| *Soumashree et al.* [49], rehabilitation hospital, India | Spinal cord injury, n=27 (15/12), IG: 29±12.6 years, CG: 34.4±13 years, 82% male | Inspiratory training (40% MIP, 15 min, five times per week, 4 weeks) | Maximum inspiration with tactile feedback, 60 reps, twice daily, five times per week, 4 weeks | MIP/MEP, dyspnoea, functional capacity |
| **Duchenne muscular dystrophy** |                                                        |                      |            |                        |
| *Stein et al.* [41], community, Australia* | Duchenne’s muscular dystrophy, n=24 (12/12), IG: 14.5 years, CG: 14.5 years, 100% male | Inspiratory training (inhalation through mask at variable inspiratory pressures connected to computer game, 20 min sessions, five times per week, 6 months) | Standard care initially then delayed start intervention at 6 months | Spirometry, $P_{\text{Imax}}$ |
| **Multiple sclerosis** |                                                        |                      |            |                        |
| *Topin et al.* [42], home-based programme, France¶ | Duchenne’s muscular dystrophy, n=16 (8/8), IG: 14.7±4.5 years, CG: 12.6±1.8 years, 100% male | Inspiratory training (30% MIP, 10 min, twice daily, 6 weeks) | Sham training, 5% MIP, same protocol | Spirometry, MEP |
| *Van Houtte et al.* [43], inpatient, Belgium | Spinal cord injury, n=14 (7/7), IG: 45 years, CG: 42 years, 14% male | Inspiratory and expiratory normocapnic hyperpnoea training (30% of MVV, respiratory rate 45, 30 min·day$^{-1}$, four times per week, 8 weeks) | Sham training 15% of MVV with respiratory rate 15, same protocol | Spirometry, $P_{\text{Imax}}$, $P_{\text{Emax}}$, Index of pulmonary dysfunction |
| **Downs syndrome** |                                                        |                      |            |                        |
| *Vural et al.* [50], community, Turkey* | Downs syndrome, n=16 (9/7), IG: 11.1±2.9 years, CG: 11.5±3.5 years, 56% male | Inspiratory training (40% MIP, 30 breaths, two sets, five times per week, 4 weeks) | Sham training, 0% MIP, same protocol | Spirometry, MIP/MEP, PEF |
| **Spinal cord injury** |                                                        |                      |            |                        |
| *Wanke et al.* [44], home-based programme, Austria | Duchenne’s muscular dystrophy, n=30 (15/15), IG: 13.6±4.5 years, CG: 14.5±3.8 years, 100% male | Inspiratory training (maximal static inspiratory efforts against almost occluded resistance, 1 min duration, 10 reps, plus 10 maximal static inspiratory efforts, twice daily, 6 months) | Standard care | Spirometry, $P_{\text{max}}$, maximal sniff, oesophageal and transdiaphragmatic pressure |
| **Spinal cord injury** |                                                        |                      |            |                        |
| *West et al.* [45], community, UK | Spinal cord injury, n=10 (5/5), IG: 30.5±2.2 years, CG: 27.9±2.8 years, 10% male | Inspiratory training (50–60% $P_{\text{max}}$ load increased when achieving 30 breaths consecutively, 30 reps, twice daily, five times per week, 6 weeks) | Sham training, placebo inhaler daily, 6 weeks | Diaphragm thickness, spirometry, $P_{\text{max}}$, dyspnoea, physical response to exercise |
| **Multiple sclerosis** |                                                        |                      |            |                        |
| *Westerdahl et al.* [46], home-based programme, Sweden | Multiple sclerosis, n=48 (23/25), IG: 55±12 years, CG: 56±9 years, 8% male | Expiratory training (10–15 cmH$_2$O, 30 reps, twice daily, 8 weeks) | Standard care | Spirometry, MIP/MEP, thoracic excursion, subjective symptoms |
| **Spinal cord injury** |                                                        |                      |            |                        |
| *Xi et al.* [51], inpatient, China | Spinal cord injury, n=18 (8/10), IG: 54±6.6 years, CG: 52±6.8 years, no gender data | Normocapnic hyperventilation (15–20 min·day$^{-1}$, five times per week, 4 weeks) | Standard care | Spirometry, dyspnoea |

6MWT: 6-min walk test; CG: control group; IG: intervention group; MEP ($P_{\text{Emax}}$): maximal expiratory pressure; MIP ($P_{\text{Imax}}$): maximal inspiratory pressure; MVV: maximal voluntary ventilation; PCF: peak cough flow; PEF: peak expiratory flow; QoL: quality of life; reps: repetitions; RPE: rating of perceived exertion; SNIP: sniff nasal inspiratory pressure; VC: vital capacity; $V_{O2}$: oxygen uptake. 

* studies assessing children. ¶: only the initial assessment period for PINTO [32] is included in the review as there is no control group after the first assessment at 4 months.
Duchenne muscular dystrophy (n=4), Parkinson’s disease (n=3), amyotrophic lateral sclerosis (n=3),
general NMD (n=2), Huntington disease (n=1), myasthenia gravis (n=1), late-onset Pompe’s disease (n=1)
and Down syndrome (n=1). Severity of lung disease at baseline varied: ten studies on participants with VC
or FVC (presented henceforth as F(VC)) less than 2 L or 50% predicted, 14 studies with F(VC) between
2–3 L or 50–80% predicted, seven studies with F(VC) greater than 3 L or 80% predicted, and the
remaining six studies with unknown severity. Three studies [26, 27, 45] investigated the impact of RMT
on athletes with SCI; baseline characteristics of these participants were markedly different to other studies
therefore these findings were not included in meta-analyses.

RMT interventions comprised IMT (20 studies) [15–18, 21–24, 27, 28, 30, 32, 34, 41, 42, 44, 45, 49, 50, 52],
EMT (seven studies) [19, 20, 33, 38–40, 46] or IMT+EMT (10 studies) [2, 3, 25, 29, 35–37, 43, 47, 48, 51].
The comparison groups with sham training (n=23) used either a device with no load, or active control
sessions with no RMT but which may have been perceived as treatment by participants (such as incentive
spirometry). 14 studies used standard care as the control. In Gozal et al. [3], four comparison groups were
reported (intervention and control groups for participants with NMD and age-matched healthy subjects);
only the data from NMD participants were included. In Mohamed et al. [52], there were three comparison
groups and only the data pertaining to IMT or the control were extracted.

Training intensity varied between studies, with the majority targeting between 30% and 60% of MIP and/
or MEP. The median training duration was eight weeks, with five studies investigating longer periods of 4
[32, 37] and 6 months [3, 41, 44].

Risk of bias and evidence quality
Most included studies had risk of bias in all ROB2 domains (figure 2). All but one article reported primary
outcome data, although 18 incompletely reported their findings (presenting results as figures only,
providing partial outcome data, or reporting findings as “not significant”). Most design and reporting
weaknesses were related to randomisation, poor allocation concealment, inadequate blinding, not
conducting intention to treat analyses and high attrition rates. Of the included studies, only two
demonstrated low risk of bias in all domains and half had a high risk of bias in at least one domain.
Evidence quality was rated low or very low for all meta-analyses (table 2), mainly due to the quality of the
studies and imprecision related to small overall sample size.

Primary outcome measures
Individual study data for the primary outcomes are presented in table 3. Meta-analyses with subgrouping
by intervention type (IMT, EMT or IMT+EMT) were possible for all primary outcomes of interest, except
for PCF and dyspnoea. Reyes et al. [35] included both IMT and EMT experimental groups, and as such
their control group participants’ data were included only once in each meta-analysis by halving the control
group sample size [12]. Additionally, the two experimental groups for Mueller et al. [30] were combined
to reflect one experimental group in the meta-analyses since both were inspiratory training interventions.
Subgroup analyses across all diagnosis were not possible due to too few studies with data able to be
included in meta-analyses for most diagnostic groups (Huntington’s disease, myasthenia gravis, late onset
Pompe’s disease, Down syndrome and a general multiple NMD groupings [2, 3]). Exploratory analyses of
the FVC, MIP and MEP data across those diagnoses with at least three meta-analysable datasets (SCI,
multiple sclerosis, Duchenne muscular dystrophy, Parkinson’s disease and amyotrophic lateral sclerosis)
were performed and the contribution of disease to overall heterogeneity in the reported data are reported in
Appendix 2. A single disease study risk of bias table is also available (Appendix 3).

