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RESPIRATORY STRENGH TRAINING IN INDIVIDUALS WITH AMYOTROPHIC LATERAL SCLEROSIS: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Running title: *Respiratory training in amyotrophic lateral sclerosis*

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KKPM, LDL, LBC, VPCV, and JVSA. The first draft of the manuscript was written by KKPM, LDL, LBC, PRA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To investigate the effects of respiratory strength training in individuals with ALS, through a systematic review with meta-analysis. **Methods:** The searches were conducted in the electronic databases MEDLINE, Lilacs, Scielo and PEDro, in addition to a manual search, between August and October 2024, carried out by two independent evaluators. Randomized clinical trials investigating respiratory strength training in ALS patients at different stages of the disease were included. The outcomes of interest were respiratory strength, pulmonary function, and functional status of individuals with ALS. The methodological quality of the studies was assessed using the PEDro scale. The Comprehensive Meta-Analysis program, Version 3.0, was used to perform the analysis. **Results:** Five studies were included, involving 158 participants. The meta-analysis indicated that respiratory strength training in ALS patients showed a significant improvement in maximum inspiratory pressure of 13.4 cm H_2O (95% CI 4.3 to 22.5; I^2=0%; p=0.004), maximum expiratory pressure of 35.2 cm H_2O (95%CI 15.9 to 54.7; I^2=0%; p<0.001), and peak expiratory flow of 1.3 L/s (95%CI 0.4 to 2.3; I^2=0%; p=0.006), in favor of the experimental group when compared to the control. For forced vital capacity (1.1% of predicted; 95%CI -5.7 to 7.9; I^2=0%; p=0.75), peak inspiratory flow (-0.7 L/s; 95%CI -1.5 to 0.1; I^2=0%; p=0.07), and functionality assessed by the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (2.4 points; 95%CI -2.9 to 7.8; I^2=0%; p=0.38), no significant differences were found. **Conclusion:** This systematic review revealed that respiratory strength training can significantly contribute to improving inspiratory and expiratory muscle strength, as well as peak expiratory flow in ALS patients. However, the effects for the other variables remain uncertain, Futures randomized clinical trials of high methodological quality are recommended.

Key words: Amyotrophic Lateral Sclerosis. Respiratory Muscle Training. Systematic review. Meta-analysis.

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a multisystem neurodegenerative disease that causes muscle paralysis, resulting in loss of movement and other functions such as the ability to communicate verbally, swallow and even the development of respiratory failure[1]. Epidemiological studies show that the global prevalence and incidence of ALS is currently 4.42 per 100,000 inhabitants, with 1.59 cases per 100,000 people per year[2]. This condition is more prevalent in the elderly population, with the peak of diagnostics being between 60 and 70 years of age[3]. The geographical prevalence shows a higher number of cases in developing compared to developed regions, which may be related to population ageing[2]. In addition, the incidence of ALS is more common among the white and male population[4].

Among the disabling symptoms of the ALS, one of the most serious is the involvement of the respiratory system, as it reduces the ability to generate negative intrathoracic pressure, reduces thoracic expansion during inspiration and reduces elastic retraction forces during expiration[5]. In addition, the decreased speed, range of motion and weakness of the respiratory, laryngeal and bulbar muscles further affect airway clearance abilities, resulting in additional difficulties in secretion management, airway defense and efficient ejection of tracheal aspirate[6]. In this context, ALS patients are at high risk of respiratory complications[7]. Furthermore, the main cause of death in ALS is respiratory failure[8].

The treatment of the ALS is individualized and aims to relieve symptoms, provide supportive care and promote well-being to prolong the life of the patients[9]. Thus, respiratory muscle rehabilitation is essential for this population. One approach that has the potential to increase the strength of the respiratory muscles and improve pulmonary function is respiratory strength training, when individuals are requested to breathe multiple times against an external load[10]. When the respiratory muscles are overloaded, their fibers tend to respond to training

stimuli by undergoing adaptations to their structure in the same manner as any other skeletal muscles. Thus, respiratory strength training has the potential to reduce dyspnea and prevent fatigue, increasing functional capacity[11], maintaining adequate ventilation[12] and improving cough ability and lung volumes[13,14].

