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Systematic Review

Effectiveness of Respiratory Exercises on Perceived Symptoms of Fatigue among Multiple Sclerosis Patients: A Systematic Review

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Abstract: Multiple sclerosis (MS) is an autoimmune disease in which fatigue is one of the most frequent and disabling symptoms, and it is believed to be associated with respiratory involvement. Individuals who are physically inactive for long lengths of time display greater symptomatic fatigue. The objective of this systematic review was to analyze the effectiveness of breathing exercises within rehabilitation programs in improving fatigue in patients with MS. A systematic search of electronic databases, including PubMed, Web of Science, Scopus, and PEDro, was conducted up until November 2022. Nine articles, with a total of 290 participants, were selected. The studies combined breathing exercises with other treatment techniques, such as Ai-Chi, Pilates, and upper and lower limb exercises. Four studies used the Modified Fatigue Severity scale, observing a reduction in the perception of fatigue, in favor of the experimental group. Incorporating respiratory exercises into physical exercise programs, such as Ai-Chi and Pilates, may help to reduce the perception of fatigue. However, the heterogeneity in the protocols and outcome measures makes the generalization of the results difficult. Nonetheless, further studies that include specific respiratory variables are needed to analyze whether this perceived improvement is associated with enhanced pulmonary capacity.

Keywords: multiple sclerosis; breathing exercises; patients; fatigue; physiotherapy

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Citation: Torres-Álamo, L.; López-Liria, R.; Valverde-Martínez, M.Á.; Benzo-Iglesias, M.J.; Rubio-Arias, J.Á. Effectiveness of Respiratory Exercises on Perceived Symptoms of Fatigue among Multiple Sclerosis Patients: A Systematic Review. *Sustainability* **2023**, *15*, 12887. https://doi.org/10.3390/su151712887

Academic Editors: Daniela Cojocaru and Liviu Oprea

Received: 27 June 2023
Revised: 10 August 2023
Accepted: 15 August 2023
Published: 25 August 2023

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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease characterized by an inflammatory demyelinating affectation of the central nervous system [1]. It is the most common neurological non-traumatic disabling disease in young adults, affecting almost 2.5 million people worldwide, and women to a greater extent [2,3]. The prevalence of MS varies depends on geographical area; in North America and Europe, it is high, with more than 100 cases per 100,000 inhabitants, while Eastern Asia and sub-Saharan Africa have an average of 2 cases per 100,000 inhabitants [4]. In Spain, there is a prevalence of 26.6 per 100,000 inhabitants, and an incidence of 1.34 per 100,000 inhabitants, with the higher-latitude areas presenting the highest figures [5].

A predisposition to MS is complex, and involves both environmental and genetic factors [6]. It can trigger important physical and mental symptoms, such as reduced mobility, balance disorders, muscle weakness, cognitive impairment, decreased gait function, double vision, spasticity, and fatigue [7]. Respiratory infections and complications pose a significant risk of mortality among this population, with a staggering 11.7-fold higher

likelihood of death attributed to respiratory issues, compared to the general population [8]. The sustained management of these symptoms is essential in the long term, as MS typically lacks a complete cure, leading to a potential decline in quality of life, and considerable healthcare expenses. Research suggests that lifetime expenses for individuals with MS in the United States surpass USD 4 million [3]. Among all the manifestations of this disease, fatigue is one of the most frequent and disabling symptoms presented by people with MS [9–11]. In this sense, there are various definitions of fatigue; the American MS Association in 1998 stated that fatigue was a: "subjective lack of physical and/or mental energy, perceived by the person or caregiver, which interferes with usual and desired activities" [11,12]. It also affects all types of activities in daily life, such as household chores or leisure activities [13]. Despite its impact and prevalence, its pathophysiology is poorly understood. It is believed that primary aspects, such as inflammation, gray matter lesions, and functional disconnection are involved in this symptom [10,14,15].

Various tools and scales have been developed to measure fatigue, but there is no consensus on any particular 'gold standard' [16]. When attempting to measure it, however, it should be considered that there are different types of fatigue. Individuals with MS are capable of discerning between physical fatigue and other physical manifestations of the condition, such as muscle weakness in specific groups, impaired neurologic function resulting in inadequate muscle strength, and general physical exhaustion. Furthermore, they can distinguish mental fatigue from the emotional and cognitive symptoms associated with depression, such as reduced motivation, diminished mood, difficulty in task completion, and impaired concentration [13]. Among the most widely used scales are the Fatigue Severity Scale (FSS), developed by Kupp et al. in 1988 [17], the Fatigue Impact Scale (FIS), developed by Fisk et al. in 1994 [18], and the Modified Fatigue Impact Scale (MFIS), derived from the FIS, developed by the National Multiple Sclerosis Society (NMSS) of the United States [19].

It is challenging to achieve a complete resolution of fatigue in MS through treatment, but there are multiple interventions focused on improving functionality and trying to prevent an increase in disability in future stages [20]. Aerobic training improves gait speed, walking endurance, and balance, yet no significant differences were found in cardiorespiratory fitness and fatigue perception in a review and meta-analysis including 43 studies on people with MS [21]. On the other hand, recent research has associated fatigue perception with physical activity and sedentary behavior in patients with MS [22]. Regarding pharmacological treatment, the evidence supporting the use of drugs to treat fatigue is minimal and contradictory [16,23]. Amantadine, modafinil, and amphetamine-type stimulants (such as methylphenidate, amphetamine/dextroamphetamine, and lisdexamfetamine) are among the most widely used drugs [12,23,24].

A meta-analysis conducted in 2023 highlights that resistance training programs, consisting of six weeks of high-intensity training twice a week, may serve as an effective stimulus to enhance strength, functional capacity, balance, and fatigue among individuals with MS [25]. It is believed that respiratory involvement, including weakened respiratory muscles and altered breathing patterns, is associated not only with fatigue, but also with reduced motor performance and potential psychological or behavioral changes [8,26]. From conservative treatment, some recently published systematic reviews study the efficacy of respiratory training in improving expiratory force, lung function, and coughing in patients with MS [27,28]. However, to our knowledge, there is no systematic review that studies the relationship between breathing exercises and fatigue in patients with MS. The present systematic review is, thus, carried out with the objective of analyzing and descry-bing the efficacy of breathing exercises within physical exercise programs to improve fatigue in patients with MS.

2. Materials and Methods

2.1. Study Design

A systematic review was carried out on 18 November 2022, following the standards of the PRISMA declaration [29] (see PRISMA checklist in the Supplementary Material). It was registered in the database of the International Prospective Registry of Systematic Reviews, PROSPERO (identifier: CRD42023390576).

2.2. Search Strategy

The descriptors used for the search were the following: "Multiple Sclerosis" [Mesh], "Multiple Sclerosis", "Sclerosis, Multiple", "Breathing Exercises" [Mesh], "Breathing Exercises", "Exercise, Breathing", "Respiratory Muscle Training", and "Muscle Training, Respiratory", in the following databases: PUBMED, Web of Science, Scopus, and PEDro. As for the Boolean operators, "AND" and "OR" were used, according to Table 1. The search strategy was conducted in all fields. Certain databases that did not provide any results were omitted.