Lung volumes
31 of the included studies reported VC or FVC. For the synthesis and meta-analyses, VC and FVC were
combined and presented as (F)VC. The total pooled (F)VC when expressed as absolute volume improved
significantly with RMT; SMD 0.43 (0.16–0.70), but not when expressed as a percent of predicted value;
SMD 0.23 (–0.03–0.49; Appendix 4A and B). Most of the six studies that were not able to be included in
the meta-analysis reported no significant benefit of RMT [15, 32, 38, 43], apart from one study finding a
20% improvement in the experimental group following EMT [19], and another finding an improvement
ratio of 7.8% (so 17.6%) following normocapnic hyperpnoea [51]. Subgroup analyses by intervention type
found a significant benefit of IMT on absolute (F)VC volume; SMD 0.54 (0.14–0.94). For all other
intervention types (i.e., EMT or IMT+EMT), point estimates favoured the RMT by a similar amount but
with wide confidence intervals. Whilst total pooled (F)VC % predicted volume results did not indicate a
benefit of RMT, the subgroup of IMT+EMT favoured the experimental group; SMD 0.60 (0.08–1.12).
IMT and EMT alone demonstrated no statistically significant differences between groups (figure 3).
| Study                          | Randomisation | Deviation from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result |
|-------------------------------|---------------|----------------------------------------|----------------------|---------------------------|---------------------------------|
| ASLAN et al. [2]              | +             | ?                                      | ?                    | +                         | Low risk                        |
| BOSWELL-RUYS et al. [48]      | +             | +                                      | ?                    | ?                         | Some concerns                   |
| CHEAN et al. [15]             | +             | ?                                      | ?                    | ?                         | High risk                       |
| DERRICKSON et al. [16]        | ?             | ?                                      | ?                    | ?                         |                                 |
| FREGONEZI et al. [17]         | ?             | ?                                      | ?                    | ?                         |                                 |
| Fryt et al. [18]              | ?             | ?                                      | ?                    | ?                         |                                 |
| GOSSELINK et al. [19]         | ?             | ?                                      | ?                    | ?                         |                                 |
| GOUNDEN et al. [20]           | ?             | ?                                      | ?                    | ?                         |                                 |
| GOZAL et al. [3]              | ?             | ?                                      | ?                    | ?                         |                                 |
| INZELBERG et al. [21]         | ?             | ?                                      | ?                    | ?                         |                                 |
| JONES et al. [47]             | ?             | ?                                      | ?                    | ?                         |                                 |
| KIM et al. [22]               | ?             | ?                                      | ?                    | ?                         |                                 |
| KLEFBECK et al. [23]          | ?             | ?                                      | ?                    | ?                         |                                 |
| LIAW et al. [24]              | ?             | ?                                      | ?                    | ?                         |                                 |
| LITCHKE et al. [27]           | ?             | ?                                      | ?                    | ?                         |                                 |
| LITCHKE et al. [25]           | ?             | ?                                      | ?                    | ?                         |                                 |
| LOVERIDGE et al. [28]         | ?             | ?                                      | ?                    | ?                         |                                 |
| MARTIN et al. [29]            | ?             | ?                                      | ?                    | ?                         |                                 |
| MOHAMED et al. [52]           | ?             | ?                                      | ?                    | ?                         |                                 |
| MUELLER et al. [30]           | ?             | ?                                      | ?                    | ?                         |                                 |
| PINTO et al. [32]             | ?             | ?                                      | ?                    | ?                         |                                 |
| PLOWMAN et al. [33]           | ?             | ?                                      | ?                    | ?                         |                                 |
| POSTMA et al. [34]            | ?             | ?                                      | ?                    | ?                         |                                 |
| REYES et al. [37]             | ?             | ?                                      | ?                    | ?                         |                                 |
| REYES et al. [35]             | ?             | ?                                      | ?                    | ?                         |                                 |
| ROTH et al. [38]              | ?             | ?                                      | ?                    | ?                         |                                 |
| SAPIENZA et al. [39]          | ?             | ?                                      | ?                    | ?                         |                                 |
| SMELTZER et al. [40]          | ?             | ?                                      | ?                    | ?                         |                                 |
| SOUMYASHREE et al. [49]       | ?             | ?                                      | ?                    | ?                         |                                 |
| STERN et al. [41]             | ?             | ?                                      | ?                    | ?                         |                                 |
| TOPIN et al. [42]             | ?             | ?                                      | ?                    | ?                         |                                 |
| VAN HOUTTE et al. [43]        | ?             | ?                                      | ?                    | ?                         |                                 |
| VURAL et al. [50]             | ?             | ?                                      | ?                    | ?                         |                                 |
| WANKE et al. [44]             | ?             | ?                                      | ?                    | ?                         |                                 |
| WESTET et al. [45]            | ?             | ?                                      | ?                    | ?                         |                                 |
| WESTERDAHL et al. [46]        | ?             | ?                                      | ?                    | ?                         |                                 |
| Xi et al. [51]                | ?             | ?                                      | ?                    | ?                         |                                 |

**FIGURE 2** Results of risk of bias assessment for included studies.
| Outcome       | $k$ | $n$ | SMD (95% CI) | $I^2$ (p-value) | Heterogeneity | Indirectness | Bias | Imprecision | Publication bias | Evidence quality |
|---------------|-----|-----|--------------|----------------|---------------|--------------|------|-------------|-----------------|-----------------|
| FVC (L)      | 19  | 573 | 0.43 (0.16–0.70) | 58% (0.001) | Serious | Serious | Very serious | None | None | Low          |
| Inspiratory  | 12  | 295 | 0.54 (0.14–0.94) | 62% (0.002) | Serious | Serious | Very serious | None | None | Low          |
| Expiratory   | 5   | 192 | 0.36 (−0.10–0.83) | 58% (0.05) | Serious | Serious | Very serious | Serious | NA     | Low          |
| Combined     | 2   | 86  | 0.16 (−0.49–0.82) | 48% (0.17) | None | None | None | None | Serious | NA | Low          |
| FVC (% pred) | 9   | 235 | 0.23 (−0.03–0.49) | 0% (0.8) | None | Serious | Very serious | Serious | None | Very low |
| Inspiratory  | 5   | 127 | 0.13 (−0.22–0.48) | 0% (0.75) | None | Serious | Very serious | Serious | None | Low          |
| Expiratory   | 1   | 48  | 0.04 (−0.52–0.61) | NA | None | None | Serious | Very serious | None | NA | Low          |
| Combined     | 3   | 60  | 0.60 (0.08–1.12) | 0% (1.0) | None | Serious | Very serious | None | NA | Low          |
| MIP (cmH$_2$O) | 22 | 549 | 0.57 (0.25–0.88) | 65% (<0.0001) | Serious | Serious | Very serious | Serious | None | Very low |
| Inspiratory  | 12  | 277 | 0.56 (0.16–0.97) | 59% (0.008) | Serious | Serious | Very serious | None | None | Very low |
| Expiratory   | 5   | 125 | 0.14 (−0.33–0.61) | 35% (0.19) | None | Serious | Very serious | Very serious | NA | Very low |
| Combined     | 5   | 147 | 1.12 (0.22–2.03) | 81% (0.0003) | Very serious | Serious | Very serious | None | Very low |
| MIP (% pred) | 7   | 168 | 0.43 (0.05–0.81) | 27% (0.22) | None | Serious | Very serious | None | NA | Low          |
| Inspiratory  | 4   | 20  | 0.60 (−0.06–1.26) | 0% (0.46) | None | Serious | Very serious | Very serious | NA | Low          |
| Expiratory   | 2   | 64  | −0.09 (−0.59–0.41) | 0% (0.37) | None | None | Very serious | Very serious | NA | Low          |
| Combined     | 3   | 64  | 0.74 (0.23–1.26) | 0% (0.56) | None | Serious | Very serious | Very serious | NA | Low          |
| MEP (cmH$_2$O) | 22 | 661 | 0.71 (0.37–1.07) | 74% (<0.0001) | Very serious | Serious | Very serious | Serious | None | Very low |
| Inspiratory  | 9   | 241 | 0.36 (−0.10–0.83) | 66% (0.007) | Serious | Serious | Very serious | Very serious | NA | Very low |
| Expiratory   | 8   | 273 | 0.86 (0.43–1.30) | 63% (0.009) | Serious | Serious | Very serious | Very serious | NA | Very low |
| Combined     | 5   | 147 | 1.34 (0.22–2.45) | 87% (<0.0001) | Very serious | Serious | Serious | Very serious | NA | Very low |
| MEP (% pred) | 8   | 208 | 0.28 (−0.02–0.58) | 12% (0.34) | None | Serious | Very serious | None | NA | Low          |
| Inspiratory  | 3   | 81  | 0.32 (−0.27–0.90) | 35% (0.21) | None | Serious | Very serious | Very serious | NA | Low          |
| Expiratory   | 2   | 63  | 0.32 (−0.73–1.37) | 65% (0.09) | Serious | None | Very serious | Very serious | NA | Low          |
| Combined     | 3   | 64  | 0.41 (−0.10–0.91) | 0% (0.50) | None | None | Very serious | Very serious | NA | Low          |
| PEF           | 9   | 299 | 0.33 (−0.02–0.67) | 50% (0.11) | None | Serious | Very serious | Serious | NA | Very low |
| Inspiratory  | 7   | 191 | 0.39 (−0.07–0.86) | 56% (0.09) | None | None | Very serious | Grey | NA | Low          |
| Expiratory   | 2   | 108 | 0.22 (−0.33–0.77) | 52% (0.15) | Serious | None | Very serious | Grey | NA | Low          |
| PCF           | 6   | 227 | 0.28 (−0.07–0.64) | 40% (0.14) | None | Serious | Very serious | Grey | NA | Very low |
| Dyspnoea      | 5   | 151 | −0.33 (−1.16–0.49) | 81% (0.0003) | Very serious | Serious | Very serious | Grey | NA | Very low |

FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; PCF: peak cough flow; PEF: peak expiratory flow; Pred: predicted; SMD: standardised mean difference. #: none if $I^2$<50%; serious if $I^2$ 51–69%; very serious if $I^2$ $\geq$ 70% [12]. ¶: serious: some indirectness from patient, intervention, comparison and outcome; very serious: multiple indirectness. +: serious: evidence from trials of unclear risk of bias or trials with high risk of bias for one criterion; very serious: evidence from trials of high risk of bias (multiple criteria). §: serious: <400 participants, confidence intervals (CIs) include little/no effect and benefit/harm spans an effect size of 0.5 in either direction; very serious: <400 participants, CIs include little/no effect and benefit/harm spans an effect size of 0.5 in both directions). †: NA means publication bias unable to be assessed as insufficient (less than 10 trials ($k$) per outcome). ²: starts at high quality and is downgraded – can be low (downgraded by one) or very low (downgraded by two).
| Study                        | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|-----------------------------|-------------------------------------|------------------------------------------|--------------------------|----------|---------------------------------------------------------------|-------------------------------|
| **ASLAN et al. [2]**        | VC (L): IGΔ: 0.1 (0.2) CGΔ: −0.2 (0.7) DiffΔ: (p=0.2) | MIP (cmH₂O): IGΔ: 24.2 (13.7) CGΔ: 5.6 (10.8) DiffΔ: (p=0.002) MEP (cmH₂O): IGΔ: 14.6 (11.1) CGΔ: 5.1 (6.8) DiffΔ: (p=0.04) SNIP: IGΔ: 17.3 (15.6) CGΔ: 5.7 (5.1) DiffΔ: (p=0.04) | PCF (L·min⁻¹): IGΔ: 42.1 (38.7) CGΔ: 17.0 (20.0) DiffΔ: (p=0.07) | Nil adverse events; 8% |
| **Boswell-Ruys et al. [48]** | FVC (L): IGΔ: 0.2 CGΔ: 0.1 DiffΔ: (p=0.349) | MIP (cmH₂O): IGΔ: 15.3 CGΔ: 3.4 DiffΔ: 11.5 (5.6–17.4) MEP (cmH₂O): IGΔ: 5.6 CGΔ: 4.2 DiffΔ: (p=0.799) | PCF (L·min⁻¹): IGΔ: 0.1 CGΔ: 0.1 DiffΔ: (p=0.893) | Borg: IGΔ: 0.2 CGΔ: −0.3 DiffΔ: (p=0.021) SGRQ: IGΔ: −6.6 CGΔ: −1.8 DiffΔ: (p=0.451) | SF-36 role physical domain: IGΔ: 16 CGΔ: 5.2 DiffΔ: (p=0.426) EQ-5D: IGΔ: 10.2 CGΔ: 8.7 DiffΔ: (p=0.541) | Nil adverse events; 3% |
| **Cheah et al. [15]**      | VC (% pred): DiffΔ: 1.4% (−4.2–7.1) | MIP (% pred): DiffΔ: 6.1% (6.9) (−8.6–20.8) | PCF (L·min⁻¹): IGΔ: 0.1 CGΔ: 0.1 DiffΔ: (p=0.893) | SF-36 role physical domain: IGΔ: 16 CGΔ: 5.2 DiffΔ: (p=0.426) EQ-5D: IGΔ: 10.2 CGΔ: 8.7 DiffΔ: (p=0.541) | Nil adverse events; 5% |
| **Derrickson et al. [16]** | FVC (L): IGΔ: 1.3 CGΔ: 0.5 DiffΔ: (p=0.05) | MIP (cmH₂O): IGΔ: 23.3 CGΔ: 22.6 DiffΔ: (p=0.05) | PEF (L·s⁻¹): IGΔ: 1.77 CGΔ: 0.89 DiffΔ: (p=0.05) | SF-36 role physical domain: IGΔ: 21 CGΔ: unchanged | Nil adverse events; 73% |
| **Fregonezi et al. [17]**  | FVC (L): IGΔ: 0.1 CGΔ: 0 DiffΔ: (p=0.05) | MIP (cmH₂O): IGΔ: 15 CGΔ: unchanged DiffΔ: (p=0.001) MEP (cmH₂O): IGΔ: 12 CGΔ: −3 DiffΔ: (p=0.01) | SF-36 role physical domain: IGΔ: 21 CGΔ: unchanged | Nil adverse events; 7% |