One previous systematic review, without meta-analysis, investigated the effects of inspiratory strength training in ALS patients[15]. The authors reported limited evidence that training strengthens the inspiratory muscles in this population[15]. However, this review included only two randomized clinical trials, with searches carried out until April 2013. Another systematic review with meta-analysis investigated the effectiveness of respiratory strength training in patients with multiple sclerosis (MS) and ALS and reported significant improvements in inspiratory and expiratory muscle strength (24 cmH_2O and 12 cmH_2O, respectively), and forced expiratory volume in one second (0.27 L)[16]. However, besides this study only included three randomized clinical trials, with searches carried out up to January 2015, the meta-analysis results were not reported separately for ALS individuals.

The protocol of the present systematic review has been designed to improve previous methods by specifically investigating the effect of the respiratory strength training in individuals with ALS. In addition, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was incorporated to quantify the quality of the evidence. Finally, a functional status measure was included as an outcome of interest to examine carryover effects of improved respiratory function to daily activities. Thus, the aim of this study was to investigate the effects of respiratory strength training on respiratory strength, pulmonary function, and functional status of individuals with ALS, through a systematic review with meta-analysis.

METHODS

Design

This is a systematic review with meta-analysis, previously registered in PRÓSPERO (CRD42024622215), and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.

Procedures

Searches were conducted in the CINAHL (1986 to October 2024), LILACS (1986 to October 2024), MEDLINE (1946 to October 2024), and Physiotherapy Evidence Database (PEDro) (to October 2024) databases for relevant studies, without date or language restrictions. Search terms included words related to ALS and randomized trials, and words related to respiratory strength training. Title and abstracts were displayed and screened to identify relevant studies. Full-text copies of peer-reviewed relevant articles were retrieved, and their reference lists were screened to identify further relevant studies. The method section of the retrieved articles was extracted and independently reviewed by two researchers, using predetermined criteria. Both reviewers were blinded to authors, journals, and results of the studies. Disagreement or ambiguities were solved by consensus, after discussion with a third reviewer.

Inclusion and exclusion criteria

Design: Clinical trials.

Participants: Trials involving individuals with ALS and weakness of respiratory muscles were included. Participants were considered weak when the strength of their respiratory muscles, reported as maximal inspiratory or expiratory pressures, was lower than 90% of that predicted for age and sex matched.15 Information regarding the number

of participants, sex, age, time since diagnostic, and magnitude of respiratory muscle weakness were recorded to describe the trials.

Intervention: The experimental intervention was respiratory strength training that produced repetitive contractions of the respiratory muscles, against resistance, aiming at increasing strength. The control intervention could be no intervention, placebo intervention, sham intervention, or minimal intervention (ie, nonspecific, or low dose intervention).

Outcomes: The outcome measures of interest were respiratory muscle strength, pulmonary function, as well as functional status, assessed using specific tests or questionnaires.

Methodological quality

The methodological quality of the experimental studies included was assessed using the PEDro scale, developed to rate the methodological quality of randomized clinical trials. It consists of 11 items, each of which scored as yes (1 point) or no (0 points). The final score is given by the sum of the items defined as “yes”, being that the item 1 is not included. The score of the studies described on the database's website was used. The scoring of the studies not found in the PEDro database was carried out by two authors, independently.

Statistical analysis

Two reviewers independently extracted information regarding the method (ie, design, participants, intervention, outcome measures) and results (ie, number of participants, and mean standard deviation [SD] of outcomes of interest), which were checked by a third reviewer. When information was not available in the published trials, details were requested from the corresponding author. For metal analysis, post-intervention measures (mean and standard deviation) were used, due to the availability of only these values in most studies,

using the random effects model. The analyses were performed using the Comprehensive Meta-Analysis Program, version 3.0. Values of I^2 greater than 50% are indicative of important heterogeneity.16,18 The critical value for rejecting the null hypothesis was set at a level of 0.05 (2-tailed). The pooled data for each outcome were reported as a difference between experimental and control groups and their 95% confidence intervals (95% CIs). When data was not available to be included in the pooled analyses, between-group results were reported.

The GRADE system was used to summarize the overall quality of evidence for each outcome. The GRADE system ranges from high to very low quality.14 We rated evidence from the high-quality level and downgraded it 1 point if one of the following prespecified criteria was present: low methodological quality (most of trials with PEDro score < 6); inconsistency of estimates among pooled studies (I^2 > 50%), or when assessment was not possible (no pooling); indirectness of participants (more than 50% of the studies did not report time since diagnostic); and imprecision (pooling <300 participants for each outcome).19,20 Two reviewers assessed the quality of the evidence using the GRADE system, with potential disagreements resolved by consensus.