Table 1. Search strategy in the different databases.

Databases and Search Terms	Initial Search Results	Records Identified
PUBMED (((("Multiple Sclerosis"[Mesh]) OR ("multiple sclerosis")) OR ("Sclerosis, Multiple") AND (randomized controlled trial [Filter])) AND ((((((("Breathing Exercises"[Mesh]) OR ("Exercise, Breathing")) OR ("Respiratory Muscle Training")) OR ("Muscle Training, Respiratory")) OR ("Training, Respiratory Muscle")) OR ("Breathing Exercises"))	17	16
WEB OF SCIENCE (((("Multiple Sclerosis"[Mesh]) OR (multiple sclerosis)) OR (Sclerosis, Multiple) AND (randomized controlled trial [Filter])) AND ((((((("Breathing Exercises"[Mesh]) OR (Exercise, Breathing)) OR (Respiratory Muscle Training)) OR (Muscle Training, Respiratory)) OR (Training, Respiratory Muscle)) OR (Breathing Exercises))	148	32
SCOPUS ("Multiple Sclerosis"[Mesh]) OR (multiple sclerosis) OR (Sclerosis, Multiple) AND ("Breathing Exercises"[Mesh]) OR (Exercise, Breathing) OR (Respiratory Muscle Training) OR (Muscle Training, Respiratory) OR (Training, Respiratory Muscle) OR (Breathing Exercises)	164	54
PEDRO (Multiple Sclerosis) AND (Breathing exercises)	11	9

The search strategy was developed by two researchers independently (LTA and RLL). A third researcher (MAVM) was consulted if there was any disagreement. After an initial review, 111 articles were considered potentially relevant, and an exhaustive reading of their full text was carried out, with special attention paid to the intervention, relief of symptoms, number of sessions, and duration of treatment. Reference lists in the selected studies were manually searched for eligible studies, and papers found to cite the selected studies were assessed.

2.3. Selection Criteria

The following PICOS eligibility criteria were used in the selection of articles:

- Participants: people with MS
- Intervention: respiratory physiotherapy techniques or training of the respiratory muscles.
- Comparison: control group, with or without treatment.
- Outcome: results of fatigue, before and after treatment.
- Study design: clinical trials.

Articles were excluded if they used a sample population with other pathologies, such as Parkinson's or others related to nervous system involvement, and those articles whose main treatment component was not breathing exercises. Also excluded were articles not available in the English or Spanish language, observational studies, case study reports, and systematic reviews.

2.4. Study Selection Process and Data Extraction

Two authors (LTA and RLL) independently retrieved relevant articles and extracted data from the included studies. If needed, any disagreements were discussed with, and resolved by, a third author (MAVM). The reference lists of included articles were also screened for more relevant articles, and the corresponding authors of some articles were contacted for nonreported information. The following information was codified: author, year, type of study, sample size, age, duration, measured variables, (scales and measures), and aim of results (intervention, comparison, follow up).

2.5. Risk of Bias Assessment

To assess the methodological quality of clinical trials, the Physiotherapy Evidence Database (PEDro) scale—one of the most widely used in the field of physical therapist interventions [30]—was applied by the two leading researchers independently (LTA and RLL). The PEDro Scale consists of 10 criteria, each receiving either a yes or no score. The PEDro score allocates three points according to the methods of blinding used (blinding of subject, therapist, and assessor), two points for randomization procedures (random allocation, concealment of allocation), two points for the reporting of appropriate data (baseline characteristics and point-estimates and measures of variability), and 1 point each for the analysis of the data (intent-to-treat analysis) and the adequacy of the follow-up.

3. Results

3.1. Study Selection

Finally, nine articles were selected that met the inclusion criteria and aligned with the objective of the study. The search strategy used to identify the clinical trials for this review in the different databases is described in Table 1. Figure 1 shows the process for the selection of articles.

3.2. Study Characteristics

The nine articles contain a total of 290 participants. A summary of the main characteristics of each study is presented in Tables 2 and 3.

In addition, an analysis of the content of the studies was carried out, based on the following variables:

Table 2. Main characteristics of the study and of the participants.

Author, Year	Type of Study	Sample Size (Participants)	Age	Duration	Measured Variables	Aim of Results
Klefbeck et al., 2003 [31].	Randomized controlled trial	15 participants: 9 women and 6 men	Between 37 and 61 years (average age: 49)	10 weeks	PImax, PEmax, VC, FVC, FEV1, FEV%, PEF, and fatigue	PImax and PEmax improved after 10 weeks in the GA, without changes in the CG. There were no significant differences between the groups in FSS.
Fry et al., 2007 [32].	Randomized controlled trial	46 participants: 38 women and 8 men.	Mean age: EG 50 years and CG 46.2 years.	10 weeks	FVC, FEV1, MIP, MEP, MVV, and fatigue	FEV1 and FVC improved in the experimental group. There were no significant differences between the groups in FSS.
Castro-Sanchez et al., 2012 [33].	Randomized controlled trial	73 participants: 50 women and 23 men. EG: 36 (26 F, 10 M) and CG: 37 (24F, 13M).	Mean age: EG 46 $\pm$ 9.97 and CG 50 $\pm$ 12.31	20 weeks	Pain, disability, spasticity, depression, fatigue, and autonomy	Improvements in pain, spasms, fatigue, disability, autonomy, depression, and functional independence in the EG.
Bayraktar et al., 2013 [34].	Non-randomized controlled trial	18 participants: 18 women (11 EG and 7 CG).	Mean age: EG 38 years and CG 39 years	8 weeks	Static standing balance, functional mobility, upper and lower muscle strength, and fatigue	Improvements in balance, functional mobility, muscle strength in upper and lower limbs, and fatigue in the experimental group. There were no significant differences in the CG.
Ray et al., 2013 [35].	Quasi-experimental before–after trial	21 participants: 16 women and 5 men. EG: 11 (9 F, 2 M) and CG: 10 (7 F, 3 M).	Mean age: EG 50.9 $\pm$ 5.7 and CG 56.2 $\pm$ 8.8	5 weeks	PImax, Pemax, fatigue, FVC, FEV1, MVV	Improvements in Pimax and Pemax and fatigue in EG. There were no significant differences in the CG.
Bulguroglu et al., 2017 [36].	Randomized controlled trial	38 participants: Mat pilates: 12 participants Pilates reformer: 13 participants CG: 13 participants.	Mean ages: Mat pilates: 45 years (39.3–45.5) Pilates reformer: 37 (29.5–40) CG: 40 (26–43)	8 weeks	Balance, CORE stability, mobility, fatigue, and quality of life	Improvements in balance, TUG, ABC, core stability, fatigue, mental health, and quality of life in the Pilates groups, before and after. In the CG, there were no differences.

