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

Kathryn Watson[1], Thorlene Egerton[2], Nicole Sheers [3,4], Sarah Retica[5], Rebekah McGaw[5], Talia Clohessy[5], Penny Webster [6] and David J. Berlowitz [2,3,4,5]

[1]Department of Physiotherapy, Fiona Stanley Hospital, Perth, Australia. [2]Department of Physiotherapy, The University of Melbourne, Melbourne, Australia. [3]Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, Australia. [4]Institute for Breathing and Sleep, Melbourne, Australia. [5]Department of Physiotherapy, Austin Hospital, Heidelberg, Australia. [6]Hunter 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

Cite this article as: Watson K, Egerton T, Sheers N, *et al*. Respiratory muscle training in neuromuscular disease: a systematic review and meta-analysis. *Eur Respir Rev* 2022; 31: 220065 [DOI: 10.1183/16000617.0065-2022].

Received: 12 April 2022
Accepted: 1 Sept 2022

Abstract

Background Neuromuscular 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),

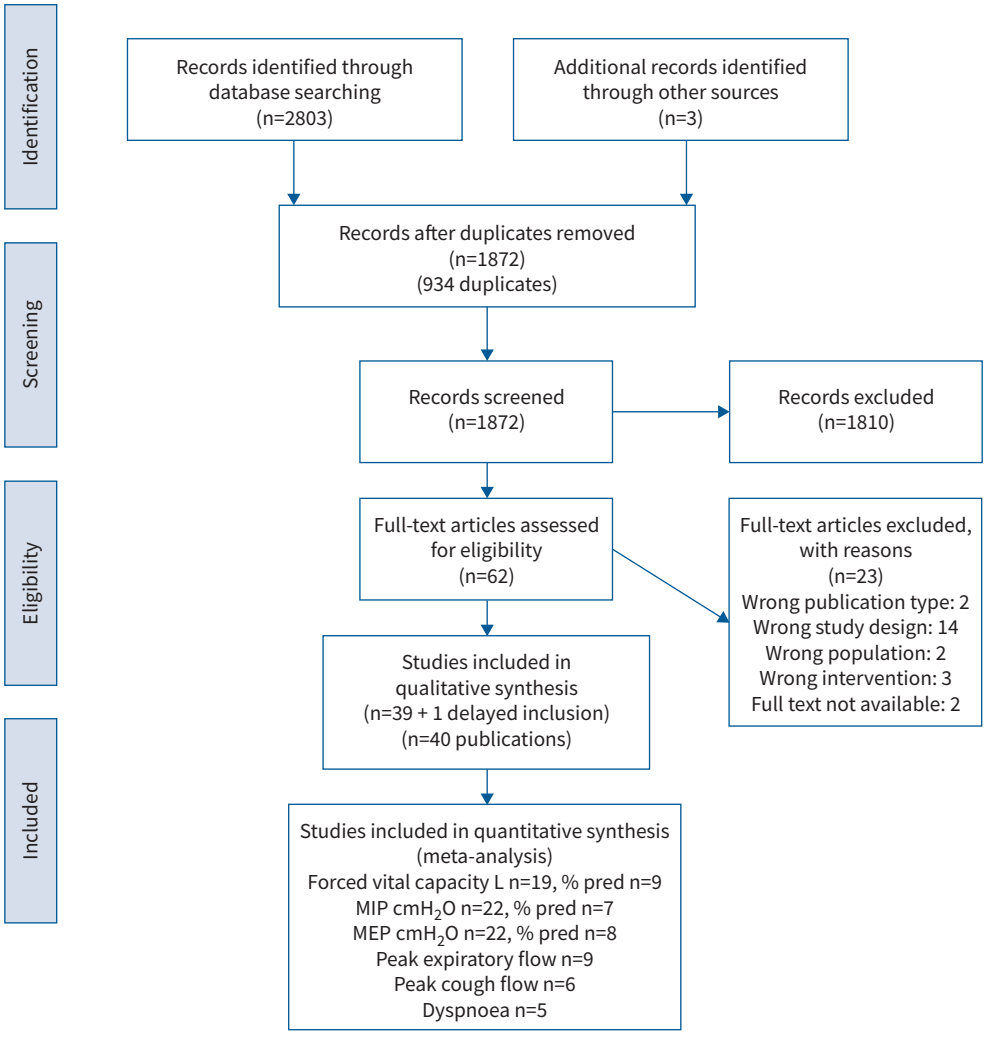

FIGURE 1 Flow diagram (based on PRISMA statement) [11]. MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