Continued
| Study                  | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|-----------------------|--------------------------------------|--------------------------------------------|--------------------------|-----------|----------------------------------------------------------------|-------------------------------|
| FRY et al. [18]       | FVC (L): IGΔ: 0.3 (0.29) CGΔ: 0.01 (0.29) DiffΔ: (p=0.04) | MIP (cmH₂O): IGΔ: 23.5 CGΔ: −0.7 DiffΔ: (p=0.001) MEP (cmH₂O): IGΔ: 4.5 CGΔ: −3.6 DiffΔ: (p=0.29) | PEF (L): IGΔ: 0.23 CGΔ: −0.16 DiffΔ: (p=0.02) | Dyspnoea | 6MWT: IGΔ: 12.3 (29) CGΔ: 9 (44.9) DiffΔ: (p=0.086) Gait velocity: IGΔ: 0.03 (0.08) CGΔ: 0.03 (0.12) DiffΔ: (p=0.086) | Nil adverse events; 11% |
| GOSSELINK et al. [19] | FVC (L): IGΔ: 25% (63) CGΔ: 5% (35) | MIP (cmH₂O): IGΔ: 39% (41) CGΔ: 11% (36) DiffΔ: (p=0.06) MEP (cmH₂O): IGΔ: 30% (46) CGΔ: −4% (26) DiffΔ: (p=0.07) | Dyspnoea | 6MWT: IGΔ: 12.3 (29) CGΔ: 9 (44.9) DiffΔ: (p=0.086) Gait velocity: IGΔ: 0.03 (0.08) CGΔ: 0.03 (0.12) DiffΔ: (p=0.086) | Nil adverse events; 14% |
| GOUNDEN et al. [20]   | VC (L): IGΔ: 0.5 (0.42) CGΔ: −0.1 (0.55) DiffΔ: (p=0.0004) | MEP (cmH₂O): IGΔ: 24.3 (18.2) CGΔ: 2.25 (13.43) DiffΔ: (p=0.0001) | Dyspnoea | 6MWT: IGΔ: 12.3 (29) CGΔ: 9 (44.9) DiffΔ: (p=0.086) Gait velocity: IGΔ: 0.03 (0.08) CGΔ: 0.03 (0.12) DiffΔ: (p=0.086) | Nil adverse events; 0% |
| GOZAL et al. [3]      | FVC (L): no data provided – no significant change | MIP (cmH₂O): IGΔ: 19.8 (3.8) CGΔ: 4.2 (3.6) DiffΔ: (p=0.02) MEP (cmH₂O): IGΔ: 27.1 (4.9) CGΔ: −1.8 (3.4) DiffΔ: (p=0.004) | Dyspnoea | 6MWT: IGΔ: 12.3 (29) CGΔ: 9 (44.9) DiffΔ: (p=0.086) Gait velocity: IGΔ: 0.03 (0.08) CGΔ: 0.03 (0.12) DiffΔ: (p=0.086) | Nil adverse events; 0% |
| INZELBERG et al. [21] | FVC (L): no data provided – no significant change | MIP (cmH₂O): IGΔ: 16 CGΔ: no data DiffΔ: (p=0.05) | Dyspnoea index: IGΔ: −3.9 CGΔ: no data provided DiffΔ: (p=0.05) | Dyspnoea | 6MWT (m): IGΔ: 22 (28.8) CGΔ: 9.8 (20.1) DiffΔ: (p=0.34) | Nil adverse events; 0% |
| JONES et al. [47]     | MIP (cmH₂O): IGΔ: 7.6 (15.9) CGΔ: 2.7 (7.6) DiffΔ: (p=0.47) MEP (cmH₂O): IGΔ: 14 (25.9) CGΔ: 0 (12) DiffΔ: (p=0.19) | PCF (L·s⁻¹): IGΔ: 0.4 (1.8) CGΔ: 0.7 (2.3) DiffΔ: (p=0.55) | Dyspnoea | 6MWT (m): IGΔ: 22 (28.8) CGΔ: 9.8 (20.1) DiffΔ: (p=0.34) | Nil adverse events; 0% |
| Study          | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|---------------|-------------------------------------|--------------------------------------------|-------------------------|----------|---------------------------------------------------------------|-------------------------------|
| **KIM et al. [22]** | FVC (L):  IGΔ: 0.15 (0.06)  CGΔ: 0.03 (0.01)  DiffΔ: (p=0.002) | MIP (cmH2O):  IGΔ: 25  CGΔ: 2  DiffΔ: (p=0.01)  MEP (cmH2O):  IGΔ: 17  CGΔ: 0  DiffΔ: (p=0.02) | PEF: no change (no data reported) | Borg RPE: No change (no data reported) | Nil adverse events; 12% |
| **KLEFBECK et al. [23]** | FVC (L):  IGΔ: 66% (74)  CGΔ: 28% (36)  DiffΔ: (p=0.172) | MIP (cmH2O):  IGΔ: 29% (21)  CGΔ: 27% (27)  DiffΔ: (p=0.844)  MEP (cmH2O):  IGΔ: 2% (52)  CGΔ: 44% (21)  DiffΔ: (p=0.915) | PEF (L·s⁻¹):  IGΔ: 39% (36)  CGΔ: 23% (40)  DiffΔ: (p=0.384) | Borg:  IGΔ: 22% (4)  CGΔ: −11% (9)  DiffΔ: (p=0.003) | Nil adverse events; 33% |
| **LIU et al. [24]** | FVC (L):  IGΔ: 66% (74)  CGΔ: 28% (36)  DiffΔ: (p=0.172) | MIP (cmH2O):  IGΔ: 33  CGΔ: 0.6  DiffΔ: (p=0.039) | PEF (L·s⁻¹):  IGΔ: 0.6  CGΔ: 0.1  DiffΔ: (p=0.05) | V̇O₂ peak:  IGΔ: 0.6  CGΔ: 0.1  DiffΔ: (p=0.05) | Nil adverse events; 10% |
| **LITCHE et al. [25]** | FVC (% pred):  IGΔ: 1%  CGΔ: 3%  DiffΔ: (p=0.05) | MIP (cmH2O):  IGΔ: 44.2% (32.7)  CGΔ: 30.2% (18.9)  DiffΔ: (p=0.05) | PEF (L·s⁻¹):  IGΔ: 0.6 (4.9)  CGΔ: −2.3 (2.9)  DiffΔ: (p=0.05) | MEP (mmHg):  IGΔ: 0.2 (2)  CGΔ: 0.5 (3.3)  DiffΔ: (p=0.05) | Nil adverse events; 0% |
| **LOVERIDGE et al. [28]** | FVC (% pred):  IGΔ: 1.9 (4.3)  CGΔ: −0.8 (4.3)  DiffΔ: (p=0.05) | MIP (cmH2O):  IGΔ: 44.2% (32.7)  CGΔ: 30.2% (18.9)  DiffΔ: (p=0.05) | PEF (L·s⁻¹):  IGΔ: 0.6 (4.9)  CGΔ: −2.3 (2.9)  DiffΔ: (p=0.05) | MEP (mmHg):  IGΔ: 0.2 (2)  CGΔ: 0.5 (3.3)  DiffΔ: (p=0.05) | Nil adverse events; 5% |