Table 2. *Cont.*

Author, Year	Type of Study	Sample Size (Participants)	Age	Duration	Measured Variables	Aim of Results
Grubic et al., 2019 [37].	Randomized semicontrolled parallel group	19 participants: 7 women and 12 men. EG: 10 (4 F, 6 M) and CG: 9 (3 F, 6 M).	Mean age: EG 53.9 ± 10.7 and CG 48.2 ± 9.3	4 weeks	Fatigue, quality of life	Improvements in fatigue in both the EG and CG. Improvement in quality of life only in the EG.
Grubic et al., 2021 [38].	Pilot randomized controlled trial	24 participants: 14 women and 10 men. EG: 13 (8 F, 5 M) and CG: 11 (6 F, 5 M)	Mean age: EG 50 ± 9.3 and CG 53.8 ± 11.8	8 weeks	Sleep quality, insomnia, psychological stress, and fatigue	Improvements in insomnia, fatigue, psychological stress, and sleepiness in EG. No change in the CG.
Ghannadi et al., 2022 [39].	Single-blinded randomized controlled trial	36 participants: 27 women and 9 men. EG: 17 (13 F, 4 M) and CG: 19 (14 F, 5 M)	Mean age: EG 36.47 ± 7.62 and CG 39.36 ± 9.83	8 weeks	PEmax, PImax, functionality, fatigue, quality of life	Improvements in PImax and PEmax in both groups, although higher in the EG. There were no significant changes in TUG and 6MWT. Improvement in fatigue in the EG with respect to the CG.

6MWT: 6-Minute Walking Test; ABC: Activities Specific Balance Confidence Scale; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 s; FEV%: Forced Expiratory Volume; FSS: Fatigue Severity Scale; CG: Control Group; EG: Experimental Group; MIP: Maximal Inspiratory Pressure; MEP: Maximal Expiratory Pressure; MVV: Maximal Voluntary Ventilation; PEF: Peak Expiratory Flow; PEmax: Maximal Expiratory Pressure; PImax: Maximal Inspiratory Pressure; TUG: Test Up and Go; VC: Vital Capacity.

Table 3. Characteristics of the intervention in the selected articles.

Author, Year	Intervention (EG)	Comparison (CG)	Follow Up	Scales and Measures
Klefbeck et al., 2003 [31]	IMT training, 10 min, 2 times/day, every 2 days, with 4 h between each session, for 10 weeks, participated from home, weekly telephone contact with help and feedback.	Breathing exercises were part of their physiotherapy session. No telephone contact to resolve doubts.	The measurements were taken at the beginning, at the end of the 10 weeks of treatment, and one month after the end of the treatment.	FSS, RPE Scale
Fry et al., 2007 [32]	Daily IMT exercises for 10 weeks; 3 series of 15 repetitions at 30% MIP, increasing in intensity weekly.	IMT with instructions on use and progression. Optional telephone advice.	Measurements were taken at the beginning and end of the 10 weeks of treatment.	EDSS, FSS, Borg Scale
Castro-Sanchez et al., 2012 [33]	Ai-Chi exercise in the pool 60 min × 2 times/week.	Conventional treatment in a therapy room.	Measurements were taken before treatment, and at 4 and 10 weeks.	Pain (VAS, PRI, PPI, MPQ), RMDQ, Spasticity (VAS spasm), MSIS-29, Beck's depression inventory, MFIS, Barthel index

Table 3. *Cont.*

Author, Year	Intervention (EG)	Comparison (CG)	Follow Up	Scales and Measures
Bayraktar et al., 2013 [34].	Ai-Chi exercise in the pool 60 min × 2 times/week.	Active leg exercises with abdominal exercises at home, 60 min × 2 times/week, for 8 weeks.	Measurements were taken before and after treatment.	Balance (One-leg standing test), functional mobility (TUG test, 6MWT), strength (dynamometer), fatigue (FSS)
Ray et al., 2013 [35]	RMT 30 min, 3 days/week, for 5 weeks.	No treatment.	Measurements were taken at baseline, every week, and between 4 and 7 days after the last session.	MFIS, 6MWT, MMSE, SF-36
Bulguroglu et al., 2017 [36]	Both Pilates groups: between 1 h–1 h 30 min of Pilates 2 days/week for 8 weeks.	Home program of breathing and relaxation exercises 2 times/week for 8 weeks.	Measurements were taken before and after treatment.	Single Leg Stance, TUG, ABC, side bridge test, modified Biering–Sorensen test, trunk flexion test, prone bridge test, FSS, MSQOL-54
Grubic et al., 2019 [37]	Upper limb and respiratory exercises 60 min/2 days a week at a center, and at least 20 min/3 days a week performed independently. In total, 4 weeks.	No treatment, but they attended the center twice a week for 60 min to socialize.	Measurements were taken before and after treatment.	MFIS, SF-36
Grubic et al., 2021 [38]	Upper and lower limb exercises, along with breathing exercises for 60 min/2 times a week for 8 weeks.	No treatment, but they attended the center twice a week for 60 min to socialize for 8 weeks.	Measurements were taken before and after treatment.	PSQI, ISI, CORE-OM, MFIS
Ghannadi et al., 2022 [39]	IMT with POWERbreathe device at the beginning at 30% resistance, 15 breaths/3 series (1 min rest between sets) × 2 times a day for 8 weeks.	No treatment; they only received brochures on physical activity, education, and the importance of regular physical activity along with lifestyle modifications.	Measurements were taken before and after treatment.	6MWT, TUG, MFIS, SF36

6MWT: 6-Minute Walking Test; ABC: Activities Specific Balance Confidence Scale; CORE-OM: Clinical Outcomes in Routine Evaluation; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; CG: Control Group; EG: Experimental Group; IMT: Inspiratory muscle training; ISI: Insomnia Severity Index; MFIS: Modified Fatigue Impact Scale; MIP: Maximal Inspiratory Pressure; MPQ: McGill Pain Questionnaire; MSIS-29: Multiple Sclerosis Impact Scale; MSQOL-54: Multiple Sclerosis Quality of Life; MMSE: Mini-Mental State Examination; PPI: Present Pain Intensity; PRI: Pain Rating Index; PSQI: Pittsburgh Sleep Quality Index; RMDQ: Roland–Morris Disability Questionnaire; RMT: Respiratory Muscle Training; RPE: Borg Rating of Perceived Exertion; SF-36: Short Form 36; TUG: Test Up and Go; VAS: Visual Analogue Scale.

