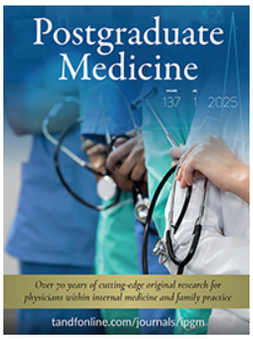

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REVIEW

Determining the outcome measures and clinical relevance of respiratory muscle training with multiple sclerosis patients: a systematic review

Veleska Wills, Francesco V Ferraro and Mark A. Faghy

Clinical Exercise and Rehabilitation Research Centre, University of Derby, Derby, UK

ABSTRACT

The following systematic review aimed to gather information on the effectiveness of Respiratory Muscle Training (RMT) with Multiple Sclerosis (MS) patients. The method followed the ENTREQ and PRISMA protocol. MEDLINE, Cochrane, and Science Direct databases were used to source relevant literature. Articles included participants diagnosed with MS in randomized, controlled trial studies with objectively measured outcomes, and RMT methods were standardized. Eleven students were included in the results ($n = 396$, 50.5 ± 9.8 years, 68% F 31% M) and show that RMT (minimum 8 weeks of training) is effective in improving respiratory muscle strength (MIP in 7 out of 9 studies, MEP in 6 out of 11 studies and FVC in 6 out of 7 studies) and health-related outcomes, including mobility. Although muscle strength increased, increases in FVC had moderate effects on functional ability, which were negligible, and patient-reported fatigue. Findings suggest that muscle strength increases were predominantly in inspiratory muscles, and expiratory results were combined. However, the review shows a lack of research concerning the use of RMT and its prescription for MS patients.

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KEYWORDS
Respiratory muscle training; multiple sclerosis rehabilitation; exercise intervention; health-related quality of life; systematic review methodology

1 Introduction

Multiple Sclerosis (MS) is the most common non-traumatic disease disabling young adults [1]. It is defined as a chronic neurological auto-immune disease of the central nervous system (CNS) characterized by demyelination, neuro-axonal damage, inflammation and lesions on the brain [2]. Coetzee & Thompson [3] found the incidence of MS is continually increasing globally, only in Europe has increased by 32% since 2013 (142.81 per 100,000 population), making it a focal point for new research into diagnosis and treatment [4].

The most common symptoms of Multiple Sclerosis are motor impairments, and up to 85% of MS patients report reduced mobility and quality of life [5]. Gait, balance, and mobility are perceived to be the most crucial bodily functions on the MS disability spectrum because instability often leads to falls and injury, significantly reducing a patient's quality of life [6]. Balance deficits can be detected in Patients with MS (PwMS) even during the initial stages of the disease, with minimal or no clinically diagnosed disability, and worsen over time [7]. Cameron & Nilsagard [8] explain worsening of balance through PwMS, having decreased ability to maintain position, slowed movement toward stability limits, and delayed response to postural displacements.

Various respiratory disorders are also associated with MS, including respiratory muscle weakness and spasticity, sleep-disordered breathing and sleep apnea, and central respiratory dysregulation [9]. Although respiratory impairment in the initial stages is not thoroughly explained in the literature, it is prevalent in most late-stage [10]. The risk of respiratory death is 12 times higher than the general population and accounts for approximately 47% of all patient deaths [11]. Respiratory muscle weakness is the most common respiratory symptom in PwMS, particularly in those who are bedridden or use wheelchairs [12]. Patients' muscles often weaken asymptomatically from the early stages of the disease but are sometimes not diagnosed until late-stage MS as symptoms have gradually worsened.

Respiratory Muscle Training (RMT) is a specific training focusing on improving the strength and endurance of the inspiratory muscles, expiratory muscles, or both [13] and recently has been reported to enhance balance and mobility function [14]. However, RMT is not currently a prescribed treatment method for MS. Limited research investigating the effects of RMT on MS has been conducted along with other illnesses, but other therapeutic options are thought to be more beneficial at this point in time. This review analyses the literature investigating RMT and MS, and clinicians can use these insights to explore RMT as a complementary therapy, advocating for further research into its long-term benefits and integration into personalized rehabilitation plans.

2 Methods

2.1 Literature search protocol

This systematic review follows the guidelines of ENTREQ and the preferred guidelines for preferred reporting items for systematic review and meta-analysis (PRISMA). The literature was gathered from the electronic databases MEDLINE (PubMed),

CONTACT Francesco V Ferraro f.ferraro@derby.ac.uk Clinical Exercise and Rehabilitation Research Centre, University of Derby, Kedleston Rd, Derby DE22 1GB, UK

Cochrane Central, Science Direct, and Google Scholar, as well as a manual search of relevant references in published studies.

The key search terms were 'respiratory muscles AND respiratory muscle training AND synonyms AND inspiratory muscle training AND expiratory muscle training AND multiple sclerosis AND randomized control trial.' To ensure similarities of intervention equipment technology, the minimum research date was 2000. Data collection took place between 20 September 2022 and 27 April 2023. Reference lists of the included articles were searched for further eligible studies.