RESULTS

Flow of trials through the review

The electronic search identified 2,783 articles. After screening, 2,710 were excluded after reading the titles, 61 after analyzing the abstracts and seven after reviewing the full text. Thus, five studies were included according to the established inclusion criteria[17-21]. The main reasons for exclusion were duplicated studies, non-experimental studies, different populations, and studies with other interventions and/or other outcome measures. Figure 1 graphs the flow of articles through the review, while Table 1 shows the characteristics of the included studies.

Characteristics of the included studies

The mean PEDro score of the included trials was 7.4, ranging from 6 to 9 (Table 2). All trials had similar groups at baseline, had less than 15% dropouts, and reported between-group differences, as well as point estimate and variability data. In addition, most trials reported random allocation (80%), blinding of participants (80%), blinding of assessors (80%), and intention-to-treat analysis (60%). Most trials did not report concealing the allocation (80%) and blinding of therapists (80%). The quality of evidence was rated as low.

The trials included a total sample of 158 participants, ranging from 19 to 48, with a mean age ranging from 50 to 63 years old, and with a time since diagnosis ranging from 12 to 32 months. Two studies did not report this information[20,21]. Regarding the interventions, three studies performed inspiratory strength training[17,18,21], one study performed expiratory strength training[19], and one study performed both inspiratory and expiratory strength training[20]. Four studies performed placebo training in the control group[17-20], while one group did no intervention[21]. Considering the training protocol, the devices used were the Threshold IMT[17,18,20], Threshold PEP[19], EMST 150[20] and POWERbreath[21]. The training ranged from 10 minutes to 15/25 repetitions, from 1 to 3x/day, from 5 to 7x/week, from 8 to 16 weeks. The training loads ranged from 15 to 60% of the maximal respiratory pressure. Finally, regarding the outcome measures, four studies assessed maximum inspiratory pressure (MIP)[17,18,20,21], four studies assessed maximum expiratory pressure (MEP)[17-20], four studies assessed forced vital capacity (FVC)[17-20], two studies assessed peak inspiratory flow (PIF)[19,20], three studies assessed peak expiratory flow (PEF)[18-20], and four studies assessed functional status using the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS)[17-19,21].

Effect of respiratory muscle training

The meta-analysis was carried out for the outcome measures MIP, MEP, FVC, PIF, PEF and functional status (assessed by the ALSFRS).

Two studies, with a mean PEDro score of 6.5, involving 65 participants, investigated the effects of respiratory strength training on MIP, and found a significant improvement of 13.4 cm H_2O (95% CI 4.3 to 22.5; I^2=0%; p=0.004) (Figure 2) in favor of the experimental group. Although two studies[17,18] did not find significant results for MIP in the experimental group compared to the control group (p>0.05), these studies did not report the data required for inclusion in the meta-analysis.

Two studies, with a mean PEDro score of 8, involving 93 participants, investigated the effects of respiratory strength training on MEP, and found a significant improvement of 35.2 cm H_2O (95%CI 15.9 to 54.7; I^2=0%; p<0.001) (Figure 3) in favor of the experimental group. Although two studies[17,18] did not find significant results for MEP in the experimental group compared to the control group (p>0.05), these studies did not report the data required for inclusion in the meta-analysis. The quality of evidence was rated as low.

Two studies, with a mean PEDro score of 8, involving 93 participants, investigated the effects of respiratory strength training on FVC, and found no significant difference (1.1% of predicted; 95% CI -5.7 to 7.9; I^2=0%; p=0.75) (Figure 4). Although two studies[17,18] did not find significant results for FVC in the experimental group compared to the control group (p>0.05), these studies did not report the data required for inclusion in the meta-analysis. The quality of evidence was rated as low.

Considering peak flow, two studies, with a mean PEDro score of 8, involving 93 participants, investigated the effects of respiratory strength training on PIF and PEF. No significant difference was found for PIF (-0.7 L/s; 95%CI -1.5 to 0.1; I^2=0%; p=0.07) (Figure 5), while a significant improvement was found for PEF of 1.3 L/s (95%CI 0.4 to 2.3; I^2=0%; p=0.006) (Figure 6) in favor of the experimental group. Although one study[18] did not find

significant results for PEF in the experimental group compared to the control group (p>0.05), this study did not report the necessary data for inclusion in the meta-analysis.

Finally, two studies, with a mean PEDro score of 6.5, involving 93 participants, investigated the effects of respiratory strength training on functional status, assessed by the ALSFRS, and found no significant difference (2.4 points; 95%CI -2.9 to 7.8; I^2=0%; p=0.38) (Figure 7). Although two studies[17,18] did not find significant results for the ALSFRS in the experimental group compared to the control group (p>0.05), these studies did not report the data required for inclusion in the meta-analysis.