https://doi.org/10.1183/16000617.0065-2022

TABLE 1 Characteristics of included studies

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 cmH_2O, 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_{Imax}, 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_{Imax}, P_{Emax}, 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_{Imax}
Fregonezi *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_{Imax} 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_{Imax}/P_{Emax}, thoracic mobility
Fry *et al.* [18], community, USA	Multiple sclerosis, n=41 (20/21), IG: 50±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
Gosselink *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_{Emax}, three sets, 15 reps, twice daily, 3 months)	Breathing exercises	Spirometry, P_{Imax}, P_{Emax}, functional measures
Gounden *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_{Emax}, 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_{Emax}
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_{Imax}/P_{Emax}, twice daily, 6 months)	Sham training	Spirometry, P_{Imax}, P_{Emax}, load perception
Inzelberg *et al.* [21], outpatient clinic, Israel	Parkinson's disease, n=20 (10/10), IG: 59.4 ±2.4 years, CG: 65.2±3.6 years, 60% male	Inspiratory training (15% of P_{Imax}, 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 cmH_2O, same protocol	Spirometry, P_{Imax}, 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
Klefbeck *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_{Imax}, twice every second day, three sets, 10 reps, 10 weeks)	Standard care	Spirometry, P_{Imax}/P_{Emax}, subjective reporting

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https://doi.org/10.1183/16000617.0065-2022

TABLE 1 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	V_{O_2} 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
Mueller *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 cmH_2O, same protocol	
Plowman *et al.* [33], home-based programme, USA	Amyotrophic lateral sclerosis, n=48 (23/23), IG: 63.1±10.0 years, CG: 60.1±10.3 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, CG: 70.2±6.7 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

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TABLE 1 Continued

Citation, setting, country	Diagnosis, sample size (IG/CG), IG age, CG age, gender	Intervention (dosage)	Comparator	Study primary outcomes
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, MIP, MEP
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_{Imax}, P_{Emax}
Soumyashree *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
Stern *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_{Imax}
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, MIP
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_{Imax}, P_{Emax}, index of pulmonary dysfunction
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
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_{Imax}, maximal sniff, oesophageal and transdiaphragmatic pressure
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_{Imax} 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_{Imax}/P_{Emax}, dyspnoea, physical response to exercise
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_2O, 30 reps, twice daily, 8 weeks)	Standard care	Spirometry, MIP/MEP, thoracic excursion, subjective symptoms
Xi *et al.* [51], inpatient, China	Spinal cord injury, n=18 (8/10), IG: 54.3±6.6 years, CG: 52.9±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_{Emax}): maximal expiratory pressure; MIP (P_{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_{O_2}: oxygen uptake. [#]: studies assessing children. [¶]: only the initial assessment period for Pinto *et al.* [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% (SD 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).