2.2 Inclusion/exclusion criteria

Literary research was initially limited to full-text, English-written, peer-reviewed journal articles. English-written articles were chosen because research shows the predicted effectiveness of an intervention does not differ in language-inclusive analysis' as it does in language-exclusive analysis' [15]. Randomized control trials comparing an intervention group (with a clearly defined intervention protocol) to a control measure were reviewed. Non-controlled studies were excluded from this review, as were studies that included other health conditions or diseases because randomized control trial methods are known to reduce bias and provide a valid and rigorous cause–effect relationship between an intervention and outcome; for this reason, these are considered the gold standard in clinical trials [16]. If a trial had multiple publications, it was only used once. Different types of interventions were used, if the process was standardized and reliable, and only one intervention was being used.

Participants must have been 18 years old or above and diagnosed with MS as reported elsewhere [17], for a minimum of 1 year. Exclusion criteria included studies with participants who: had been hospitalized for at least 1 month prior to the study, had an acute illness, currently smoked, or had other ongoing health conditions. Participants were also excluded if they experienced a relapse or disease progression during the trial or changed their medication. The population reviewed contained independent, mobile participants and wheelchair-bound participants. Details about Population, Intervention, Comparison, and Outcomes are reported in Table 1.

2.3 Study selection and data extraction

Following the initial screening based on the title and abstract, two reviewers independently selected studies using predetermined inclusion criteria. For each study, data were extracted on several key aspects, including the first author and date of publication; study design, as well as inclusion and exclusion criteria, method of randomization, control of variables, and sample size; characteristics of participants, such as sample number, age, gender, EDSS score, type of MS, and functional ability; description of the control and intervention; outcomes, including objective measures, unit of measurement, and data at set time points; and the author's conflicts of interest.

Abstracts that did not provide sufficient information about inclusion and exclusion were selected for full-text evaluation. The same reviewers (VW and FVF) then reviewed the full articles and assessed selections according to the pre-specified criteria. Data were extracted from the studies using a standardized protocol.

2.4 Reported outcomes

To report the efficacy of RMT, a series of outcomes were selected from the studies; these include Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP), which measure respiratory muscle strength, and Forced Vital Capacity (FVC), a marker of lung function. Patient-reported measures such as the Fatigue Severity Scale (FSS), functional assessments like the 6-Minute Walk Test (6MWT), and health-related quality of life (HRQoL) questionnaires, including the SF-36. Additional functional and performance outcomes, such as voluntary cough strength, speech production quality, and spirometry indices, were also included. These outcomes were selected to capture both the physiological and functional effects of RMT. Data on these measures were systematically extracted and analyzed following ENTREQ and PRISMA protocols to ensure consistency and reliability across the included studies.

2.5 Assessed risk of bias

The methodological quality was analyzed descriptively, according to the Cochrane Collaboration protocol [15]. The methodology assessed were randomization sequencing, concealed allocation, blinding of researchers and participants, blinding outcome, incomplete data, and selective reporting. These characteristics helped to determine whether included studies contained selection, performance, attrition, or reporting bias. The studies' methodology was assessed to be at low, high, or unclear risk of bias, in line with the Cochrane Handbook for Systematic Reviews [18,19]. Reviewers (VW and FVF) also used the Physiotherapy Evidence Database Risk of Bias (PEDro) Scale to further evaluate the possibility of bias. The PEDro scale and the Cochrane tool consider varying study characteristics, but are proven effective ways of assessing bias in studies [20]. The highest possible score on the PEDro scale is 10. The PEDro scale results help to distinguish research with poor (0–3), fair (4–5), good (6–8), and excellent (9–10) methodology.

Table 1. PICO table showing the population, intervention, comparative measures, and outcomes of respiratory muscle training (RMT).

Population	People diagnosed with Multiple Sclerosis according to the criteria and its revisions [17] for a minimum of one year.
Intervention	Respiratory Muscle Training using a threshold trainer for varying lengths of time.
Comparison	A repeated measures method, so patient data being compared pre- and post-intervention in included research.
Outcome	An improvement in outcomes such as MIP, MEP, FFS scores, or 12-minute walk performance.

3 Results

3.1 Characteristics of included studies

Figure 1 shows the PRISMA flow chart and studies screening progress. Table 2 outlines the characteristics of the studies included. Nine studies focused on Inspiratory Muscle Training, and two used Expiratory Muscle Training interventions. Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) were the most prevalent outcome measures for this type of research. Nine studies focused on MIP, and all eleven focused on MEP as an outcome measure. Seven studies used Forced Vital Capacity (FVC) as a primary outcome measure. Just two studies measured the effects of respiratory training on the 6-minute walk, and three evaluated the effects on the Fatigue Severity Scale (FSS). Training protocols are described in Table 1. The studies were carried out for 8 weeks to 36 weeks at a frequency of 1–3 times daily, every other day, or three times weekly. Sets and repetitions are used in this comparison, using the knowledge that three sets of RMTs are equivalent to 10 minutes of training [32]. Full data are reported in Table 2. The PEDro scale (Table 3) and Cochrane tool show the probability of risk in the 11 studies in this review. Although most studies had an overall low risk of bias, there are methodological flaws leading to decreased reliability. Subject blinding was the most common study characteristic, increasing bias risk, followed by concealed allocation and assessor blinding. All studies compared base measures accounted for variability and had a proper continuation.