DISCUSSION

The aim of this review was to investigate the effects of respiratory strength training on respiratory strength, pulmonary function, and functional status of individuals with ALS, through a systematic review with meta-analysis. The results showed that training was able to increase the strength of the inspiratory and expiratory muscles, as well as PEF. No significant results were found for FVC, PIF and functional status, assessed by the ALSFRS.

This meta-analysis showed significant improvements in MIP and MEP in patients with ALS. A previous systematic review with meta-analysis, published in 2016, evaluating the efficacy of respiratory strength training in patients with MS and ALS, also reported a significant improvement in MIP, with an effect size of 23.50 cmH_2O (95% CI: 7.82 to 39.19), and MEP of 12.03 cmH^2O (95% CI: 5.50 to 18.57)[16]. Although the values reported by this study are different from those found in the present review (13.4 cmH_2O and 35.2 cmH_2O, respectively), this previous meta-analysis included both individuals with ALS and MS, which may justify this difference. Considering the significant improvement for both muscle groups, such results were indeed expected, since the aim of training is to increase strength. The training against a constant

linear load results in skeletal muscle hypertrophy, improving chest strength and stability, ventilatory pattern and preventing respiratory fatigue[22].

Regarding the effects of respiratory strength training on PEF, a significant improvement of 1.3 L/s was found. In fact, a moderate-intensity program focused on the expiratory muscles has shown short-term improvements in the physiological ability to clear the airways, reflected in the maximum expiratory pressure and peak expiratory flow in individuals with ALS in the early stages of disease[23]. In addition, considering the two studies included in the meta-analyses for PEF and PIF, one performed inspiratory and expiatory strength training[20], while the other only performed expiratory training[19], which may help explain the presence of effects on PEF, and not on PIF.

Finally, the results of this review also found no significant improvement in FVC and functional status. Similarly, the previous reported systematic review[16] did also not find significant results for FVC. However, as mentioned in previous studies, although respiratory muscle training may achieve its goal of increasing muscle strength, it had a little influence on lung capacity, not changing the FVC[10,24]. In addition, no significant improvements were observed in functional status. It should be noted that this construct was assessed using the ALSRFS-R scale, which covers the motor function of the upper and lower extremities during activities of daily living, as well as speech and swallowing[25], with most of these factors not being related to respiratory functions.

This systematic review with meta-analysis is the first to investigate the effects of respiratory strength training on respiratory strength, pulmonary function, and functional status exclusively in individuals with ALS. However, although the results are encouraging, some limitations need to be considered. Firstly, the methodological heterogeneity between the studies included, especially between the training protocols, makes it difficult to directly compare and generalize the results. In addition, the small number of studies with small samples, and studies

which did not report sufficient value for inclusion in the meta-analysis, also compromises the robustness of the conclusions, with low quality of the evidence. Therefore, future randomized clinical trials should prioritize greater standardization, larger samples, with training at appropriate intensities, clearly reporting all the results obtained, in order to support the evidence of the respiratory strength training in individuals with ALS.

CONCLUSION

This systematic review provides low-quality evidence that respiratory strength training increases inspiratory and expiratory muscle strength in individuals with ALS and may also improve PEF. However, no effects were found on PIF and FVC or carried over to functional status. Further randomized trials with larger samples and standardized protocols are warranted to investigate potential additional benefits of respiratory strength training in individuals with ALS.