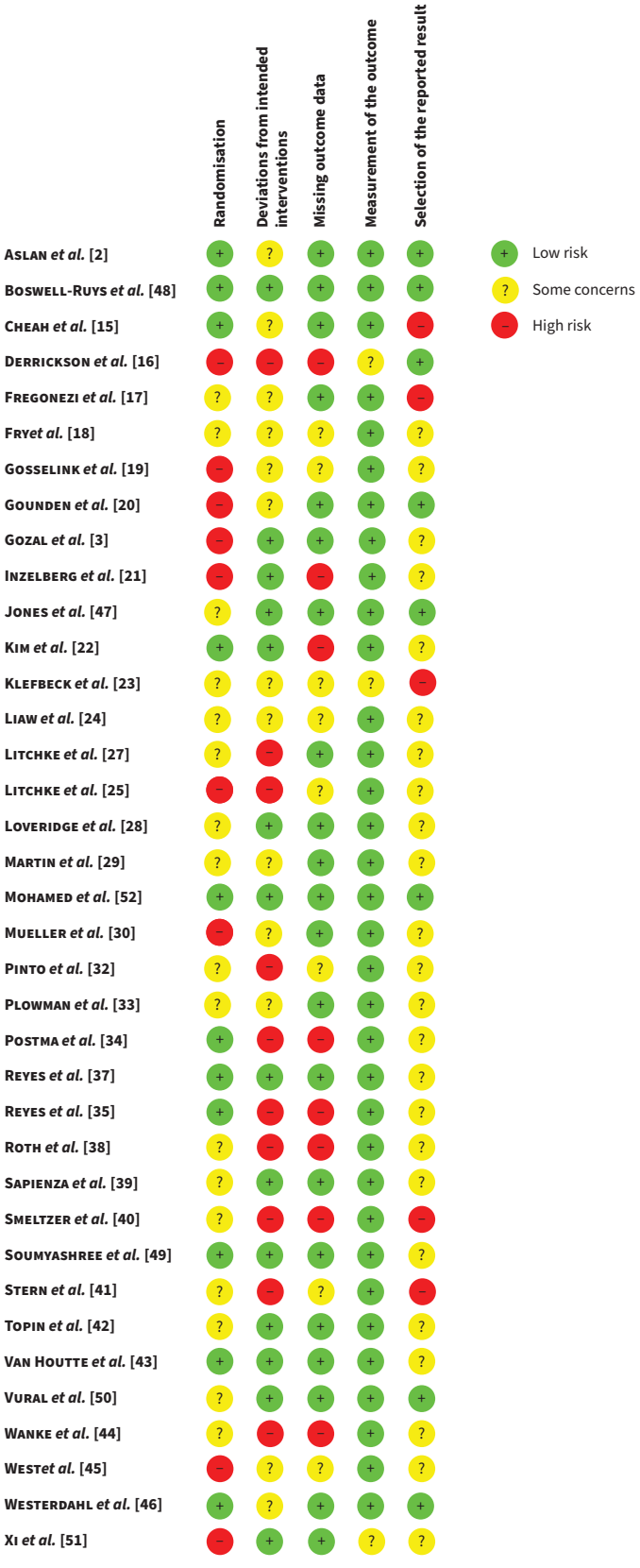

FIGURE 2 Results of risk of bias assessment for included studies.

https://doi.org/10.1183/16000617.0065-2022

TABLE 2 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool assessment for outcomes entered in meta-analyses

Outcome	*k*	*n*	SMD (95% CI)	I^2 (p-value)	Heterogeneity[#]	Indirectness[¶]	Bias[+]	Imprecision[§]	Publication bias[f]	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	Serious	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	Serious	NA	Low
FVC (% pred)	**9**	**235**	**0.23 (−0.03–0.49)**	**0% (0.8)**	**None**	**Serious**	**Very serious**	**Serious**	**NA**	**Low**
Inspiratory	5	127	0.13 (−0.22–0.48)	0% (0.75)	None	Serious	Very serious	Very serious	NA	Low
Expiratory	1	48	0.04 (−0.52–0.61)	NA	NA	None	Serious	Very serious	NA	Low
Combined	3	60	0.60 (0.08–1.12)	0% (1.0)	None	Serious	Serious	Very serious	NA	Low
MIP (cmH_2O)	**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	Very serious	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	Serious	Very serious	NA	Very low
MIP (% pred)	**7**	**168**	**0.43 (0.05–0.81)**	**27% (0.22)**	**None**	**Serious**	**Very serious**	**Serious**	**NA**	**Low**
Inspiratory	2	40	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	Serious	Very serious	NA	Low
MEP (cmH_2O)	**22**	**661**	**0.71 (0.37–1.04)**	**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**	**Serious**	**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	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	Serious	NA	Low
Expiratory	2	108	0.22 (−0.33–0.77)	52% (0.15)	Serious	None	Serious	Serious	NA	Low
PCF	**6**	**227**	**0.28 (−0.07–0.64)**	**40% (0.14)**	**None**	**Serious**	**Very serious**	**Serious**	**NA**	**Very low**
Dyspnoea	**5**	**151**	**−0.33 (−1.16–0.49)**	**81% (0.0003)**	**Very serious**	**Serious**	**Serious**	**Serious**	**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⩾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). [f]: NA means publication bias unable to be assessed as insufficient (less than 10 trials (*k*) per outcome). [##]: starts at high quality and is downgraded – can be low (downgraded by one) or very low (downgraded by two).