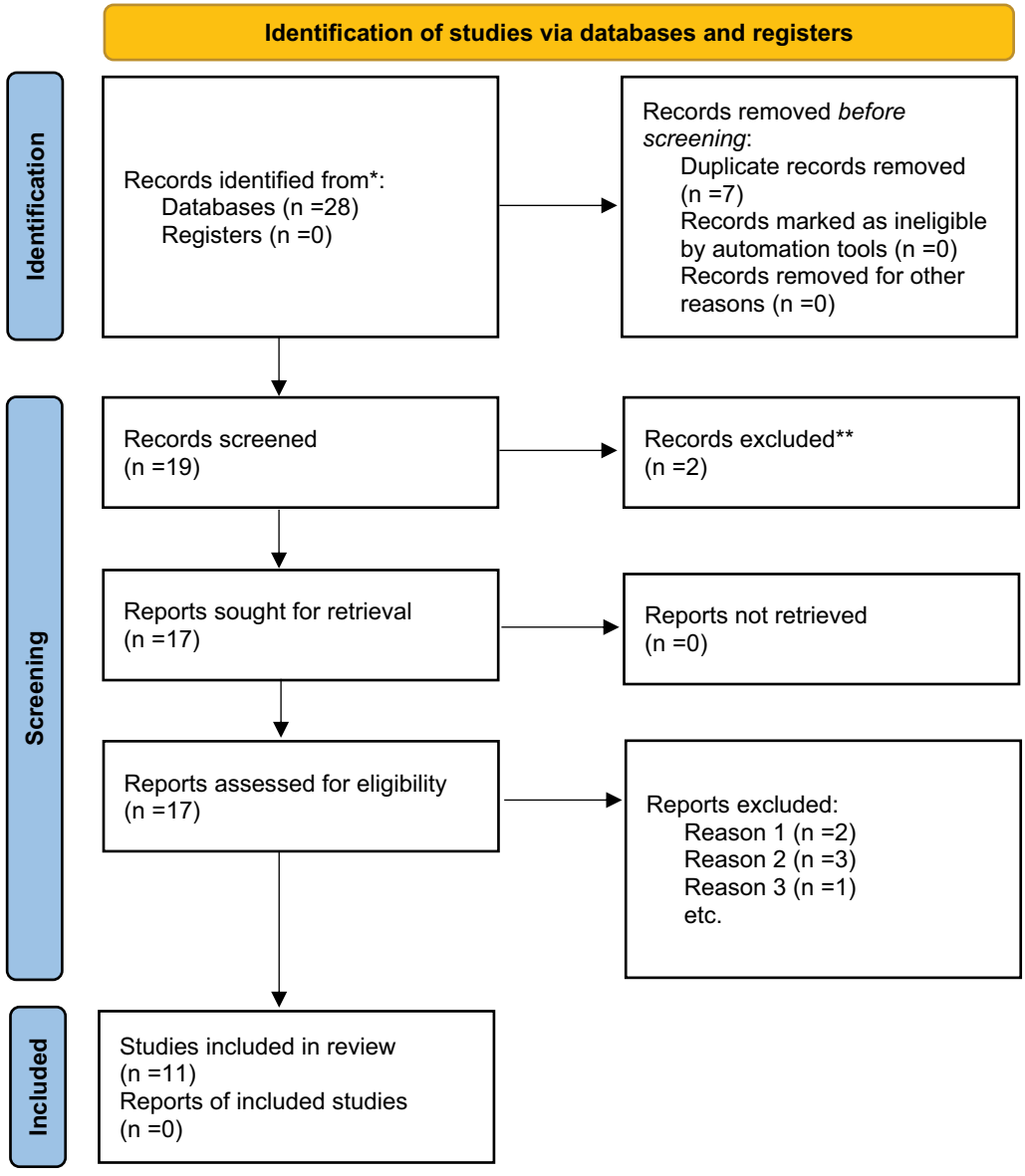

Figure 1. PRISMA flow chart and studies screening progress.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. For more information, visit: http://www.prisma-statement.org/

Table 2. Characteristics of included studies.