Continued
| Study | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|-------|------------------------------------|--------------------------------------------|-------------------------|-----------|-------------------------------------------------------------------------------------------------|-------------------------------|
| MOHAMED et al. [52] | VC (L): IGΔ: 0.08 (p=0.001) CGΔ: 0.03 (p=0.003) DiffΔ: 0.05 (p=0.003) | MIP (cmH₂O): IGΔ: 8.53 (p=0.001) CGΔ: 1.4 (p=0.02) DiffΔ: 8.06 (p=0.001) MEP (cmH₂O): IGΔ: 8.60 (p=0.001) CGΔ: 2.67 (p=0.001) DiffΔ: 5.93 (p=0.001) | PEF (L·min⁻¹): IGΔ: 6.41 (p=0.001) CGΔ: 1.8 (p=0.02) DiffΔ: 5.26 (p=0.001) | Dyspnoea: 6MWT (m): IGΔ: 18.6 (p=0.001) CGΔ: 7.14 (p=0.02) DiffΔ: 15.46 (p=0.002) | Nil adverse events; 0% |
| MUELLER et al. [30] | VC (L): IG (IH): 0.5 (0.4) IG (IRT): 0.3 (0.3) CGΔ: 0.32 (0.5) DiffΔ: (p>0.05) MIP (cmH₂O): IG (IH): 7.0 (10.0) IG (IRT): 35.4 (29.4) CGΔ: 8.9 (15.2) MEP (cmH₂O): IG (IH): 8.5 (39.4) IG (IRT): 7.5 (14.7) CGΔ: 3.3 (13.3) DiffΔ: (p>0.05) | PEF (L·s⁻¹): IG (IH): 0.4 (0.5) IG (IRT): 1.2 (1.2) CGΔ: 0.6 (0.9) Cough (VAS): IG (IH): −0.05 (1.6) IG (IRT): 1.1 (1.5) CGΔ: 0.9 (3.4) DiffΔ: (p>0.05) | Dyspnoea: Sustained phonation time: IG (IH): −0.3 (1.1) IG (IRT): −0.3 (2.7) CGΔ: −0.2 (3.1) DiffΔ: (p>0.05) | Nil adverse events; 7.6% |
| PINTO et al. [32] | FVC (L): IGΔ: 4.6 CGΔ: −1.2 DiffΔ: 10.9 (7.3) (−4.254–25.978) MIP (cmH₂O): DiffΔ: −8.2 (10.5) (−29.85–15.358) MEP (cmH₂O): DiffΔ: −7.7 (11.8) (−32.06–16.287) SNIP: DiffΔ: −10.4 (9.7) (−30.442–9.673) | PEF (L·s⁻¹): DiffΔ: −5.5 (9.7) (−25.55–14.66) VAS dyspnoea: DiffΔ: −0.2 (0.7) (−1.71–1.24) | EQ-5D: DiffΔ: 0.8 (8.7) (−17.09–18.63) | Nil adverse events; 16% |
| PLLOWMAN et al. [33] | FVC (% pred): IGΔ: −7.6% (−14.9–0.3) CGΔ: −8.3% (−14.7–1.9) DiffΔ: (p=0.86) MIP (cmH₂O): IGΔ: 25.5 (14.3–36.7) CGΔ: 6.6 (−3.4–16.5) DiffΔ: 0.009 | PCF (L·s⁻¹): IGΔ: 0 (−1.3–1.3) CGΔ: −0.6 (−1.5–0.4) DiffΔ: (p=0.09) | Nil adverse events; 4% | Continued |
| Study                  | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|-----------------------|--------------------------------------|--------------------------------------------|--------------------------|-----------|---------------------------------------------------------------|-------------------------------|
| **Postma et al. [34]** | FVC (L): IGΔ: 0.42; CGΔ: 0.41       | MIP (cmH2O): IGΔ: 26.3; CGΔ: 14.6          | PEF (L·s⁻¹): IGΔ: 0.72; CGΔ: 0.49 | Perceived talking function: IGΔ: −3; CGΔ: −1.67 | Nil adverse events; 34% events; 34% attrition rate | Nil adverse events; 34% |
|                       | Diff Δ: −0.04 (−0.3−0.22)            | Diff Δ: 11.67 (4.33–19.02)                 | Diff Δ: 0.25 (−0.53–1.03) | Diff Δ: −0.28 (−1.5–0.94) | 6MWT: IG effect size: 0.35 (−0.60–1.26); CG effect size: 0.02 (−0.91–0.94) | Nil adverse events; 0% |
|                       | MEP (cmH2O): IGΔ: 13.8; CGΔ: 8.8    | Diff Δ: 2.65 (−8.55–13.85)                | PCF (L·s⁻¹): IGΔ: 0.76; CGΔ: 0.7 | SF-36: IGΔ: 2.1; CGΔ: 5.9 | Nil adverse events; 0% |
|                       | Diff Δ: 0.16 (−0.52–0.83)           | Diff Δ: 0.49 (−0.74–1.72)                 | Diff Δ: −0.17 (−1.10–0.75) | Diff Δ: −5.47 (−15.12–4.19) | 6MWT: IG effect size: 0.35 (−0.60–1.26); CG effect size: 0.02 (−0.91–0.94) | Nil adverse events; 0% |
| **Reyes et al. [37]**  | FVC (% pred): IG: 0.26 (−0.67, 1.19) | MIP (cmH2O): IG effect size: 0.47 (−0.46–1.41) | PEF (% pred): IG effect size: 0.39 (−0.55–1.32) | Dyspnoea: IG effect size: −0.87 (−1.84–0.1); CG effect size: 0.00 (−0.92–0.92) | Nil adverse events; 0% |
|                       | CG: −0.06 (−0.99–0.86)              | CG effect size: 0.32 (−0.61–1.25)         | CG effect size: −0.17 (−1.10–0.75) | Diff effect size: 0.8 | Nil adverse events; 0% |
|                       | MEP (cmH2O): IG effect size: 0.37 (−0.56–1.3) | Diff Δ: −0.06 (−0.32–0.39)                 | Diff Δ: −0.25 (−0.43–−0.07) | Diff Δ: −0.25 (−1.3–1.09) | Nil adverse events; 0% |
|                       | Diff Δ: −0.09 (−1.01–0.84)          | Diff Δ: 0.49 (−0.74–1.72)                 | Diff Δ: 2.65 (−8.55–13.85) | Diff Δ: 0.49 (−0.74–1.72) | Nil adverse events; 0% |
| **Reyes et al. [35]**  | FVC (L): IG (inspiratory) effect size: 0.14 (−0.19–0.47) | MIP (cmH2O): IG (inspiratory) effect size: 0.03 (−0.32–0.39) | Voluntary PCF (L·s⁻¹): IG (inspiratory) effect size: 0.07 (−0.32–0.46) | Mean subglottic pressure: IG (inspiratory) effect size: −0.12 (−0.79–0.55) | Nil adverse events; 23% |
|                       | IG (expiratory) effect size: 0.19 (−0.45–0.82) | IG (inspiratory) effect size: 0.03 (−0.32–0.39) | IG (inspiratory) effect size: 0.07 (−0.32–0.46) | IG (inspiratory) effect size: −0.12 (−0.62–0.37) | Mean subglottic pressure: IG (inspiratory) effect size: −0.12 (−0.79–0.55) | Nil adverse events; 23% |
|                       | CG effect size: 0.24 (−0.51–0.99)   | IG (inspiratory) effect size: 0.04 (−0.44–0.52) | IG (expiratory) effect size: 0.04 (−0.44–0.52) | IG (expiratory) effect size: 0.04 (−0.44–0.52) | IG (expiratory) effect size: 0.43 (−0.45–1.31) | Nil adverse events; 23% |
|                       | Diff Δ: −0.06 (−0.23–0.34)          | CG effect size: 0.03 (−0.27–0.33)         | Reflexive PCF (L·s⁻¹): IG (inspiratory) effect size: −0.12 (−0.62–0.37) | Diff Δ: 0.24 (−0.51–0.99) | Nil adverse events; 23% |
|                       | IG (expiratory) effect size: 0.54 (−0.40–0.7) | Diff Δ: 0.34 (−0.44–1.09)                 | IG (expiratory) effect size: 0.34 (−0.44–1.09) | Diff Δ: −0.22 (−0.75–0.31) | Nil adverse events; 23% |
|                       | Diff Δ: −0.18 (−0.18–−0.46)         | CG effect size: 0.17 (−0.21–0.56)         | CG effect size: −0.22 (−0.75–0.31) | Diff Δ: −0.22 (−0.75–0.31) | Nil adverse events; 23% |
| Study                  | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|-----------------------|-------------------------------------|---------------------------------------------|--------------------------|----------|---------------------------------------------------------------|-------------------------------|
| **Roth et al. [38]**  | FVC (L): IGΔ: 0.28, CGΔ: 0.34, DiffΔ: −0.05 (p=0.88) | MIP (cmH₂O): IGΔ: 24, CGΔ: 15, DiffΔ: −15 (p=0.2) | | | | Nil adverse events; 44% |
| **SAPIENZA et al. [39]** | FVC (L): IGΔ: 0.01, CGΔ: 0.03, DiffΔ: (p>0.05) | MEP (cmH₂O): IGΔ: 27.97, CGΔ: −4.42, DiffΔ: (p=0.01) | | | | Nil adverse events; 0% |
| **SMELTZER et al. [40]** | | MIP (cmH₂O): IGΔ: 3.3 (16.1), CGΔ: 9.2 (11.9), MEP (cmH₂O): IGΔ: 19.4 (9.9), CGΔ: −1.2 (11.1), DiffΔ: (p=0.003) | | | | Nil adverse events. 25% |
| **SOUMYASHREE et al. [49]** | | MIP (cmH₂O): IGΔ: 28.7, CGΔ: 7.5, DiffΔ: 21.6 (30.2–12.1) | Borg: IGΔ: −3.1, CGΔ: −1.4, DiffΔ: (p=0.001) | 6MPT (m): IGΔ: 51, CGΔ: 20.8, DiffΔ: (p=0.001) | | Nil adverse events; 0% |
| **STEIN et al. [41]**  | FVC (% pred): IGΔ: −4.33% (2.9), CGΔ: −5.83% (8.4), DiffΔ: (p=0.62) | MIP (% pred): IGΔ: 2.5% (10.3), CGΔ: −4.25% (5.5), DiffΔ: (p=0.07) | | | | Nil adverse events; 33% |
| **TOPIN et al. [42]**  | VC (L): IGΔ: −0.01, CGΔ: −0.16, DiffΔ: (p=0.06) | MIP (cmH₂O): IGΔ: 1.4, CGΔ: −1.5, DiffΔ: (p=0.06) | | | | Nil adverse events; 0% |
| **VAN HOUTTE et al. [43]** | FVC (L): DiffΔ: (p=0.06) | MIP (cmH₂O): DiffΔ: (p=0.06) | | | | Nil adverse events; 0% |
### TABLE 3 Continued