https://doi.org/10.1183/16000617.0065-2022

TABLE 3 Results from included studies

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 (cmH_2O): IGΔ: 24.2 (13.7) CGΔ: 5.6 (10.8) DiffΔ: (p=0.002) MEP (cmH_2O): 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 ($L{\cdot}min^{-1}$): 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 (cmH_2O): IGΔ: 15.3 CGΔ: 3.4 DiffΔ: 11.5 (5.6–17.4) MEP (cmH_2O): IGΔ: 5.6 CGΔ: 4.2 DiffΔ: (p=0.799)	PCF ($L{\cdot}min^{-1}$): 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)			6MWT: DiffΔ: 6.0% (3.6) (−1.8–13.8) SF-36: no differences	Nil adverse events; 5%
Derrickson *et al.* [16]	FVC (L): IGΔ: 1.3 CGΔ: 0.5 DiffΔ: (p>0.05)	MIP (cmH_2O): IGΔ: 23.3 CGΔ: 22.6 DiffΔ: (p>0.05)	PEF ($L{\cdot}s^{-1}$): IGΔ: 1.77 CGΔ: 0.89 DiffΔ: (p>0.05)			Nil adverse events. 73%
Fregonezi *et al.* [17]	FVC (L): IGΔ: 0.1 CGΔ: 0 DiffΔ: (p>0.05)	MIP (cmH_2O): IGΔ: 15 CGΔ: unchanged DiffΔ: (p=0.001) MEP (cmH_2O): IGΔ: 12 CGΔ: −3 DiffΔ: (p=0.01)			SF-36 role physical domain: IGΔ: 21 CGΔ: unchanged	Nil adverse events; 7%

Continued

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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
Fry *et al.* [18]	FVC (L): IGΔ: 0.3 (0.29) CGΔ: 0.01 (0.29) DiffΔ: (p=0.04)	MIP (cmH_2O): IGΔ: 23.5 CGΔ: −0.7 DiffΔ: (p=0.001) MEP (cmH_2O): IGΔ: 4.5 CGΔ: −3.6 DiffΔ: (p=0.291)	PEF (L): IGΔ: 0.23 CGΔ: −0.16 DiffΔ: (p=0.02)		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 (cmH_2O): IGΔ: 39% (41) CGΔ: 11% (36) DiffΔ: (p=0.06) MEP (cmH_2O): IGΔ: 30% (46) CGΔ: −4% (26) DiffΔ: (p=0.07)				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 (cmH_2O): IGΔ: 24.3 (18.2) CGΔ: 2.25 (13.43) DiffΔ: (p=0.0001)				Nil adverse events; 0%
Gozal *et al.* [3]#		MIP (cmH_2O): IGΔ: 19.8 (3.8) CGΔ: 4.2 (3.6) DiffΔ: (p<0.02) MEP (cmH_2O): IGΔ: 27.1 (4.9) CGΔ: −1.8 (3.4) DiffΔ: (p<0.004)				Nil adverse events; 0%
Inzelberg *et al.* [21]	FVC (L): no data provided – no significant change	MIP (cmH_2O): IGΔ: 16 CGΔ: no data DiffΔ: (p<0.05)		Dyspnoea index: IGΔ: −3.9 CGΔ: no data provided DiffΔ: (p<0.05)		Nil adverse events; 0%
Jones *et al.* [47]		MIP (cmH_2O): IGΔ: 7.6 (15.9) CGΔ: 2.7 (7.6) DiffΔ: (p=0.47) MEP (cmH_2O): IGΔ: 14 (25.9) CGΔ: 0 (12) DiffΔ: (p=0.19)	PCF ($L{\cdot}s^{-1}$): IGΔ: 0.4 (1.8) CGΔ: 0.7 (2.3) DiffΔ: (p=0.55)		6MWT (m): IGΔ: 22 (28.8) CGΔ: 9.8 (20.1) DiffΔ: (p=0.34)	Nil adverse events; 0%