Author/Year	Study Type & Characteristics	Participants (PPs) (Age, sex, number,	Type of Intervention	Intervention Modalities	Measured Outcomes
Gosselink et al, 2000 [21]	RCT- Between subject's design.	18 pp's completed. Intervention (n = 9,5 female, mean age = 54 (13). Control= (n = 9, 3 female,mean age = 59 (14). All MS Types	EMT threshold device (60% MEP)	3X15 2X daily, 3 months Control-Exhalation breathing exercises daily.	Primary=MEP, MIP, MFIS. Secondary=EDSS
Klefbeck et al, 2003 [22]	RCT-Between subject's design.	15 severely disabled pp's. Intervention (n = 7;6 female, mean age 46). Control (n = 8;3 female, mean age 52).	IMT using threshold trainer	3X10 (40–60% MIP) twice every other day for 10 weeks. Control-No intervention	Primary-MIP, MEP, Spirometry, Clinical Assessments, MFIS
Fry et al, 2007 [23]	RCT, between subject's design. Control group: no interventions used).	46 ambulatory pp's control (17 female) & Intervention (21 female). Ave age = 50 (9.1). All MS types.	IMT with threshold trainer	10 weeks. 3 × 15reps daily. Initial resistance = 30% pretest MIP. Progressed weekly by RPE and pp symptoms.	Primary= MIP, MEP, and maximal voluntary ventilation (MVV). Secondary= EDSS and MFIS scales.
Chiara et al, 2007 [24]	RCT- Between subject's design. Intervention group (MS patients) compared against a healthy control group's base measure.	17pp's (age 20–59) with MS (14 female) was compared against 14 healthy controls (12 female).	Positive Expiratory Pressure threshold trainer	8 weeks, 5 days a week (1 supervised, four home-based). 4 × 6reps once daily. Intensity = 40% MEP during week 1, 60% MEP 2nd week, 80% MEP the weeks following. Compliance was logged. 4-week detraining phase.	Primary=MEP, Speech production (acoustic recording, dysarthria scale). Secondary=Quality of Life Scale, EDSS.
Pfalzer& Fry, 2011 [25]	RCT- Single-blinded, between subject's design (pretest, posttest, compared against control group).	46 ambulatory pp's started, and 39 finished. Intervention (n = 20, 18f, 2 m, average age = 49.6 (9.5). Control (n = 19, 13f, 6f, mean age = 46 (9.8).	IMT with threshold trainer	10 weeks. 3X15 reps daily at 30% MIP resistance. Control group: no interventions used.	Primary=MIP, MEP, MVV, mobility tests (balance, functional stair test, sit-to-stand, and 6-minute walk test) Secondary=EDSS
Ray et al, 2013 [26]	RCT, Between subject's design.	21 pp's. Intervention (n = 11;9f,2 m, mean age 51 (5.7). Control (n = 10; 7f,3 m, mean age 56 (8.8). All MS Types	Resisted RMT	30 min training session three times week. 5-week progressive plan. Control=No intervention	MIP, MEP, MFIS, MVV. Secondary=Functional Tests (6-minute walk, stair climb), MS Self-Efficacy Scale
Westerdahl et al (2016) [27]	RCT- Single-blinded, between-subjects design.	48 pp's finished the trial intervention (n = 23, 6 male, 17f, mean age 55) and control n = 25, 7 male, 18f, mean age 56). All MS types.	Threshold breathing device	8 weeks. Thirty breaths 1/2X daily. Control group: no interventions used).	Primary=Respiratory muscle strength (MIP & MIP). Secondary=Lung function (assessed through spirometer, peripheral oxygen saturation& subjective breathing ability), self-reported health status, EDSS.
Martin-Sanchez et al, 2020 [28]	RCT, double-blind Between subject's trial. Intervention= IMT.	67pp`s Intervention (n = 36;14 m,22f, mean age 50 (10). Control (n = 31;12 m,19f, mean age 53 (12). All MS Types	IMT with threshold trainer	12 weeks, 5 days a week, 15 min a day. Started with 20% MIP for 2 weeks, progressed to 30% the second week. Control-Nasal breathing and exhalation exercise daily.	Primary=MIP, Secondary=MEP, spirometry, dyspnea & health-related quality of life.
Huang et al, 2020 [29]	RCT. Repeated measures/within subjects' method.	37 pp's, 27 female, 10 male non-ambulatory patients. Average age = 60.5 All MS types	IMT with threshold trainer	10 weeks. 3X 15 reps one time daily. Resistance progressed weekly but was determined by the perceived rate of exertion (RPE).	Primary= MIP and MEP. Secondary= EDSS score
Srp et al, 2021 [30]	RCT-Between subject's design. Intervention=MS patients. Control=Healthy pp's. Intervention= IMT	52 pp's, Intervention (n = 26; mean age 52.7 (10.2). Matched to healthy control group by sex & age. Control (n = 26; mean age 53.5 (5.8). All MS Types	EMT	36-week study, 12-week non-training period, 12 weeks of, 12 weeks detraining period)	Primary= MEP and voluntary cough strength (voluntary peak cough flow).
Ghannadi et al, 2022 [31]	Single-blinded RCT. Within subject's design (One group performed self-directed treatment (pretest, posttest) and was compared against a control group (no interventions used).	36 pp is, 27 female, 9 male. Diagnosed with relapsing remitting MS. Average age = 38 (8.86) years.	IMT with threshold trainer	Home-based IMT with pressure threshold devices for 8 weeks. 3X15 reps two times daily. Thirty percent baseline MIP, increased by 1 level each week	Primary=MIP, MEP using respiratory MPM. Secondary outcomes= spirometric indices, functional tests (6 min walk& timed get up& go test), fatigue MFIS questionnaire) and quality of life questionnaire (SF36).

MIP=Maximal Expiratory Pressure, MIP= Maximal Inspiratory Pressure, MFIS =Modified Fatigue Impact Scale, EDSS= Expanded Disability Scale Status, MVV=Maximal Voluntary Ventilation, IMT = Inspiratory Muscle Training, EMT = Expiratory Muscle Training, RMT = Respiratory Muscle Training.

Table 3. Pedro scale for assessing risk of bias.