| Study                  | Respiratory muscle function (VC/FVC) | Respiratory muscle strength (MIP/MEP/SNIP) | Cough efficacy (PCF/PEF) | Dyspnoea | Secondary outcomes: physical capacity, quality of life, voice | Adverse events; attrition rate |
|------------------------|-------------------------------------|-------------------------------------------|--------------------------|----------|--------------------------------------------------------------|-------------------------------|
| **Vural et al. [50]^a** | FVC (L): IGΔ: 0.41 (0.4)            | MIP (cmH₂O): IGΔ: 7.89 (4.59)             | PEF (L·s⁻¹): IGΔ: 0.51 (0.48) |          |                                                             | Nil adverse events; 0%        |
|                        | CGΔ: −0.01 (0.06)                    | CGΔ: 0 (2)                                 | CGΔ: −0.01 (0.18)         |          |                                                             |                               |
|                        | DiffΔ: (p<0.05)                      | DiffΔ: (p<0.05)                            | DiffΔ: (p<0.05)           |          |                                                             |                               |
| **Wanke et al. [44]^a** | VC (L): IGΔ: 0.02                    | MIP (cmH₂O): IGΔ: −2                      | PEF (L·s⁻¹): IGΔ: 0.44    |          |                                                             | Nil adverse events; 25%       |
|                        | CGΔ: −0.02                           | CGΔ: −6                                   | CGΔ: 0.51                 |          |                                                             |                               |
|                        | DiffΔ: (p<0.05)                      | DiffΔ: (p<0.05)                            | DiffΔ: (p=0.081)          |          |                                                             |                               |
| **West et al. [45]**   | FVC (L): IGΔ: 0.1%                   | MIP (cmH₂O): IGΔ: 14                      | PCF (L·s⁻¹): DiffΔ: (p=0.305) | Dyspnoea whilst walking: DiffΔ: 0 (0–6) | EQ-5D VAS: DiffΔ: (p=0.136). | Nil adverse events; 17%       |
|                        | CGΔ: −3%                             | CGΔ: −6                                   | PEF (L·s⁻¹): IGΔ: 8.2     |          |                                                             |                               |
|                        | DiffΔ: −4.8% (−9.0–0.6)              | DiffΔ: 1% (−7–9)                           | CGΔ: 1                    |          |                                                             |                               |
|                        |                                      | DiffΔ: (p<0.05)                            | DiffΔ: (p=0.081)          |          |                                                             |                               |
|                        |                                      | MEP (cmH₂O): IGΔ: 16                      | PCF (L·s⁻¹): DiffΔ: (p=0.305) | Dyspnoea whilst walking: DiffΔ: 0 (0–6) | EQ-5D VAS: DiffΔ: (p=0.136). | Nil adverse events; 17%       |
|                        | IGΔ: 5%                              | IGΔ: −6                                   | PEF (L·s⁻¹): IGΔ: 8.6%    |          |                                                             |                               |
|                        | DiffΔ: −8.2% (−1.1–4.4)              | DiffΔ: 0.4%                               | CGΔ: 0.4%                 |          |                                                             |                               |
|                        | Perceived coughing ability:          | DiffΔ: (p<0.05)                            | DiffΔ: (p=0.081)          |          |                                                             |                               |
| **Westerdahl et al. [46]** | FVC (% pred): IGΔ: (p<0.05)        | MIP (cmH₂O): IGΔ: 0%                      | Borg: DiffΔ: (p<0.05)     |          |                                                             | Nil adverse events; 8%        |
|                        | CGΔ: (p<0.05)                        | CGΔ: 0.01%                                | IGΔ: (p<0.05)             |          |                                                             |                               |
|                        | DiffΔ: (p=0.022)                     | DiffΔ: 1% (−7–9)                           | CGΔ: (p<0.05)             |          |                                                             |                               |
|                        |                                      | MEP (cmH₂O): IGΔ: 5%                      | DiffΔ: (p=0.022)          |          |                                                             |                               |
|                        | IGΔ: 5%                              | IGΔ: 5%                                   | SGRQ: DiffΔ: (p<0.05)     |          |                                                             |                               |
|                        | DiffΔ: (p=0.05)                      | DiffΔ: 4% (−7.9–1.4)                      | CGΔ: (p<0.05)             |          |                                                             |                               |
|                        | Perceived coughing ability:          | DiffΔ: (p=0.022)                           | DiffΔ: (p=0.037)          |          |                                                             |                               |
|                        | DiffΔ: −3% (−12–6)                   | DiffΔ: (p=0.022)                           | DiffΔ: (p=0.037)          |          |                                                             |                               |
|                        |                                      | DiffΔ: −3% (−12–6)                         | DiffΔ: (p=0.022)          |          |                                                             |                               |
| **Xi et al. [51]**     | FVC (% pred): IGΔ: (p<0.05)          | MIP (cmH₂O): IGΔ: 0%                      | Borg: DiffΔ: (p<0.05)     |          |                                                             | Nil adverse events; 0%        |
|                        | CGΔ: (p<0.05)                        | CGΔ: 0.01%                                | IGΔ: (p<0.05)             |          |                                                             |                               |
|                        | DiffΔ: (p=0.05)                      | DiffΔ: 1% (−7–9)                           | CGΔ: (p<0.05)             |          |                                                             |                               |
|                        |                                      | MEP (cmH₂O): IGΔ: 16                      | DiffΔ: (p=0.022)          |          |                                                             |                               |
|                        | IGΔ: 5%                              | IGΔ: 5%                                   | SGRQ: DiffΔ: (p<0.05)     |          |                                                             |                               |
|                        | DiffΔ: (p=0.05)                      | DiffΔ: 4% (−7.9–1.4)                      | CGΔ: (p<0.05)             |          |                                                             |                               |
|                        | Perceived coughing ability:          | DiffΔ: (p=0.022)                           | DiffΔ: (p=0.037)          |          |                                                             |                               |
|                        | DiffΔ: −3% (−12–6)                   | DiffΔ: (p=0.022)                           | DiffΔ: (p=0.037)          |          |                                                             |                               |

Attrition rate (%) refers to the percentage of randomised participants without follow-up data. Mean (standard deviation) within-group changes for each group, and mean (standard deviation) between group difference in changes (95% CI), p-value provided when 95% CI unavailable. % pred: percentage predicted; 6MPT: 6-min push test; 6-MWT: 6-min walk test; Diff: difference; CFR: concurrent flow resistance; CG: control group; CPTR: concurrent pressure threshold resistance; EQ-5D: EuroQol five dimensions; FVC: forced vital capacity; IG: intervention group; IH: isocapnic hyperpnoea; IRT: inspiratory resistance training; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; PCF: peak cough flow; PEF: peak expiratory flow; RPE: rating of perceived exertion; SF-36: 36-item short form; SGRQ: St George’s respiratory questionnaire; SNIP: sustained nasal inspiratory pressure; VAS: visual analogue scale; VC: vital capacity; VO₂: oxygen uptake. ^a: Indicates studies assessing children.
### Respiratory muscle strength

At least one test of respiratory muscle strength outcomes (MIP, MEP, SNIP) was reported in all but three [22, 44, 51] studies. The total pooled meta-analysis showed RMT improved MIP absolute pressure; SMD 0.57 (0.25–0.88) (Appendix 4C). Five studies were not included due to inadequate data [17, 21, 23, 43] or an athletic population [45]. Four of the omitted studies identified significant strength improvements in the experimental group [17, 21, 23, 45], with the other reporting no change. Subgroup analyses of studies that utilised IMT alone and IMT+EMT showed greater improvements in MIP absolute pressure in the experimental compared to the control groups; SMD 0.56 (0.16–1.05). However, the EMT alone subgroup analysis found no difference. Similar results were found for MIP % predicted with pooled studies finding a benefit of RMT; SMD 0.43 (0.05–0.81) (Appendix 4D) and the IMT+EMT subgroup favouring RMT; SMD 0.74 (0.23–1.26).