Continued

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
Kim *et al.* [22]	FVC (L): IGΔ: 0.15 (0.06) CGΔ: 0.03 (0.01) DiffΔ: (p= 0.002)					Nil adverse events; 12%
Klefbeck *et al.* [23]		MIP (cmH_2O): IGΔ: 25 CGΔ: 2 DiffΔ: (p<0.01) MEP (cmH_2O): IGΔ: 17 CGΔ: 0 DiffΔ: (p<0.02)	PEF: no change (no data reported)	Borg RPE: No change (no data reported)		Nil adverse events; 6%
Liaw *et al.* [24]	FVC (L): IGΔ: 66% (74) CGΔ: 28% (36) DiffΔ: (p=0.172)	MIP (cmH_2O): IGΔ: 29% (21) CGΔ: 27% (27) DiffΔ: (p=0.844) MEP (cmH_2O): IGΔ: 2% (52) CGΔ: 44% (21) DiffΔ: (p=0.915)	PEF ($L{\cdot}s^{-1}$): 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%
Litchke *et al.* [27]		MIP (cmH_2O): IGΔ: 33 CGΔ: 0.6 DiffΔ: (p=0.039)			V_{O_2} peak: IGΔ: 0.6 CGΔ: 0.1 DiffΔ: (p>0.05)	Nil adverse events; 10%
Litchke *et al.* [25]		MIP (cmH_2O): IG (CPTR)Δ: 22 IG (CFR group)Δ: 4.8 CGΔ: 2.6			Time trial: IG (CPTR)Δ: −60.03 IG (CFR)Δ: −0.07 CGΔ: −0.14 DiffΔ CPTR *versus* CG: (p=0.038) DiffΔ CFR *versus* CG: (p>0.05)	Nil adverse events; 33%
Loveridge *et al.* [28]	FVC (% pred): IGΔ: 1% CGΔ: 3% DiffΔ: (p>0.05)	MIP (cmH_2O): IGΔ: 44.2% (32.7), CGΔ: 30.2% (18.9) DiffΔ: (p>0.05)				Nil adverse events; 0%
Martin *et al.* [29]#	VC (% pred): IGΔ: 1.9 (4.3) CGΔ: −0.8 (4.3) DiffΔ: (p>0.05)	MIP (mmHg): 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%

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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
Mohamed *et al.* [52]	VC (L): IGΔ: 0.08 (p=0.001) CGΔ: 0.03 (p=0.003) DiffΔ: 0.05 (p=0.03)	MIP (cmH_2O): IGΔ: 8.53 (p=0.001) CGΔ: 1.4 (p=0.02) DiffΔ: 8.06 (p=0.001) MEP (cmH_2O): IGΔ: 8.60 (p=0.001) CGΔ: 2.67 (p=0.001) DiffΔ: 5.53 (p=0.001)	PEF ($L{\cdot}min^{-1}$): IGΔ: 6.41 (p=0.001) CGΔ: 1.8 (p=0.02) DiffΔ: 5.26 (p=0.001)		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)Δ: 0.3 (0.3), IG (IRT)Δ: 0.5 (0.4) CGΔ: 0.32 (0.5) DiffΔ: (p>0.05)	MIP (cmH_2O): IG (IH)Δ: 7 (10.0) IG (IRT)Δ: 35.4 (29.4) CGΔ: 8.9 (15.2) MEP (cmH_2O): IG (IH)Δ: 8.5 (39.4) IG (IRT)Δ: 7.5 (14.7) CGΔ: 3.3 (13.3) DiffΔ: (p>0.05)	PEF ($L{\cdot}s^{-1}$): IG (IH)Δ: 0.4 (0.5) IG (IRT)Δ: 1.2 (1.2) CGΔ: 0.6 (0.9) Cough (VAS): IG (IH)Δ: −0.05 (1.6) IG (IH)Δ: 1.1 (1.5) CGΔ: 0.9 (3.4) DiffΔ: (p>0.05)	Dyspnoea: IG (IH)Δ: −0.3 (1.1) IG (IRT)Δ: 0.03 (2.7) CGΔ: −2.2 (3.1) DiffΔ: (p>0.05)	Sustained phonation time: IG (IH)Δ: 1.7 (5.4) IG (IRT)Δ: 2.7 (6.2) CGΔ: 0.6 (3.3) Loudness of voice: IG (IH)Δ: 1.9 (6.5) IG (IRT)Δ: −0.8 (6.3) CGΔ: 2.9 (3.0) SF-12 (physical): IG (IH)Δ: 2.2 (7.5) IG (IRT)Δ: 1.6 (4.1) CGΔ: −2.8 (6.4)	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 (cmH_2O): DiffΔ: −8.2 (10.5) (−29.85–13.538) MEP (cmH_2O): DiffΔ: −7.7 (11.8) (−32.06–16.827) SNIP: DiffΔ: −10.4 (9.7) (−30.442–9.673)	PEF ($L{\cdot}s^{-1}$): 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%
Plowman *et al.* [33]	FVC (% pred): IGΔ: −7.6% (−14.9–−0.3) CGΔ: −8.3% (−14.7–1.9) DiffΔ: (p=0.86)	MEP (cmH_2O): IGΔ: 25.5 (14.3–36.7) CGΔ: 6.6 (−3.4–16.5) DiffΔ: (p=0.009)	PCF ($L{\cdot}s^{-1}$): IGΔ: 0 (−1.3–1.3) CGΔ: −0.6 (−1.5–0.4) DiffΔ: (p=0.09)			Nil adverse events; 4%