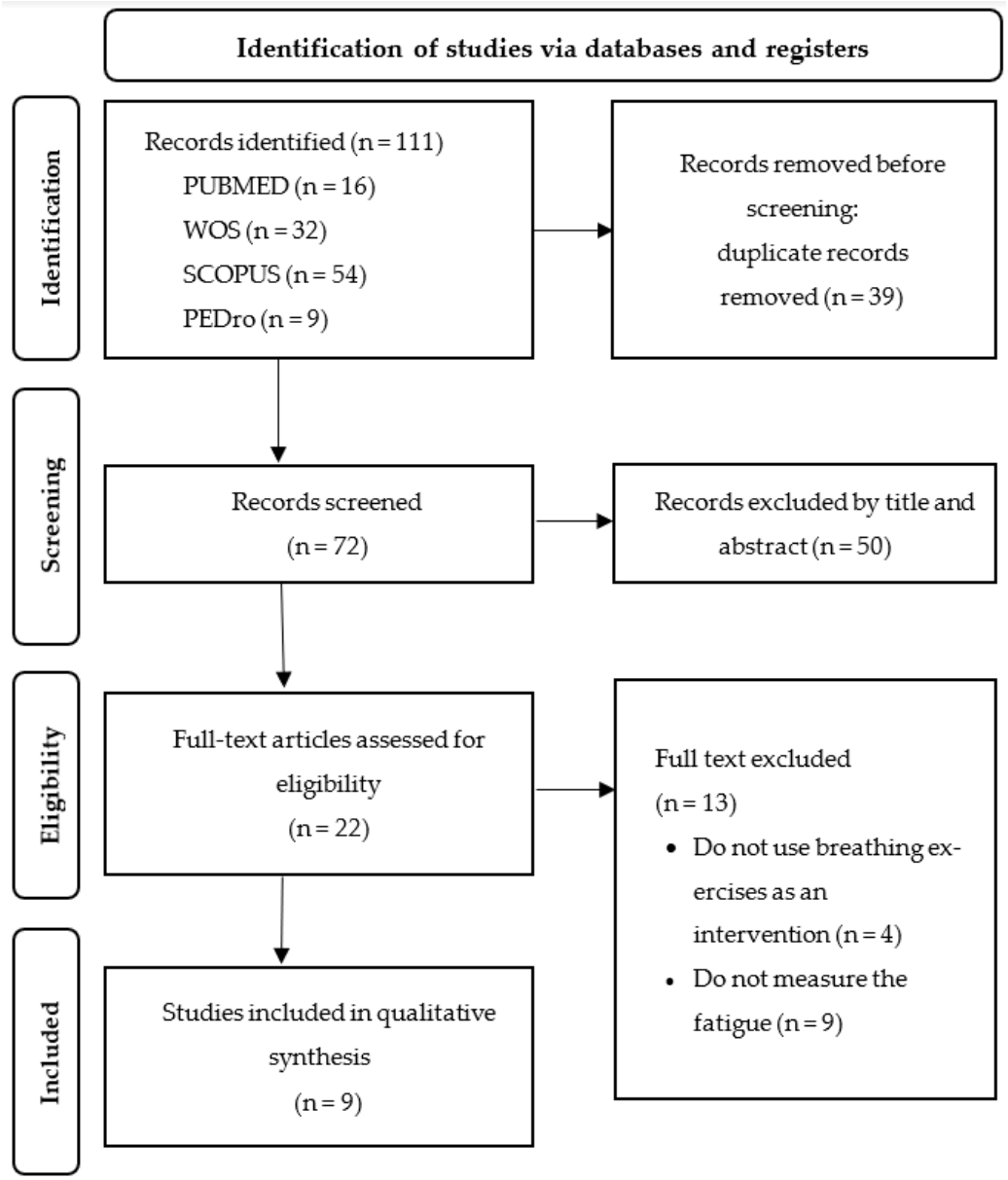

Figure 1. Stages carried out to obtain the selected articles [29].

3.3. Evaluation or Questionnaires Used

To measure fatigue, the Fatigue Severity Scale (FSS) was used in four studies [31,32,34,36], and the Modified Fatigue Severity Scale (MFIS) in five studies [33,35,37–39].

Various tools were used to measure pain in the study by Castro-Sanchez et al. (2012) [33], including the Visual Analogue Scale (VAS), Pain Rating Index (PRI), Present Pain Intensity Scale (PPI), and the McGill Pain Questionnaire (MPQ) [33]. They also assessed disability using the Roland–Morris Disability Questionnaire (RMDQ) [33], and spasticity using the Visual Analogue Scale of Spasticity (spasm VAS) [33].

Functionality was evaluated in three studies using the Test Up and Go (TUG) [34,36,39]; cardiovascular capacity using the 6-Minute Walking Test (6MWT) [34,39]; autonomy with the Barthel Index [33]; muscle strength with a dynamometer [34]; and balance through the one-legged balance test [34,36], and the Balance Activities Scale (ABC) [36].

The CORE was measured with several tests, such as the side bridge test, the modified Biering–Sorensen test, the trunk flexion test, and the prone bridge test [36].

Quality of life was analyzed in four of the studies with the SF-36 [37,39], the Multiple Sclerosis Quality of Life Questionnaire (MSQOL-54) [36], and the Multiple Sclerosis Impact Scale (MSIS-29) [33].

Sleep quality and insomnia were measured using the Pittsburgh Sleep Quality Questionnaire (PSQI) and the Insomnia Severity Index (ISI) [38].

Finally, psychological stress was measured in one of the studies by means of the Scale of Clinical Results in the Routine Assessment (CORE-OM) [38]; and depression, using the Beck Depression Inventory [33].

3.4. Intervention and/or Treatments Applied

Four of the studies used devices to perform respiratory muscle training [31,32,35,39], as follows.

The Inspiratory Muscle Training (IMT) device blocks airflow until the patient generates enough inspiratory pressure to overcome the resistance provided by the valve [32]. In Klefbeck et al. (2003) [34], patients had one week to become familiar with the Threshold device, and training consisted of three sets of 10 resisted breaths, performed at home, with follow-up. The training resistance began at between 40% and 60% of the previously calculated PImax, if they did not report a value greater than 17 on the Borg scale. In contrast, the control group (CG) performed breathing exercises as part of their physiotherapy session, but did not receive any follow-up, or contact to resolve any questions [31].

The Respiratory Muscle Training (RMT) device is another customized instrument for resistance training in the respiratory muscles, developed by the Center for Research and Education in Special Environments at the University at Buffalo [35]. The patients performed three sessions, one in the laboratory and the other two at home, using a nose clip and a T-shaped mouthpiece with inlet and outlet valves. The nozzle was connected to a pressure transducer and a laptop computer. Following a 10 s cycle, the patients inhaled and exhaled with pre-set resistances based on the percentage of their PImax and PEmax. The CG also received a device with instructions on its use and the progression of its application, with the option of telephone counselling [35].

Ghannadi et al. (2022) used a POWERbreathe device, with an initial resistance of 30% of the initial MIP. A follow-up was conducted with patients via telephone. The CG did not undergo any treatment; they only received brochures on lifestyle education and the importance of regular physical activity [39].

Castro-Sanchez et al. (2012) [37] and Bayraktar et al. (2013) [37] applied an Ai-Chi treatment in a swimming pool. During the 60 min session, relaxing music was played, and the Ai-Chi exercises were supported using abdominal breathing for 10 min, which involved exercises with deep breathing and wide and slow movements in the arms, legs and trunk. They focused on balance, strength, relaxation, flexibility, and breathing with 16 movements: "contemplating", "floating", "uplifting", "folding", "soothing", "gathering", "freeing", "transferring", "accepting", "accepting with grace", "rounding", "flowing", "relaxing" and "sustaining" [33]. The CG performed the same exercise program as the experimental group (EG) during the relaxation periods, but in a supine position on a mat [33].

Bayraktar et al. (2013) [34] applied Ai-Chi therapy, with 60 min sessions with a 15 min warm-up period, based on free movements in the extremities or activities with different pool materials. They combined deep breathing and worked on balance, strength, relaxation, flexibility, and breathing. Ai-Chi's own program lasted 30 min and consisted of the 16 movements mentioned [34]. The CG performed active leg and abdominal exercises at home [34].