Absolute MEP similarly favoured the experimental interventions overall; SMD 0.71 (0.37–1.04) (Appendix 4E), in the IMT+EMT subgroup; SMD 1.34 (0.22–2.45), and in the EMT subgroup; SMD 0.86 (0.43–1.30). Four studies were not included, due to inadequate data or an incomparable study population (athletes with SCI), with three reporting a significant improvement in the experimental group [23, 43, 45] and one reporting no change [32]. When expressed as percentage of predicted values, MEP meta-analysis results were unclear, with few included studies and wide confidence intervals for the total pooled and all subgroup analyses (Appendix 4F).

### TABLE 1

| Study or subgroup | Respiratory training | Control | Total | Weight (%) | SMD IV, random, 95% CI | SMD IV, random, 95% CI |
|------------------|----------------------|---------|-------|------------|------------------------|------------------------|
| **Inspiratory training** | | | | | | |
| DERRICKSON et al. [16] | 2.6 (0.73) | 6 | 1.68 (0.32) | 5 | 2.7 | 1.44 (0.03–2.84) |
| FREGONEZI et al. [17] | 2.8 (0.83) | 14 | 2.35 (0.91) | 13 | 5.6 | 0.24 (–1.00–0.52) |
| FRI et al. [18]/PFALZER et al. [31] | 0.2 (0.29) | 20 | 0.01 (0.29) | 21 | 6.4 | 0.64 (0.01–1.27) |
| Kim et al. [22] | 0.15 (0.06) | 12 | 0.03 (0.01) | 12 | 3.5 | 2.69 (1.54–3.85) |
| LIAW et al. [24] | 0.6 (0.31) | 10 | 0.4 (0.31) | 10 | 4.7 | 0.62 (–0.28–1.52) |
| MOHAMED et al. [52] | 0.08 (0.07) | 15 | 0.03 (0.03) | 15 | 5.6 | 0.90 (0.15–1.66) |
| MUELLER et al. [30] | 0.4 (0.37) | 16 | 0.32 (0.45) | 8 | 5.0 | 0.19 (–0.66–1.05) |
| POSTMA et al. [34] | 0.42 (0.55) | 19 | 0.41 (0.55) | 21 | 6.5 | 0.02 (–0.60–0.64) |
| REYES et al. [35] | 2.76 (0.92) | 11 | 3.03 (1.25) | 5 | 3.9 | 0.25 (–1.31–0.81) |
| TOPIN et al. [42] | 1.78 (0.31) | 8 | 1.76 (0.79) | 8 | 4.3 | 0.03 (–0.95–1.01) |
| VURAL et al. [50] | 0.41 (0.4) | 9 | 0 (0.06) | 7 | 3.7 | 1.30 (0.19–2.42) |
| WANKE et al. [44] | 1.62 (0.9) | 15 | 1.48 (0.71) | 15 | 5.8 | 0.17 (–0.55–0.89) |
| **Subtotal (95% CI)** | 155 | 140 | 57.8 | 0.54 (0.14–0.94) |

**Expiratory training**

GOUNDEN et al. [20]

| | Respiratory training | Control | Total | Weight (%) | SMD IV, random, 95% CI | SMD IV, random, 95% CI |
|------------------|----------------------|---------|-------|------------|------------------------|------------------------|
| 0.5 | 0.42 | 20 | –0.1 | 0.55 | 20 | 6.1 | 1.20 (0.52–1.88) |
| 3.27 | 1.38 | 10 | 3.03 | 1.25 | 5 | 3.9 | 0.17 (–0.91–1.24) |
| 0.28 | 0.43 | 16 | 0.34 | 0.53 | 13 | 5.7 | –0.12 (–0.85–0.61) |
| 0.36 | 0.96 | 30 | 3.23 | 0.78 | 30 | 7.2 | 0.47 (–0.04–0.99) |
| 3.6 | 1 | 23 | 3.6 | 1 | 25 | 6.9 | 0.00 (–0.57–0.57) |
| **Subtotal (95% CI)** | 99 | 93 | 29.8 | 0.36 (–0.10–0.83) |

**Combined training**

ASLAN et al. [2]

| | Respiratory training | Control | Total | Weight (%) | SMD IV, random, 95% CI | SMD IV, random, 95% CI |
|------------------|----------------------|---------|-------|------------|------------------------|------------------------|
| 0.09 | 0.2 | 14 | –0.2 | 0.7 | 10 | 5.1 | 0.59 (–0.24–1.42) |
| 2.5 | 1.1 | 30 | 2.6 | 1 | 32 | 7.4 | –0.09 (–0.59–0.40) |
| **Subtotal (95% CI)** | 44 | | 12.5 | 0.16 (–0.49–0.82) |

**Total (95% CI)**

| | Respiratory training | Control | Total | Weight (%) | SMD IV, random, 95% CI | SMD IV, random, 95% CI |
|------------------|----------------------|---------|-------|------------|------------------------|------------------------|
| 298 | 275 | 100.0 | | 0.43 (0.16–0.70) |

**FIGURE 3** Forest plot for (forced) vital capacity. df: degrees of freedom; IV: inverse variance; SMD: standardised mean difference
Two of the included studies included SNIP as an outcome measure [2, 32], with one study reporting a significant improvement following IMT+EMT training [2] and the other reporting no effect on SNIP with RMT. Inadequate data precluded meta-analysis.

Measurement of cough
19 studies [2, 16, 18, 19, 23, 24, 30, 32–35, 37, 39, 45–48, 50, 52] measured cough, either with subjective reporting of cough effectiveness or measures of PEF and/or PCF. Meta-analyses for PEF included eight studies and found no benefit of RMT; SMD 0.33 (−0.02–0.67) (Appendix 4G). An additional three studies not included in the meta-analysis reported no change on PEF following RMT [23, 32, 45]. Seven studies investigated the impact of RMT on PCF [2, 33–35, 46–48], with all but one [35] identifying no differences between groups. Six provided data that could be combined, with the meta-analysis demonstrating no significant benefit of RMT on PCF; SMD 0.28 (−0.07–0.64) (Appendix 4H). No significant differences between groups were found in studies measuring cough effectiveness by self-report [19, 30, 34, 46].

Dyspnoea
12 studies investigated the impact of RMT on breathlessness [3, 21, 23, 24, 30, 32, 37, 45, 46, 48, 49, 51], using a combination of VAS, Borg rating, perception of dyspnoea and respiratory load scales. There were no between-group differences identified in five studies [23, 30, 32, 45, 46]; however, seven studies reported significant improvements in the experimental groups for respiratory load perception [3], perception of dyspnoea [21] and Borg rating [24, 37, 48, 49, 51]. A meta-analysis was conducted combining the five studies reporting Borg or VAS dyspnoea scores (Appendix 4I). The results suggest no benefit; SMD −0.33 (−1.16–0.49 where negative change indicates improvement).

Secondary outcomes
Three studies investigated phonation and voice outcomes; whilst an improvement in phonation time and peak sound pressures was found in one study after a period of IMT [36], the remaining two studies reported no training benefit [30, 34].

Six studies investigated the impact of RMT on QoL using the 36-Item Short Form Survey (SF-36; or sub-components) [15, 17, 25, 30, 34] or the EuroQol five dimensions (EQ-5D) test [32, 48]. Four found no difference between groups, one identified worsening on the EQ-5D following RMT [48], and two reported improvements in the physical and mental components of the SF-36 [17] and SF-12 [30].