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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
Postma *et al.* [34]	FVC (L): IGΔ: 0.42 CGΔ: 0.41 DiffΔ: −0.04 (−0.3–0.22)	MIP (cmH_2O): IGΔ: 26.3 CGΔ: 14.6 DiffΔ: 11.67 (4.33–19.02) MEP (cmH_2O): IGΔ: 13.8 CGΔ: 8.8 DiffΔ: 2.65 (−8.55–13.85)	PEF ($L{\cdot}s^{-1}$): IGΔ: 0.72 CGΔ: 0.49 DiffΔ: 0.25 (−0.53–1.03) PCF ($L{\cdot}s^{-1}$): IGΔ: 0.76 CGΔ: 0.7 DiffΔ: 0.16 (−0.52–0.83) Perceived cough function: IGΔ: −2 CGΔ: −2 DiffΔ: 0.49 (−0.74–1.72)		Perceived talking function: IGΔ: −3 CGΔ: −1.67 DiffΔ: −0.28 (−1.5–0.94) SF-36: IGΔ: 2.1 CGΔ: 5.9 DiffΔ: −5.47 (−15.12–4.19)	Nil adverse events; 34%
Reyes *et al.* [37]	FVC (% pred): IG: 0.26 (−0.67, 1.19) CG: −0.06 (−0.99–0.86)	MIP (cmH_2O): IG effect size: 0.47 (−0.46–1.41) CG effect size: 0.32 (−0.61–1.25) MEP (cmH_2O): IG effect size: 0.37 (−0.56–1.3) CG effect size: −0.09 (−1.01–0.84)	PEF (% pred): IG effect size: 0.39 (−0.55–1.32) CG effect size: −0.17 (−1.10–0.75) Diff effect size: 0.8	Dyspnoea: IG effect size: −0.87 (−1.84–0.1) CG effect size: 0.00 (−0.92–0.92)	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.* [35]	FVC (L): IG (inspiratory) effect size: 0.14 (−0.19–0.47) IG (expiratory) effect size: 0.19 (−0.45–0.82) CG effect size: 0.24 (−0.51–0.99)	MIP (cmH_20): IG (inspiratory) effect size: −0.03 (−0.32–0.39) IG (expiratory) effect size: −0.01 (−0.35–0.13) CG effect size: −0.25 (−0.43– −0.07) MEP (cmH_2O): IG (inspiratory) effect size: −0.06 (−0.23–0.34) IG (expiratory) effect size: 0.54 (−0.40–0.7) CG effect size: −0.18 (−0.18– −0.46)	Voluntary PCF ($L{\cdot}s^{-1}$): IG (inspiratory) effect size: 0.07 (−0.32–0.46) IG (expiratory) effect size: 0.04 (−0.44–0.52) CG effect size: 0.03 (−0.27–0.33) Reflexive PCF ($L{\cdot}s^{-1}$): IG (inspiratory) effect size: −0.12 (−0.62–0.37) IG (expiratory) effect size: 0.34 (−0.44–1.09) CG effect size: −0.22 (−0.75–0.31)		Mean subglottic pressure: IG (inspiratory) effect size: −0.12 (−0.79–0.55) IG (expiratory) effect size: 0.43 (−0.45–1.31) CG effect size: −0.41 (−1.51–0.68) Maximum phonation time: IG (inspiratory) effect size: −0.78 (−1.26– −0.31) IG (expiratory) effect size: 0.94 (0.2–1.7) CG effect size: 0.13 (−0.23–0.5) Peak sound pressure level: IG (inspiratory) effect size: 1.44 (0.51–2.38) IG (expiratory) effect size: 1.17 (0.36–2.0) CG effect size: 0.17 (−0.21–0.56)	Nil adverse events; 23%