Bulguroglu et al. (2017) [36] applied Pilates therapy [36], wherein the subjects were divided into three groups: Mat Pilates, Reformer Pilates, and the CG. In both Pilates groups, the participants were taught the key elements of this therapy: breathing, focus, the location of the rib cage, and the location of the shoulders, head, and neck. Movements were controlled by the physiotherapist, and corrections were made through tactile and verbal prompts and images. Stretching and postural exercises were used to cool down [36]. In the

Mat Pilates group, the difficulty of the exercises was increased using different positions and elastic bands (TheraBand). In the Reformer Pilates group, the level of difficulty of the exercises was maintained through different positions and the resistance of springs. Finally, the CG did a program at home with relaxation and breathing exercises [36].

As for other interventions, Grubic et al. (2019) and (2021) [40,41] used upper and lower limb exercises accompanied by breathing exercises in their treatment. The patients performed exercises both at the Multiple Sclerosis Society Center (MSSC) under the guidance of a physical therapist, and at home. The program included a 15 min warm-up phase, followed by diaphragmatic and thoracic breathing exercises, as well as movements in the upper limbs [37] and lower limbs [38]: a range of motion, coordination, and strengthening with minimal resistance (0.5 kg dumbbells or TheraBands). At the end of each session, 10 min were devoted to stretching the muscles used. The CG did not receive any treatment, but attended the center for social activities [37].

3.5. Methodological Quality Assessment

The methodological quality of the clinical trials included was assessed using the PEDro scale [30], (see Table 4):

Table 4. Evaluation of the methodological quality of the articles included, using the PEDro Scale.

Item (PEDRro Scale)	1	2	3	4	5	6	7	8	9	10	11	Total Score
Klefbeck et al. [31] 2003	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Fry et al. [32] 2007	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6
Castro-Sanchez et al. [33] 2012	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	6
Ray et al. [35] 2013	Y	N	N	Y	N	N	N	Y	Y	Y	Y	5
Bayraktar et al. [34] 2013	Y	N	N	N	N	N	Y	N	Y	N	Y	3
Bulguroglu et al. [36] 2017	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5
Grubic et al. [37] 2019	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	6
Grubic et al. [38] 2021	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Ghannadi et al. [39] 2022	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8

N: the criteria is not satisfied; Y: the criteria is satisfied. Criterion 1: this item is not used to calculate the PEDro score.

Of the nine articles included in this review, five of them scored greater than or equal to 6 on the PEDro scale [32,33,37–39], indicating a good methodological quality. All the included studies presented appropriate data in point-estimates and measures of variability. Eight studies showed adequate baseline comparability or between-group comparisons. These articles did not meet some of the scale items: neither the subjects nor the therapists were blinded to the study (however, this issue could not be omitted, because of the peculiarity of the interventions), or allocations were not concealed (seven studies), among others risk of bias. However, most of studies had a low or moderate risk of bias for the characteristics analyzed. Bayraktar et al. (2013) [34] featured the lowest score, not satisfying the random and concealed allocation, baseline comparability, methods of blinding, follow-up, or between-group comparisons.

4. Discussion

The objective of this systematic review was to describe the effectiveness of breathing exercises on fatigue in patients with MS. Despite us finding a low number of published articles in this field, when considered together, the studies included in this review show different alternatives for carrying out respiratory muscle training. Whether they opt for a direct treatment of these muscles [31,32,35,39], or combine such training with active exercises [33,34,36–38], the studies indicate that treatment with breathing exercises leads to a reduction in fatigue in patients with MS [33–39]. In addition, some evaluate the positive

impact on improving the quality of life among these patients, as they are able to carry out different tasks more easily during the day. Five articles included in this review [32,33,37–39] display a good methodological quality.

The implementation of respiratory exercises primarily involved utilizing a device specifically designed for the direct strengthening of the respiratory muscles, as well as incorporating other types of therapies that combine diaphragmatic and respiratory muscle work. Most of the authors opt for a device to work resistance during inspiration [31,32,39], while others apply resistance during both inspiration and expiration [35].

According to Klefbeck et al. (2003) [31], IMT aided by a Threshold device benefits the inspiratory muscle strength, while also maintaining said improvement for up to one month after the end of treatment. These results are supported by Fry et al. (2007) [32], who also obtain improvements in the inspiratory muscle strength and even a reduction in the inspiratory muscle deterioration after treatment. However, neither of the two studies achieved significant improvements in the FSS scale values, so these patients did not show changes in fatigue after specific respiratory muscle strength training with devices. On the other hand, Ghannadi et al. (2022) [39] achieved an improvement in inspiratory function, and reduced fatigue, according to the MFIS scale. Participants reported feeling better and being able to do more tasks throughout the day with less fatigue. These results are very similar to those reported by Ray et al. (2013) [35], who obtained improvements in the values of the MFIS scale and a reduction in fatigue in patients, who also received RMT.

Several studies [31,32,35,39] agree that RMT and IMT substantially improve inspiratory muscle strength and reduce muscle deterioration, an observation already made by authors such as Huang et al. (2020) [40], in which patients with severe MS improved their PImax and PEmax values after a ten-week IMT treatment. However, Ray et al. (2013) and Ghannadi et al. (2022) [35,39] show a reduction in fatigue, yet they do also describe improvements in the ability to perform everyday tasks.

One aspect to consider regarding this systematic review is that, when comparing the studies, differences in the level of severity of the MS were detected. In three studies, patients had a mild-to-moderate disease state, with scores of up to a maximum of 6.5 points according to the EDSS scale [32,35,39]; Klefbeck et al. (2003) [31] included patients with a severe-to-major condition, with a score between 6.5 and 9.5 points [31]. However, it is observed that the results of these studies are not directly related to the EDSS scale score, or to a reduction or not in fatigue after respiratory treatment. In contrast, the studies by Gosselink et al. (2000) [41] and Ray et al. (2015) [26] identify weakness in the respiratory muscles as a possible factor that increases fatigue in patients with MS. Their hypothesis associates reduced fatigue with an increase in the strength of the respiratory muscles [39]. Therefore, it would have been interesting to describe whether the perception of reduced fatigue shown by people with MS in this systematic review could be due to an improvement in the respiratory muscles, but there was not enough information in the articles on this variable to allow us to test this hypothesis.

Most of the studies included in this review choose to combine breathing exercises with other treatment techniques, such as Ai-Chi [33,34], Pilates [36], and the exercising of the upper and lower limbs [37,38]. Castro-Sanchez et al. (2012) [33] and Bayraktar et al. (2013) [34], after the application of Ai-Chi [33,34], achieve a significant reduction in the levels of fatigue in the treatment group. These results can be compared with a recently published meta-analysis by Amedoro et al. (2020) [42] on the effect of aquatic therapy in MS, where they highlight not only the perception of reduced physical fatigue, but also improvements in the psychological, motivational, and emotional aspects [42].

Bulguruglu et al. (2017) [36] use Pilates as a treatment in two groups of patients with a mild level of disability. After eight weeks of treatment, the authors conclude that there is a reduction in fatigue in both EGs, reporting significantly positive results according to the FSS, and an improvement in the quality of life, thanks to there being less difficulty in carrying out daily tasks. The study suggests that fatigue decreased as a result of the postural control and balance achieved following the Pilates treatment, something that was

also described in the cohort study conducted by Soysal-Tomruk et al. (2016) [43]. This study and that by Gandolfi et al. (2015) [44] show that sensory integration is related to fatigue, although this is questioned by Brichetto et al. (2015) [45], in whose study no direct relationship was found between these variables.