Methodology	Ghannadi [30]	Huang [28]	Fry [22]	Westerdahl [26]	Pfalzer & Fry [24]	Martin-Sanchez [27]	Ray [25]	Gosselink [32]	Srp [29]	Klefbeck [21]	Chiara [23]
Eligibility Criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Random Allocation	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
Concealed Allocation	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes
Comparability of the base measure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subject Blinding	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No
Assessor Blinding	No	No	No	No	No	Yes	No	No	No	No	No
Proper Continuation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Intention to Treat	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No
Between-group statistical comparison	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Variability Measures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total	**8**	**5**	**5**	**8**	**7**	**8**	**5**	**5**	**6**	**5**	**5**

3.2 Demographic and training characteristics

The demographic characteristics and training protocols across the studies reviewed demonstrated significant variability. Gosselink et al. (2000) [21] included 18 participants, with the intervention group having 5 females and a mean age of 54 years and the control group having 3 females and a mean age of 59. Participants underwent expiratory muscle training for 3 months, with sessions consisting of 3 × 15 repetitions twice daily. Similarly, Klefbeck et al. (2003) [22] involved 15 participants, with the intervention group comprising 6 females and a mean age of 46 years, while the control group had 3 females with a mean age of 52 years. Training spanned 10 weeks using inspiratory muscle training (IMT) at 40–60% of MIP, conducted twice every other day with 3 × 10 repetitions. Fry et al. (2007) [23] recruited 46 participants with a mean age of 50 years (SD ± 9.1), of whom 21 females were in the intervention group. The intervention involved 10 weeks of IMT at 30% MIP, progressing weekly based on perceived exertion, with 3 × 15 daily repetitions.

Chiara et al. (2007) [24] included 17 MS participants with an age range of 20–59 years (14 females), who underwent 8 weeks of positive expiratory pressure training starting at 40% MEP and increasing to 80%, performed as 4 × 6 daily repetitions. In Pfalzer and Fry (2011) [25], 46 participants (39 completing the study) were included, with a mean age of 49.6 years (SD ± 9.5) in the intervention group and 46 years (SD ± 9.8) in the control group, mainly consisting of females. The 10-week IMT program involved 3 × 15 daily repetitions at 30% MIP, progressively increasing intensity. Ray et al. (2013) [26] recruited 21 participants, 11 in the intervention group (9 females, mean age 51 years, SD ± 5.7) and 10 in control (7 females, mean age 56 years, SD ± 8.8). The training lasted 5 weeks with combined inspiratory and expiratory sessions three times a week for 30 minutes.

Westerdahl et al. (2016) [27] recruited 48 participants, with the intervention group averaging 55 years (17 females) and the control 56 years (18 females). Their 8-week intervention involved 30 breaths 1–2 times daily using a threshold breathing device. Martin-Sanchez et al. (2020) [28] involved 67 participants (36 intervention, 31 control), with a mean age of 50 years (SD ± 10) in the intervention group and 53 years (SD ± 12) in the control. Participants trained for 12 weeks at 20–30% MIP, performing 15-minute sessions 5 days per week. Huang et al. (2020) [29] recruited 37 non-ambulatory participants (27 females, 10 males, mean age 60.5 years), who completed a 10-week home-based IMT program, performing 3 × 15 daily repetitions with progressive resistance based on perceived exertion.

Srp et al. (2021) [30] involved 52 participants matched for sex and age, with a mean age of 52.7 years (SD ± 10.2) in the intervention group and 53.5 years (SD ± 5.8) in the control. Their study spanned across 36 weeks, including a 12-week non-training period and 12 weeks of detraining. Finally, Ghannadi et al. (2022) [31] included 36 participants (27 females, 9 males, mean age 38 years, SD ± 8.86), who completed an 8-week IMT program using a threshold device at 30% MIP, progressively increasing intensity, with sessions of 3 × 15 repetitions twice daily.

3.3 Effect of RMT on outcome measures

3.3.1 Maximal inspiratory pressure (cmH_2O)

Nine studies evaluated MIP, totaling 319 patients. Seven of these found a statistically significant ($p = <0.05$) difference between PwMS before and after respiratory training. The Cohen's d effect size is larger than 0.8 in five of these research papers, showing that respiratory training has a large positive effect on the MIP, or in other words, has strengthened the inspiratory muscles of participants in this study [33] as reported in Table 4.

3.3.2 Maximal expiratory pressure (cmH_2O)

All 11 studies evaluated MEP, totaling 396 PwMS. Six studies found a statistically significant difference ($p = <0.05$), and five found there to be a large effect on the sample population. However, results are shown to be more varied than that of other outcomes, with some studies concluding that respiratory training decreased or had no effect on MEP. Refer to Table 5.

3.3.3 Forced vital capacity (L)

Seven studies used FVC as a primary outcome measure, totaling 267 patients. Six found a statistically significant improvement in FVC after training, although only moderate differences are shown. Refer to Table 6.

Table 4. Shows the effect of respiratory muscle training on participants' maximal inspiratory pressure (reported in cmH_2O).

	Pre-Intervention			Post – Intervention					
Study Author	Mean	SD	Total	Mean	SD	Total	Effect Size (Cohen's d)	Mean Difference	P-Value
Gosselink et al (2000) [32]	22.0	10.0	9	27.0%	18.0	9	0.343	5.0	<0.01
Fry et al (2007) [22]	53.1	25.7	17	76.6	23.3	21	0.949	23.5	<0.001
Pflazer & Fry (2011) [24]	59.3	29.7	19	94.8	30.8	20	1.173	35.5	<0.003
Ray et al (2013) [25]	70.0	24.0	10	94.0	33.0	11	0.832	24.0	<0.001
Westerdahl et al (2016) [26]	78	33	25	77	32	23	−0.030	1.0	<0.740
Martin-Sanchez et al (2020) [27]	41.83	16.40	31	62.40	24.41	36	0.989	20.57	<0.01
Huang et al (2020) [28]	25.9	16.4	18	30.6	17.6	19	0.329	4.7	<0.013
Ghannadi et al (2022) [30]	44.00	11.208	18	49.750	11.885	18	0.498	5.75	<0.01

Table 5. Shows the effect of respiratory muscle training on participant's maximal expiratory pressure.