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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
Roth *et al.* [38]	FVC (L): IGΔ: 0.28 CGΔ: 0.34 DiffΔ: −0.05 (p=0.88)	MIP (cmH_2O): IGΔ: 24 CGΔ: 15 DiffΔ: −15 (p=0.2) MEP (cmH_2O): IGΔ: 35 CGΔ: 8 DiffΔ: 39 (p=0.02)				Nil adverse events; 44%
Sapienza *et al.* [39]	FVC (L): IGΔ: 0.01 CGΔ: 0.03 DiffΔ: (p>0.05)	MEP (cmH_2O): IGΔ: 27.97 CGΔ: −4.42 DiffΔ: (p<0.01)	PEF ($L{\cdot}s^{-1}$): IGΔ: 0.11 CGΔ: −0.06 DiffΔ: (p>0.05)			Nil adverse events; 0%
Smeltzer *et al.* [40]		MIP (cmH_2O): IGΔ: 3.3 (16.1) CGΔ: 9.2 (11.9) MEP (cmH_2O): IGΔ: 19.4 (9.9) CGΔ: −1.2 (11.1) DiffΔ: (p=0.003)				Nil adverse events. 25%
Soumyashree *et al.* [49]		MIP (cmH_2O): IGΔ: 28.7 CGΔ: 7.5 DiffΔ: 21.6 (30.2–12.1) MEP (cmH_2O): IGΔ: 21.3 CGΔ: 4.1 DiffΔ: 17.1 (8.6–25.7)		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%
Stern *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) MEP (% pred): IGΔ: 1% (3.4) CGΔ: −2.5% (4.2) DiffΔ: (p=0.06)				Nil adverse events; 33%
Topin *et al.* [42]#	VC (L): IGΔ: −0.01 CGΔ: −0.16	MIP (cmH_2O): IGΔ: 1.4 CGΔ: −1.5				Nil adverse events; 0%
Van Houtte *et al.* [43]	FVC (L): DiffΔ: (p=0.06)	MIP (cmH_2O): DiffΔ: (p=0.06) MEP (cmH_2O): DiffΔ: (p<0.01)				Nil adverse events; 0%

Continued

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]#	FVC (L): IGΔ: 0.41 (0.4) CGΔ: −0.01 (0.06) DiffΔ: (p<0.05)	MIP (cmH_2O): IGΔ: 7.89 (4.59) CGΔ: 0 (2) DiffΔ: (p<0.05) MEP (cmH_2O): IGΔ: 9 (6.04) CGΔ: 0 (4.05) DiffΔ: (p<0.05)	PEF ($L{\cdot}s^{-1}$): IGΔ: 0.51 (0.48) CGΔ: −0.01 (0.18) DiffΔ: (p<0.05)			Nil adverse events; 0%
Wanke *et al.* [44]#	VC (L): IGΔ: 0.02 CGΔ: −0.02					Nil adverse events; 25%
West *et al.* [45]		MIP (cmH_2O): IGΔ: 14 CGΔ: −6 DiffΔ: (p<0.05) MEP (cmH_2O): IGΔ: 16 CGΔ: −1	PEF ($L{\cdot}s^{-1}$): IGΔ: 0.44 CGΔ: 0.51	RPE dyspnoea: IGΔ: 0.2 CGΔ: 1.1	Peak work rate: IGΔ: 8.2 CGΔ: 1 DiffΔ: (p=0.081)	Nil adverse events; 17%
Westerdahl *et al.* [46]	FVC (L): IGΔ: 0.1% CGΔ: −3% DiffΔ: −4.8% (−9.0–0.6)	MIP (cmH_2O): IGΔ: 0% CGΔ: 0.01% DiffΔ: 1% (−7–9) MEP (cmH_2O) IGΔ: 5% CGΔ: 2% DiffΔ: −3% (−12–6)	PCF ($L{\cdot}s^{-1}$): DiffΔ: (p=0.305) PEF ($L{\cdot}s^{-1}$): IGΔ: 8.6% CGΔ: 0.4% DiffΔ: −8.2% (−1.1–4.4) Perceived coughing ability: DiffΔ: 0 (0–6)	Dyspnoea whilst walking: DiffΔ: 0 (0–6)	EQ-5D VAS: DiffΔ: (p<0.136).	Nil adverse events; 8%
Xi *et al.* [51]	FVC (% pred): IGΔ: (p<0.05) CGΔ: (p>0.05) DiffΔ: (p=0.515)			Borg: IGΔ: (p<0.05) CGΔ: (p>0.05) DiffΔ: (p=0.022) SGRQ: IGΔ: (p<0.05) CGΔ: (p>0.05) DiffΔ: (p=0.372)		Nil adverse events; 0%

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; V_{O_2}: oxygen uptake. #: Indicates studies assessing children.