Nine studies measured physical capacity. Two found significantly greater improvements in walking distance (6 min walk test) in the experimental group [37, 52], while three others found no difference [15, 18, 47]. One reported a significant improvement in 6-min push test distance following IMT [49]. In athletic SCI populations, 1-mile time-trial performance improved [25] and peak work rate improved [45] compared to control groups. However, another study found that the peak work rate did not change [27].

Only one study reported any adverse effects. Westerdahl et al. [46] noted that 17% of participants with multiple sclerosis reported at least some degree of discomfort related to the exercises and adverse perceptions of dizziness, strenuousness and tediousness.

Sensitivity analyses
Sensitivity analyses that examined the summary measures of effect (Appendix 5, mean difference rather than SMD, and within-group change scores) changed the relative magnitude and the precision of the estimates of effect, but made no impact on the conclusions. Mean difference analyses on the subset of studies that reported change data indicated that across all training types, improvements in absolute FVC, MIP and MEP were by approximately 200 mL, 9 cmH2O and 13 cmH2O respectively. No sensitivity analysis based on study quality was performed due to a paucity of high-quality studies. The 15 SCI studies accounted for eight of 18 (44%) of the FVC, eight of 21 (38%) of the MIP and seven of 21 (33%) of the MEP data (Appendix 2). In the FVC, MIP and MEP SCI alone meta-analysis, significant heterogeneity and mean difference estimates were observed. The “SCI only” estimates of heterogeneity, as summarised by the I² statistics, were very similar to the effects overall (FVC, 61% versus 58%; MIP 58% versus 65%; MEP 74% versus 75%). The three next single diagnoses with the highest number of studies (multiple sclerosis, Duchenne’s muscular dystrophy and Parkinson’s disease) were not overall significant contributors to heterogeneity or estimates of mean difference apart from the mean difference in MEP in Parkinson’s disease.
Discussion

This systematic review and meta-analysis demonstrated that RMT improves lung volumes and respiratory muscle strength in NMD conditions characterised by respiratory muscle weakness, compared to usual care, sham interventions or alternative treatments. There was no demonstrated benefit of RMT on cough, dyspnoea, physical capacity, voice or QoL measures. The quality of the evidence supporting these findings was rated as low or very low because of the overall high risk of bias in included studies and the small sample sizes; however, this review of 37 trials and 951 participants is the largest review of RMT. Whilst several other reviews have investigated RMT in specific neuromuscular cohorts, this review is unique in that we took a broad view of the impact of RMT across the whole neuromuscular population. Our approach increased the clinical heterogeneity within each analysis but is more useful from a clinical perspective due to the wide variability in clinical presentations both between and also within specific NMD diagnoses.

Of the included studies in this review, 53% investigated IMT, 19% EMT and 28% a combination of both IMT and EMT. Training protocols varied widely across the studies and recommendations cannot yet be made in relation to load, intensity or duration of training; however, most studies utilised threshold loaded devices to deliver resistance.

The meta-analysis identified an overall benefit of RMT on FVC in absolute units, which was estimated to equate to a difference of 0.15 L (0.08, 0.22). This is consistent with previous systematic reviews [5, 53]. Improving or slowing the rate of decline in lung volumes is clinically important in people with NMD; reduced lung volume is associated with hypoventilation, need for noninvasive ventilation and mortality [54–57]. Further, as readiness for weaning from mechanical ventilation in people with SCI is indicated by a VC of 15 mL·kg\(^{-1}\) (approximately 1 L for a 70kg person) [58–60], and a slower decline in VC is associated with improved survival in amyotrophic lateral sclerosis and Duchenne muscular dystrophy [61–63], the benefit is likely to be clinically important.

Approximately half of the included studies demonstrated a benefit of RMT on respiratory muscle strength (MIP and MEP), with the meta-analyses demonstrating a significant benefit from the training. The findings suggest that IMT may improve inspiratory muscle strength but not expiratory muscle strength, while the reverse happens for EMT. There was evidence to support that IMT+EMT interventions can improve both inspiratory and expiratory muscle strength and therefore combined training is recommended if it can be tolerated by the patient. Emerging evidence suggests that SNIP may be a more sensitive marker of respiratory muscle strength, particularly in people with amyotrophic lateral sclerosis and children [64, 65]. Few studies reported SNIP data and it is recommended that future research include this outcome.

The estimated magnitude of effect on MIP and MEP of 8.52 cmH\(_2\)O (5.22–11.83) and 12.44 cmH\(_2\)O (6.608–18.28), respectively, are similar in magnitude but opposite in direction to the detrimental reduction in respiratory muscle strength observed in people with NMD during an acute respiratory tract infection [66]. Reductions in MIP and MEP during acute illness are associated with shortness of breath, fall in VC and acute hypercapnia and as with lung volume, decline in MIP, MEP and SNIP are predictive biomarkers of survival in people with amyotrophic lateral sclerosis [56, 65]. Taken together, these observations suggest that the observed change with RMT was likely clinically important.

The review found no impact of training on PEF, PCF or subjective reports of cough effectiveness, despite cough effectiveness being clinically important in NMD [9]. Despite PCF being interpreted as a measure of “cough effectiveness”, only one prospective study has reported a relationship between PCF and an inability to clear secretions [67]. Nonetheless, PCF has considerable currency as a surrogate measure of cough efficacy [9] and PCF values are reported as similar to PEF values in people with amyotrophic lateral sclerosis [68] or slowly progressive NMD [69].

Several studies identified significant within- [3, 21, 24, 32, 37] or between-group [24] improvements in dyspnoea, but only three were able to be meta-analysed, with no difference between groups observed. Findings for voice, physical capacity, QoL were similarly inconclusive. These outcomes are of most relevance and importance to people living with NMDs [70], so should be included in future studies.

Despite clinical concerns regarding RMT and the potential risk of overexerting already weak muscles [71], no adverse events beyond discomfort in one small study of participants with multiple sclerosis were reported. This is consistent with findings from a previous systematic review in children [7].

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Limitations
Studies without outcome data were omitted and exclusion of non-English language articles both present risk of selection bias. The heterogeneity of studies in terms of populations (children and adults, different NMDs), interventions, dosage, and comparators mean the results should be interpreted with caution. SCI comprised approximately one third of included study diagnoses, but the observed heterogeneity in these studies was comparable with that observed overall. Importantly, by examining the single diagnoses, it became apparent that most other NMDs do not have randomised controlled trial data of sufficient quality to support a series of single-disease meta-analysis. Including all NMDs increased the evidence pool and enabled determination of whether the intervention is broadly beneficial in any condition of respiratory muscle weakness. The heterogeneity was managed by using standardised mean differences for the meta-analyses; however, this then makes interpreting the clinical importance of observed differences challenging. Importantly, the sensitivity analyses using mean difference supported the primary findings. The magnitudes of observed differences in (F)VCl and MIP in particular, are likely to be clinically important.

Points for clinical practice

- Respiratory muscle weakness is a cardinal characteristic of NMD and respiratory muscles, like all skeletal muscles, are able to be trained.
- Unfortunately, the data from research examining RMT for NMDs comes largely from small clinical trials and is highly heterogeneous.
- Despite this heterogeneity, there is a clear overall signal of benefit from training.

Conclusions
This review suggests RMT has a broadly beneficial effect on lung volume and respiratory muscle strength across a wide range of NMD populations. However, study risk of bias was generally high and overall confidence in the findings was low. A paucity of data renders it impossible to determine whether the demonstrated improvements in respiratory function translate into clinically important changes in dyspnoea, voice, QoL or physical capacity and there are insufficient data to formulate recommendations regarding optimum training dosage or frequency. Based on the review findings, RMT can be safely used to increase respiratory muscle strength and lung volumes in people with NMD, but more research, especially to help clinicians select training parameters, understand the clinical importance of benefits and that includes outcomes of importance to consumers, is needed.

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