Two of the studies included in this review propose a combined treatment of diaphragmatic exercises with upper and lower limb training. In 2019, Grubić et al. [37] choose to work the upper members, while, in 2021, Grubić et al. [38] include both the upper and lower limbs. Both studies report a significant reduction in fatigue in the EG. The hypothesis defended by these authors is that fatigue is not influenced by a single aspect, but that there are multiple factors through which it can modified [37]; and they indicate improvements in the quality of life of the patients, who had initially indicated a lack of motivation to carry out work at home due to their feeling of fatigue and lack of energy [37,38]. The authors argue that the improvement in both aspects may also be related to the possibility of carrying out the exercises in a place of social support, with other patients with MS, as opposed to carrying out the treatment in laboratories or hospital centers, an aspect that is also revealed in a study by Tacchino et al. (2017) [46]. This improvement could be the result of group exercise creating more motivation to exercise, due to social interaction. Therefore, according to this hypothesis, the impact of a socially supportive and less stressful family environment with other people with MS on exercise motivation cannot be ruled out [38,46].

To elucidate the correlation between fatigue and respiratory muscle weakness, it has been noted that increased neural stimulation is required, to support alveolar ventilation and ensure proper gas exchange in the presence of weakened respiratory muscles, leading to fatigue, as well as the perception of fatigue [39,47]. Interventions such as IMT can lead to various outcomes, including enhanced diaphragm thickness, decreased blood lactate concentration resulting from the improved lactate uptake by trained respiratory muscles, improved ventilatory efficiency due to changes in motor recruitment patterns, and a reduced perception of respiratory effort and reduced perceived exertion [48]. The increased strength and endurance in the inspiratory muscles can minimize the gap between the energy demand and effort required during exercise [49].

4.1. Study Limitations

The limitations to this review include the differences in the degree of disease (according to the EDSS scale) in the patients included, as well as the diversity in the action protocols and duration of the studies selected. In addition, because fatigue is a subjective symptom, it is difficult for researchers and patients themselves to measure. None of the studies maintained the treatment for longer than 20 weeks, so it is unknown whether any improvement would be maintained in the long term. Future investigations should be carried out considering longer periods of time. During the search and selection process of the articles, Health Sciences databases, such as CINAHL, EMBASE, or Cochrane Library, were not used, so there may be some potentially relevant articles that were not selected for the study. We could not rule out some degree of selection, publication, and reference bias from the literature searches included. The majority of the papers were published in English; hence, there was a likelihood of missing data available in other languages. In addition, this systematic review included studies that were not randomized controlled trials, so the risk of bias is greater. Due to the low number of suitable studies in this field, and the heterogeneity regarding their various exercise intervention protocols and the outcome variables, a methodically sound meta-analysis might not be appropriate to conduct.

4.2. Clinical Practice and Policy Implications of This Study

Among the practical implications of this review, one of its aims was to describe alternatives within conservative treatment, through protocols that include breathing exercises to improve fatigue, which is one of the most common symptoms in patients with MS. It has been highlighted that the effectiveness of conservative treatment leads to an improvement in quality of life and in the performance of everyday tasks.

This approach could lead to a reduction in the number of drugs in these polymedicated patients and, therefore, a reduction in the economic cost that pharmacology entails, both for health management centers and for families.

5. Conclusions

This systematic review examines the effectiveness of respiratory exercises on the perceived symptoms of fatigue among MS patients. The majority of the included studies conclude that incorporating these respiratory exercises resulted in a reduction in fatigue perception after engaging in physical exercise programs, versus the control groups.

We have found a low number of published articles in this field, and a meta-analysis was impossible to conduct. Further studies are needed in order to analyze whether this perceived improvement in fatigue is associated with an enhanced pulmonary capacity. Nevertheless, more studies, a larger number of participants, and short-, medium-, and long-term follow-ups are required, to confirm the current results.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/su151712887/s1, PRISMA Checklist. Reference [50] is cited in the supplementary materials.

Author Contributions: Conceptualization, L.T.-Á., R.L.-L., J.Á.R.-A., M.Á.V.-M. and M.J.B.-I.; methodology, L.T.-Á., R.L.-L., J.Á.R.-A., M.Á.V.-M. and M.J.B.-I.; formal analysis, L.T.-Á. and J.Á.R.-A.; research, L.T.-Á., R.L.-L., J.Á.R.-A., M.Á.V.-M. and M.J.B.-I.; resources, J.Á.R.-A.; data curation, J.Á.R.-A.; writing—original draft preparation, L.T.-Á., R.L.-L., J.Á.R.-A., M.Á.V.-M. and M.J.B.-I.; writing—review and editing, L.T.-Á., R.L.-L., J.Á.R.-A., M.Á.V.-M. and M.J.B.-I.; supervision, R.L.-L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Ministerio de Ciencia e Innovación (Spain), convocatoria Proyectos de Generación de Conocimiento 2021, Plan Estatal de Investigación Científica y Técnica y de Innovación 2021–2023, grant number PID2021-123447OA-I00.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Brownlee, W.J.; Hardy, T.A.; Fazekas, F.; Miller, D.H. Diagnosis of Multiple Sclerosis: Progress and Challenges. *Lancet* **2017**, *389*, 1336–1346. [CrossRef] [PubMed]
2. Dobson, R.; Giovannoni, G. Multiple Sclerosis—A Review. *Eur. J. Neurol.* **2019**, *26*, 27–40. [CrossRef] [PubMed]
3. Zhang, T.; Yan, H.-X.; An, Y.; Yin, L.; Sun, P.-P.; Zhao, J.-N.; Yan, J.-T. The Efficacy and Safety of Manual Therapy for Symptoms Associated with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *J. Integr. Complement. Med.* **2022**, *28*, 780–790. [CrossRef] [PubMed]
4. Harirchian, M.H.; Fatehi, F.; Sarraf, P.; Honarvar, N.M.; Bitarafan, S. Worldwide Prevalence of Familial Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Mult. Scler. Relat. Disord.* **2018**, *20*, 43–47. [CrossRef]
5. García López, F.J.; García-Merino, A.; Alcalde-Cabero, E.; de Pedro-Cuesta, J. Incidencia y Prevalencia de La Esclerosis Múltiple En España. Una Revisión Sistemática. *Neurología* 2022, *in press*. [CrossRef]
6. Goodin, D.S.; Khankhanian, P.; Gourraud, P.A.; Vince, N. The Nature of Genetic and Environmental Susceptibility to Multiple Sclerosis. *PLoS ONE* **2021**, *16*, e0246157. [CrossRef]
7. Abou, L.; Qin, K.; Alluri, A.; Du, Y.; Rice, L.A. The Effectiveness of Physical Therapy Interventions in Reducing Falls among People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *J. Bodyw. Mov. Ther.* **2022**, *29*, 74–85. [CrossRef]
8. Levy, J.; Prigent, H.; Bensmail, D. Respiratory Rehabilitation in Multiple Sclerosis: A Narrative Review of Rehabilitation Techniques. *Ann. Phys. Rehabil. Med.* **2018**, *61*, 38–45. [CrossRef]
9. Royer, N.; Duboeuf, M.; Camdessanché, J.-P.; Millet, G. Prevalence of Fatigue and Its Explicative Variables among People with Multiple Sclerosis. *NeuroRehabilitation* **2022**, *51*, 509–517. [CrossRef]
10. Manjaly, Z.M.; Harrison, N.A.; Critchley, H.D.; Do, C.T.; Stefanics, G.; Wenderoth, N.; Lutterotti, A.; Müller, A.; Stephan, K.E. Pathophysiological and Cognitive Mechanisms of Fatigue in Multiple Sclerosis. *J. Neurol. Neurosurg. Psychiatry* **2019**, *90*, 642–651. [CrossRef]