https://doi.org/10.1183/16000617.0065-2022

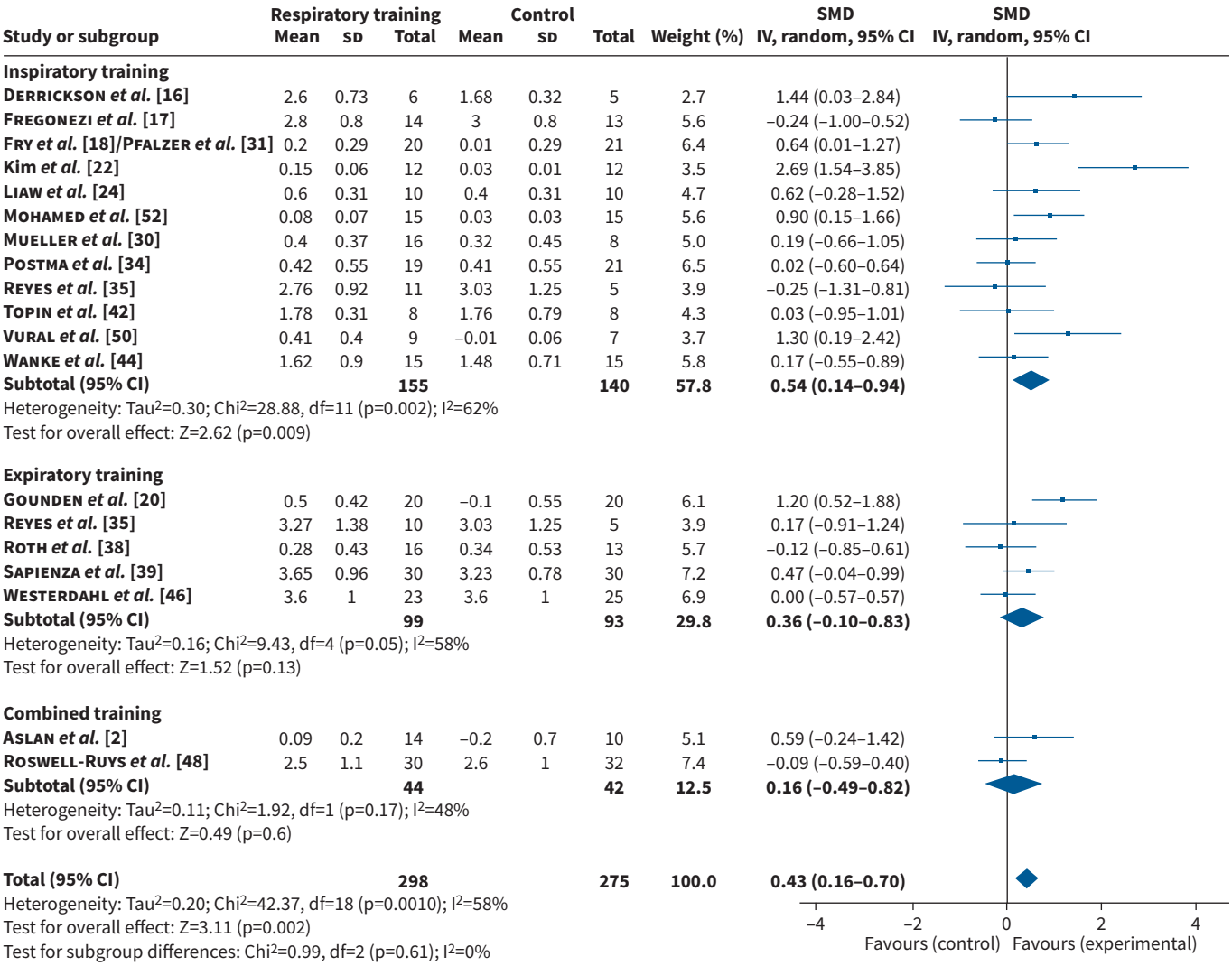

FIGURE 3 Forest plot for (forced) vital capacity. df: degrees of freedom; IV: inverse variance; SMD: standardised mean difference

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 (0.16–0.97) and SMD 1.12 (0.22–2.03), respectively. 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).

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 F(VC), MIP and MEP were by approximately 200 mL, 9 cmH_2O and 13 cmH_2O 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 I^2 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 F(VC) 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 $mL \cdot kg^{-1}$ (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_2O (5.22–11.83) and 12.44 cmH_2O (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].

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)VC 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.

Provenance: Submitted article, peer reviewed.

Prior presentation of material: This work was presented in poster format at the 30th International Symposium on ALS/MND, Perth, Australia, 4–6 December 2019.

Conflict of interest: D.J. Berlowitz has disclosed the following relationships outside the submitted work: board director for the Institute for Breathing and Sleep. The remaining authors have nothing to disclose.

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