	Control (Pre-Test)			Intervention (Post-Test)					
Study Author	Mean	SD	Total	Mean	SD	Total	Effect Size (Cohen's d)	Mean Difference	P-Value
Gosselink et al (2000) [32]	24.0	7.0	9	31.0	21.0	9	−0.447	7.0	<0.01
Klefbeck et al (2003) [21]	48.0	7.0	8	52.0	6.0	7	0.613	4.0	<0.06
Fry et al (2007) [22]	68.7	27.1	17	73.2	22.7	21	0.180	4.5	<0.181
Pflazer & Fry (2011) [24]	45.2	19.7	19	49.2	16.6	20	0.219	4	<0.335
Ray et al (2013) [25]	94.00	24.0	10	117.0	30.0	11	0.847	23	<0.001
Westerdahl et al (2016) [26]	95	31	25	98	28	23	0.101	3	<0.520
Martin-Sanchez et al (2020) [27]	45.66	20.35	31	62.26	28.44	36	0.671	16.6	<0.01
Huang et al (2020) [28]	23.5	15.7	18	24.4	12.9	19	0.063	0.9	<0.639
Srp et al (2021 [29])	92.6	27.9	26	87.9	25.3	26	−0.164	4.7	<0.002
Ghannadi et al (2022) [30]	65.70	16.119	18	77.06	19.285	18	0.639	11.357	<0.01

Table 6. Shows the effect of respiratory muscle training on participants' forced vital capacity.

	Control (Pre-Test)			Intervention (Post-Test)					
Study Author	Mean	SD	Total	Mean	SD	Total	Effect Size	Mean Difference	P-Value
Gosselink et al (2000) [32]	1.11	0.52	9	1.88	1.13	9	0.875	0.02	<0.001
Fry et al (2007) [22]	3.53	0.75	17	3.73	0.73	21	0.270	0.2	<0.04
Pflazer & Fry (2011) [24]	3.53	0.75	19	3.73	0.73	20	0.270	0.2	<0.039
Ray et al (2013) [25]	3.39	0.67	10	3.48	0.64	11	0.137	0.09	<0.02
Westerdahl et al (2016) [26]	3.3	0.8	25	3.3	0.8	23	0	0	<0.025
Martin-Sanchez et al (2020) [27]	2.70	1.11	31	2.75	1.07	36	0.459	0.05	<0.560
Ghannadi et al (2022) [30]	2.736	0.596	18	3.436	0.727	18	1.053	0.7	<0.01

3.3.4 Fatigue severity scale (FSS)

A total of 95 study participants in 3 studies were examined for the effects of respiratory muscle training on patient-reported fatigue. RMT was found not to affect this outcome. Results in Table 7.

3.3.5 The 6-minute walk test (M)

Two studies listed FSS as an outcome measure, investigating the effects of RMT on 84 patients. Ghannadi [31] found no change in the intervention group after training, whereas Pfalzer & Fry [25] found that RMT improved the distance walked by 12 m. However, this change was proven not to be statistically significant, indicating that this result may have occurred due to chance. Refer to Table 8.

4. Discussion

The review aimed to evaluate the effectiveness of Respiratory Muscle Training (RMT) in improving respiratory function and related outcomes in individuals with Multiple Sclerosis (MS). The findings indicate that RMT significantly improves Maximal Inspiratory Pressure (MIP) and, to a lesser extent, Maximal Expiratory Pressure (MEP), with moderate gains in Forced Vital Capacity (FVC). However, functional outcomes, such as the 6-Minute Walk Test and fatigue, showed limited or inconsistent effects. Despite these variations, the results suggest that RMT holds promise for enhancing respiratory function in MS, warranting further research to confirm its clinical relevance.

4.1 summary of main findings

The research aims to investigate the outcome measures of RMT with PwMS. Pulmonary functions (MIP, MEP, FVC, MVV) were the most common outcome measures [33,34]. Three of the studies' inclusion criteria included a minimum EDSS and FSS score and recorded the patient's HRQoL score [35]. This review shows that RMT methods improve pulmonary ability but do not affect patient-reported fatigue or results of the 6-minute walk, RMT helped to improve the patient's respiratory function by improving their respiratory muscle strength (MIP and MEP), as expected. Muscle strength increases were predominantly in the inspiratory muscles, and expiratory results were conflicting. Although muscle strength increased,

Table 7. A table showing the effect of RMT on participant's fatigue severity scale (FFS).

	Control (Pre-Test)			Post-Intervention					
Study Author	Mean	SD	Total	Mean	SD	Total	Effect Size (Cohen's d)	Mean Difference	P-Value
Gosselink et al (2000) [32]	5.3		9	5.2		9		0.1	<0.06
Fry et al (2007) [22]	5.2	1.1	17	5.2	1.2	21	0	0	<0.961
Pflazer & Fry (2011) [24]	47.7	8.8	19	46.3	11.3	20	−0.138	1.4	<0.054

Table 8. A table showing the effects of RMT on participant's 6-minute walk test results.