11. Razazian, N.; Kazeminia, M.; Moayedi, H.; Daneshkhah, A.; Shohaimi, S.; Mohammadi, M.; Jalali, R.; Salari, N. The Impact of Physical Exercise on the Fatigue Symptoms in Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *BMC Neurol.* **2020**, *20*, 93. [CrossRef]
12. Krupp, L.B.; Serafin, D.J.; Christodoulou, C. Multiple Sclerosis-Associated Fatigue. *Expert Rev. Neurother.* **2010**, *10*, 1437–1447. [CrossRef] [PubMed]
13. Mohebbirad, M.; Motaharinezhad, F.; Shahsavary, M.; Joveini, G. Effects of Sensory Interventions on Fatigue in People With Multiple Sclerosis: A Systematic Review. *Int. J. MS Care* **2022**, *24*, 29–34. [CrossRef] [PubMed]
14. Coates, K.D.; Aboodarda, S.J.; Krüger, R.L.; Martin, T.; Metz, L.M.; Jarvis, S.E.; Millet, G.Y. Multiple Sclerosis-Related Fatigue: The Role of Impaired Corticospinal Responses and Heightened Exercise Fatigability. *J. Neurophysiol.* **2020**, *124*, 1131–1143. [CrossRef] [PubMed]
15. Hensen, H.A.; Krishnan, A.V.; Eckert, D.J. Sleep-Disordered Breathing in People with Multiple Sclerosis: Prevalence, Pathophysiological Mechanisms, and Disease Consequences. *Front. Neurol.* **2018**, *8*, 740. [CrossRef]
16. Broch, L.; Simonsen, C.S.; Flemmen, H.Ø.; Berg-Hansen, P.; Skardhamar, Å.; Ormstad, H.; Celius, E.G. High Prevalence of Fatigue in Contemporary Patients with Multiple Sclerosis. *Mult. Scler. J.—Exp. Transl. Clin.* **2021**, *7*, 2055217321999826. [CrossRef]
17. Perrild, H.; Møller, A.; Pedersen, H.; Siersbæk-Nielsen, K. Undetectable Thyrotropin Levels Using Immunoradiometric Assay in L-Dopa-Treated Patients. *J. Neurol.* **1988**, *235*, 255. [CrossRef]
18. Fisk, J.D.; Ritvo, P.G.; Ross, L.; Haase, D.A.; Marrie, T.J.; Schlech, W.F. Measuring the Functional Impact of Fatigue: Initial Validation of the Fatigue Impact Scale. *Clin. Infect. Dis.* **1994**, *18*, S79–S83. [CrossRef]
19. Téllez, N.; Río, J.; Tintoré, M.; Nos, C.; Galán, I.; Montalban, X. Does the Modified Fatigue Impact Scale Offer a More Comprehensive Assessment of Fatigue in MS? *Mult. Scler.* **2005**, *11*, 198–202. [CrossRef]
20. Casuso-Holgado, M.J.; Martín-Valero, R.; Carazo, A.F.; Medrano-Sánchez, E.M.; Cortés-Vega, M.D.; Montero-Bancalero, F.J. Effectiveness of Virtual Reality Training for Balance and Gait Rehabilitation in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Clin. Rehabil.* **2018**, *32*, 1220–1234. [CrossRef]
21. Andreu-Caravaca, L.; Ramos-Campo, D.J.; Chung, L.H.; Rubio-Arias, J. Dosage and Effectiveness of Aerobic Training on Cardiorespiratory Fitness, Functional Capacity, Balance, and Fatigue in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Arch. Phys. Med. Rehabil.* **2021**, *102*, 1826–1839. [CrossRef]
22. Neal, W.N.; Cederberg, K.L.; Jeng, B.; Sasaki, J.E.; Motl, R.W. Is Symptomatic Fatigue Associated With Physical Activity and Sedentary Behaviors Among Persons With Multiple Sclerosis? *Neurorehabil. Neural Repair* **2020**, *34*, 505–511. [CrossRef] [PubMed]
23. Nourbakhsh, B.; Revirajan, N.; Morris, B.; Cordano, C.; Creasman, J.; Manguinao, M.; Krysko, K.; Rutatangwa, A.; Auvray, C.; Aljarallah, S.; et al. Safety and Efficacy of Amantadine, Modafinil, and Methylphenidate for Fatigue in Multiple Sclerosis: A Randomised, Placebo-Controlled, Crossover, Double-Blind Trial. *Lancet Neurol.* **2021**, *20*, 38–48. [CrossRef] [PubMed]
24. Rascol, O.; Fabbri, M.; Poewe, W. Amantadine in the Treatment of Parkinson's Disease and Other Movement Disorders. *Lancet Neurol.* **2021**, *20*, 1048–1056. [CrossRef] [PubMed]
25. Andreu-Caravaca, L.; Ramos-Campo, D.J.; Chung, L.H.; Martínez-Rodríguez, A.; Rubio-Arias, J.Á. Effects and Optimal Dosage of Resistance Training on Strength, Functional Capacity, Balance, General Health Perception, and Fatigue in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Disabil. Rehabil.* **2023**, *45*, 1595–1607. [CrossRef] [PubMed]
26. Ray, A.D.; Mahoney, M.C.; Fisher, N.M. Measures of Respiratory Function Correlate with Fatigue in Ambulatory Persons with Multiple Sclerosis. *Disabil. Rehabil.* **2015**, *37*, 2407–2412. [CrossRef]
27. Templeman, L.; Roberts, F. Effectiveness of Expiratory Muscle Strength Training on Expiratory Strength, Pulmonary Function and Cough in the Adult Population: A Systematic Review. *Physiotherapy* **2020**, *106*, 43–51. [CrossRef]
28. Ferreira, G.D.; Costa, A.C.C.; Plentz, R.D.M.; Coronel, C.C.; Sbruzzi, G. Respiratory Training Improved Ventilatory Function and Respiratory Muscle Strength in Patients with Multiple Sclerosis and Lateral Amyotrophic Sclerosis: Systematic Review and Meta-Analysis. *Physiotherapy* **2016**, *102*, 221–228. [CrossRef]
29. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Altman, D.; Antes, G.; Atkins, D.; Barbour, V.; Barrowman, N.; Berlin, J.A.; et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]
30. Maher, C.G.; Sherrington, C.; Herbert, R.D.; Moseley, A.M.; Elkins, M. Reliability of the PEDro Scale for Rating Quality of Randomized Controlled Trials. *Phys. Ther.* **2003**, *83*, 713–721. [CrossRef]
31. Klefbeck, B.; Nedjad, J.H. Effect of Inspiratory Muscle Training in Patients with Multiple Sclerosis. *Arch. Phys. Med. Rehabil.* **2003**, *84*, 994–999. [CrossRef]
32. Fry, D.K.; Pfalzer, L.A.; Chokshi, A.R.; Wagner, M.T.; Jackson, E.S. Randomized Control Trial of Effects of a 10-Week Inspiratory Muscle Training Program on Measures of Pulmonary Function in Persons with Multiple Sclerosis. *J. Neurol. Phys. Ther.* **2007**, *31*, 162–172. [CrossRef] [PubMed]
33. Castro-Sánchez, A.M.; Matarán-Peñarrocha, G.A.; Lara-Palomo, I.; Saavedra-Hernández, M.; Arroyo-Morales, M.; Moreno-Lorenzo, C. Hydrotherapy for the Treatment of Pain in People with Multiple Sclerosis: A Randomized Controlled Trial. *Evid.-Based Complement. Altern. Med.* **2012**, *2012*, 473963. [CrossRef]
34. Bayraktar, D.; Guclu-Gunduz, A.; Yazici, G.; Lambeck, J.; Batur-Caglayan, H.Z.; Irkec, C.; Nazliel, B. Effects of Ai-Chi on Balance, Functional Mobility, Strength and Fatigue in Patients with Multiple Sclerosis: A Pilot Study. *NeuroRehabilitation* **2013**, *33*, 431–437. [CrossRef] [PubMed]

35. Ray, A.D.; Udhoji, S.; Mashtare, T.L.; Fisher, N.M. A Combined Inspiratory and Expiratory Muscle Training Program Improves Respiratory Muscle Strength and Fatigue in Multiple Sclerosis. *Arch. Phys. Med. Rehabil.* **2013**, *94*, 1964–1970. [CrossRef]
36. Bulguroglu, I.; Guclu-Gunduz, A.; Yazici, G.; Ozkul, C.; Irkec, C.; Nazliel, B.; Batur-Caglayan, H.Z. The Effects of Mat Pilates and Reformer Pilates in Patients with Multiple Sclerosis: A Randomized Controlled Study. *NeuroRehabilitation* **2017**, *41*, 413–422. [CrossRef] [PubMed]
37. Grubić Kezele, T.; Babić, M.; Štimac, D. Exploring the Feasibility of a Mild and Short 4-Week Combined Upper Limb and Breathing Exercise Program as a Possible Home Base Program to Decrease Fatigue and Improve Quality of Life in Ambulatory and Non-Ambulatory Multiple Sclerosis Individuals. *Neurol. Sci.* **2019**, *40*, 733–743. [CrossRef]
38. Grubić Kezele, T.; Trope, Z.; Ahel, V.; Ružić, N.; Omrčen, H.; Dudarić, L.; Fužinac-Smojver, A. Upper-Lower Limb and Breathing Exercise Program for Improving Sleep Quality and Psychological Status in Multiple Sclerosis: A Pilot Randomized Controlled Trial. *Brain Impair.* **2021**, *24*, 86–102. [CrossRef]
39. Ghannadi, S.; Noormohammadpour, P.; Mazaheri, R.; Sahraian, M.A.; Mansournia, M.A.; Pourgharib Shahi, M.H.; Salmasi Fard, A.H.; Abolhasani, M. Effect of Eight Weeks Respiratory Muscle Training on Respiratory Capacity, Functional Capacity and Quality of Life on Subjects with Mild to Moderate Relapsing-Remitting Multiple Sclerosis: A Single-Blinded Randomized Controlled Trial. *Mult. Scler. Relat. Disord.* **2022**, *68*, 104208. [CrossRef]
40. Huang, M.H.; Fry, D.; Doyle, L.; Burnham, A.; Houston, N.; Shea, K.; Smith, H.; Wiske, L.; Goode, J.; Khitrik, E.; et al. Effects of Inspiratory Muscle Training in Advanced Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2020**, *37*, 101492. [CrossRef]
41. Gosselink, R.; Kovacs, L.; Ketelaer, P.; Carton, H.; Decramer, M. Respiratory Muscle Weakness and Respiratory Muscle Training in Severely Disabled Multiple Sclerosis Patients. *Arch. Phys. Med. Rehabil.* **2000**, *81*, 747–751. [CrossRef]
42. Amedoro, A.; Berardi, A.; Conte, A.; Pelosin, E.; Valente, D.; Maggi, G.; Tofani, M.; Galeoto, G. The Effect of Aquatic Physical Therapy on Patients with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Mult. Scler. Relat. Disord.* **2020**, *41*, 102022. [CrossRef] [PubMed]
43. Soysal Tomruk, M.; Uz, M.Z.; Kara, B.; Idiman, E. Effects of Pilates Exercises on Sensory Interaction, Postural Control and Fatigue in Patients with Multiple Sclerosis. *Mult. Scler. Relat. Disord.* **2016**, *7*, 70–73. [CrossRef] [PubMed]
44. Gandolfi, M.; Munari, D.; Geroin, C.; Gajofatto, A.; Benedetti, M.D.; Midiri, A.; Carla, F.; Picelli, A.; Waldner, A.; Smania, N. Sensory Integration Balance Training in Patients with Multiple Sclerosis: A Randomized, Controlled Trial. *Mult. Scler.* **2015**, *21*, 1453–1462. [CrossRef]
45. Brichetto, G.; Piccardo, E.; Pedullà, L.; Battaglia, M.A.; Tacchino, A. Tailored Balance Exercises on People with Multiple Sclerosis: A Pilot Randomized, Controlled Study. *Mult. Scler.* **2015**, *21*, 1055–1063. [CrossRef] [PubMed]
46. Tacchino, A.; Brichetto, G.; Zaratin, P.; Battaglia, M.A.; Ponzio, M. Multiple Sclerosis and Rehabilitation: An Overview of the Different Rehabilitation Settings. *Neurol. Sci.* **2017**, *38*, 2131–2138. [CrossRef]
47. Krupp, L.B. The fatigue severity scale. *Arch. Neurol.* **1989**, *46*, 1121. [CrossRef] [PubMed]
48. López-Pérez, M.E.; Romero-Arenas, S.; Giráldez-García, M.A.; Colomer-Poveda, D.; Márquez, G. Acute Psychophysiological Responses during Exercise While Using Resistive Respiratory Devices: A Systematic Review. *Physiol. Behav.* **2022**, *256*, 113968. [CrossRef]
49. Hoffman, M.; Augusto, V.M.; Eduardo, D.S.; Silveira, B.M.F.; Lemos, M.D.; Parreira, V.F. Inspiratory Muscle Training Reduces Dyspnea during Activities of Daily Living and Improves Inspiratory Muscle Function and Quality of Life in Patients with Advanced Lung Disease. *Physiother. Theory Pract.* **2021**, *37*, 895–905. [CrossRef]
50. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, 105906. [CrossRef]

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