	Control (Pre-Test)			Intervention (Post-Test)					
	Mean	SD	Total	Mean	SD	Total	Effect Size	Mean Difference	P-Value
Pflazer & Fry (2011) [24]	293.9	170.1	25	306.2	182.8	23	0.696	12.2	<0.405
Ghannadi et al (2022) [30]	417.176	41.249	18	417.529	77.822	18	0.006	0.353	<0.987

increases in FVC were moderate, and effects on functional ability were negligible [36].

Generally, RMT was performed using an inspiratory threshold trainer, with the guide of 3×15 reps, as discussed by previous literature [37,38], for up to 12 weeks. Twelve weeks is an adequate length of time, considering muscular adaptation occurs within 6 weeks of regular training [39]. The studies in this review hypothesize that increased muscle strength is due to muscle fiber adaptations and improved resistance to fatigue. McKenzie [40] refutes this, stating no measurable cellular structural changes are seen in humans in response to a physical training program. Additionally, it is necessary to note that in the reviewed paper, there is a lack of information about trunk muscle training and outcomes. Recent studies have reported that Blood Flow Restriction Training (BFRT), when applied to the chest ribs, has similar results to inspiratory muscle training alone [41], revealing that trunk muscles have a role too in overall respiratory outcomes. Hence, future studies should include additional outcomes and training (e.g. BFRT) to evaluate the trunk muscles [41].

Regardless of the mechanism, much research proves the effectiveness of RMT [40,42]. Although 12 weeks are enough time to see changes in respiratory muscles, no longitudinal studies have investigated the long-term effects of continued RMT on pulmonary or functional outcomes.

Most research with MS patients does not account for the effects seen regarding MS progression. Raw data from the studies were unavailable, and participants were not divided into their MS progression stages, meaning analysis of different responses MS types is not possible. No studies have investigated respiratory training and its impact on disease progression, so there is minimal knowledge of the lasting RMT effects if done during the early stages of disease. A longitudinal study is required to investigate this further and whether RMT could have a slowing effect on MS progression.

During the risk of bias assessments, some studies showed methodological flaws. Four studies failed to apply randomization when dividing groups, and six failed to conceal allocation. Given the nature of the studies, this greatly increases the risk of bias but is difficult to implement. Participants taking part in the studies may experience the placebo effect from training, subconsciously put more effort in during the posttest, and give a result not reflective of the true cause and effect. It would be more effective to have two PwMS groups (one control and one intervention), but current study samples show it is too difficult to recruit enough participants. As previously stated, symptoms negatively affecting PwMS' quality of life include fatigue, pain, disability, and depression [43]. Although the patient's respiratory function is known to improve through RMT, its effects on more functional MS symptoms have not been widely explored, even though functional outcomes would be more clinically relevant to MS patients and healthcare providers.

The 6-minute walk (following the advised protocol) is an accurate test for determining an individual's current physiological and functional status [44]. However, patients with Multiple Sclerosis are highly likely to suffer from gait problems [45]. This indicates the 6-minute walk may not be the most suitable functional outcome measure for PwMS. It is difficult to provide a single test suitable for MS patients with diverse symptoms, so it may be necessary to use a combination of functional tests to determine the effect of an intervention on function.

The Fatigue Severity Scale (FSS) is an outcome measure listed in the above research papers. Researchers cannot measure fatigue quantitively or objectively, so data is collected through self-reported methods. Although self-report scales are invaluable for subjective information and for reducing experimenter bias, they depend on the patient's viewpoint at a one-time point [46].

It was noticeable that the effect of exercise on HRQoL in MS patients has a high positive correlation [47]. Tollar [48] explains this may be due to increased fitness, mobility, and balance, reducing the perception of effort required to complete daily tasks.

Additionally, the link between improvement in respiratory muscle strength and overall perceived absence or decrement in fatigue remains unclear. Previous authors, including Romer and McConnell, have hypothesized the physiological mechanism behind it. The authors conceive that RMT might delay the recruitment of accessory muscles or improve accessory muscle function, which produces a lower work of breathing and a reduced metabolic respiratory muscles demand [49,50]. However, it is still unclear how this mechanism works and what role the metaboreflex has in diminishing the perception of fatigue [51].

4.2 Comparison to existing literature

Two literature reviews have been found that focus on the effects of RMT on MS patients [52,53]. As expected, results also show improved pulmonary function (MIP and MEP) in patients after training interventions. Our review differs as it focuses on all outcome measures and what they relate to real life for the patients. A clinical outcome measure for PwMS needs to be valid, reliable, and effective to change [54], but also relevant to the patients [55]. Other studies, such as Reyes et al. [56], and Ferreira et al. [32], investigating the benefits of RMT on neuromuscular diseases agree that respiratory strength increases, but they failed to review other outcomes or fully establish what this means for the patient. The RMT is proven to reduce the perception of effort (allowing the individual to feel more able to complete exercise-related tasks), reduce blood lactate during physiologically demanding tasks, and reduce an individual's resting heart rate [14,57–59]. Increased muscular strength and pulmonary function have been described as sufficient outcome measures, but no investigations have been done to test clinically relevant outcomes like symptom burden, functional status, or quality of life. This may be a reason why respiratory training is not currently advised as a treatment for PwMS.

4.3 Limitations of this review

Whilst conducting this review, steps have been taken to maximize reliability and validity and to limit bias, using clear search methods with strict inclusion and exclusion criteria, thorough data extraction, grading of evidence and reviewing all available publications. As with any systematic review, it also has limitations. The small sample size of 11 papers is a large limitation, as it calls into question the validity and generalizability of the review. With the prevalence of MS continually rising, 11 studies totaling only 396 participants may not be reflective of the MS population. Several studies, including larger sample sizes, were available but focused on other neuromuscular diseases. Other diseases were excluded from this study because RMT may affect their populations differently. Varying outcome measures made comparison difficult, and there were limited results focusing on functional outcomes, many of which used different methods or testing. Indeed, a limitation of this review is the small number of studies assessing clinically relevant outcomes, such as fatigue (three studies) and functional capacity, via the 6-Minute Walk Test (two studies). This limits the statistical power to detect meaningful differences and reduces the generalizability of findings, highlighting the need for more extensive, standardized studies to strengthen the evidence base for the RMT effect of fatigue and functional capacity.

Finally, the inability to analyze outcomes based on patient subgroups, particularly in relation to their Expanded Disability Status Scale (EDSS) scores, is another limitation. The included studies featured heterogeneous populations, ranging from severely disabled individuals (e.g. Gosselink et al.) to ambulatory patients (e.g. Pfalzer and Fry), each with differing baseline respiratory and functional capacities. Additionally, the diversity in training protocols, intervention durations, and outcome measures further compounded the variability. This heterogeneity precluded a subgroup analysis that could have provided valuable insights into how RMT benefits patients at different stages of MS progression. Future research should aim to stratify participants based on disability levels to better understand the differential impact of RMT and tailor interventions to specific patient needs [57].

4.4 Implications for future research

As mentioned, further research is needed to establish the actual effects RMT has on MS patients. Recommendations for further research include using more clinically relevant outcomes to determine what changes occur in the patient. Longitudinal studies may be the most effective method of investigating this by measuring symptom burden and tracking symptom changes over time. This may allow future studies to develop a tool that accurately measures symptom changes from pre- to post-intervention.

Another evident gap in the literature includes measuring the effects of RMT on patients with varying types and progressions of MS. A potential study needs to focus on maintaining or improving respiratory muscle strength before the onset of muscle wastage and respiratory muscle weakness. This would require extra resources for long-term follow-ups, but if proven to be effective, it could improve the lives of many PwMS and reduce the overall amount of clinical treatment given by healthcare providers.

Currently, there is only limited research investigating RMT and neurodegenerative diseases. More standardized, specialized research on this and similar populations may have significant clinical implications. To date, the only ways of accurately testing respiratory muscle force is through nerve stimulation techniques [60] and ultrasonography, although this does not always take the diaphragm into account [61].

4.5 Implications for practice

It is clear from the literature that IMT techniques benefit several different health conditions, but their importance for clinicians or the health service is often not established. Due to the lack of literature focusing on MS patients, RMT cannot yet be prescribed as an effective treatment method. However, it is clear RMT does impact patients, so healthcare providers should monitor research for future patient treatment. Implementing RMT in practices may reduce the progress of respiratory decline in PwMS, potentially reducing demand for extensive respiratory treatments and enabling patients to stay active and independent for longer. RMT devices are relatively low-cost devices with a long operational lifetime [62], and the technology used is continually reviewed to maximize effectiveness. This benefits healthcare providers and specialized MS clinics as they can easily access and afford suitable equipment. The use of threshold devices and new technology will hopefully increase the availability of pulmonary rehabilitation services, as currently, it is alarmingly low [63]. This should be prescribed using the current NICE guidelines for medicine optimization and the frequency

of treatments where adjustments will depend on the individuals' specific needs [64,65].

5 Conclusion

From this systematic literature review, there is an absolute lack of primary endpoints for the use of RMT in PwMS. There is a lack of a definitive end goal for the treatment due to outcome measure inconsistency. It is impossible from the range of current outcome measures, to determine whether patients' respiratory function or life has improved.

Outcome measures used to assess the effectiveness of RMT, such as MIP or spirometry, are not clinically relevant and need to be replaced by a more appropriate and clinically relevant tool.

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Author contributions

Conceptualization Ideas; Mark A. Faghy, Francesco V Ferraro. Methodology: Mark A. Faghy, Francesco V Ferraro. Validation: Mark A. Faghy, Francesco V Ferraro. Formal analysis: Mark A. Faghy, Francesco V Ferraro. Investigation: Veleska Wills, Francesco V Ferraro. Data Curation: Veleska Wills, Francesco V Ferraro. Writing – Original Draft: Veleska Wills. Writing – Review & Editing: Francesco V Ferraro. Supervision: Mark A. Faghy, Francesco V Ferraro. Project administration: Mark A. Faghy, Francesco V Ferraro

ORCID

Francesco V Ferraro http://orcid.org/0000-0002-4902-7760
Mark A. Faghy http://orcid.org/0000-0002-8163-7032

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