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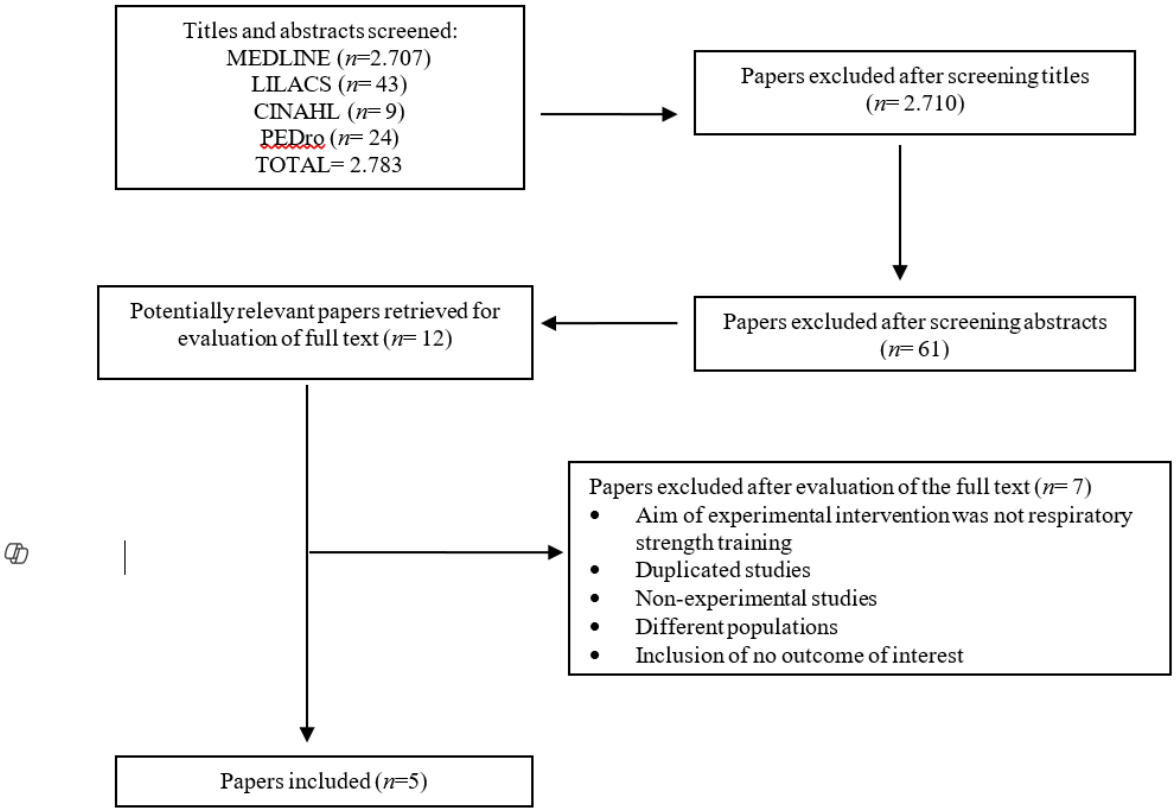

Figure 1. Flow of studies through the review.

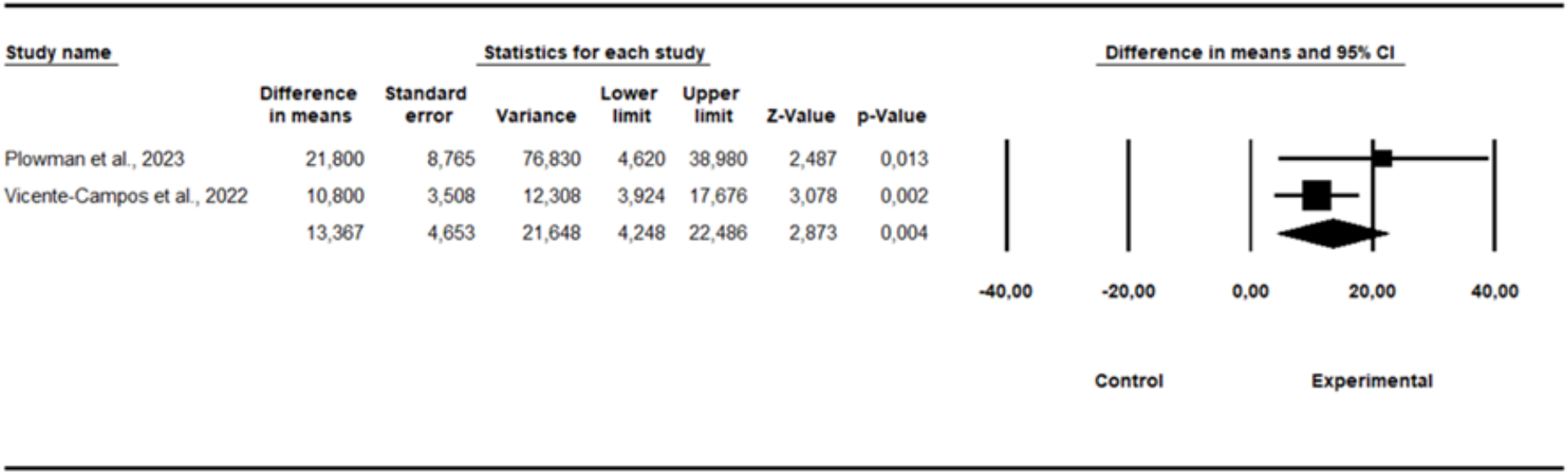

Figure 2 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on maximal inspiratory pressure, cmH_2O (*n*=65).

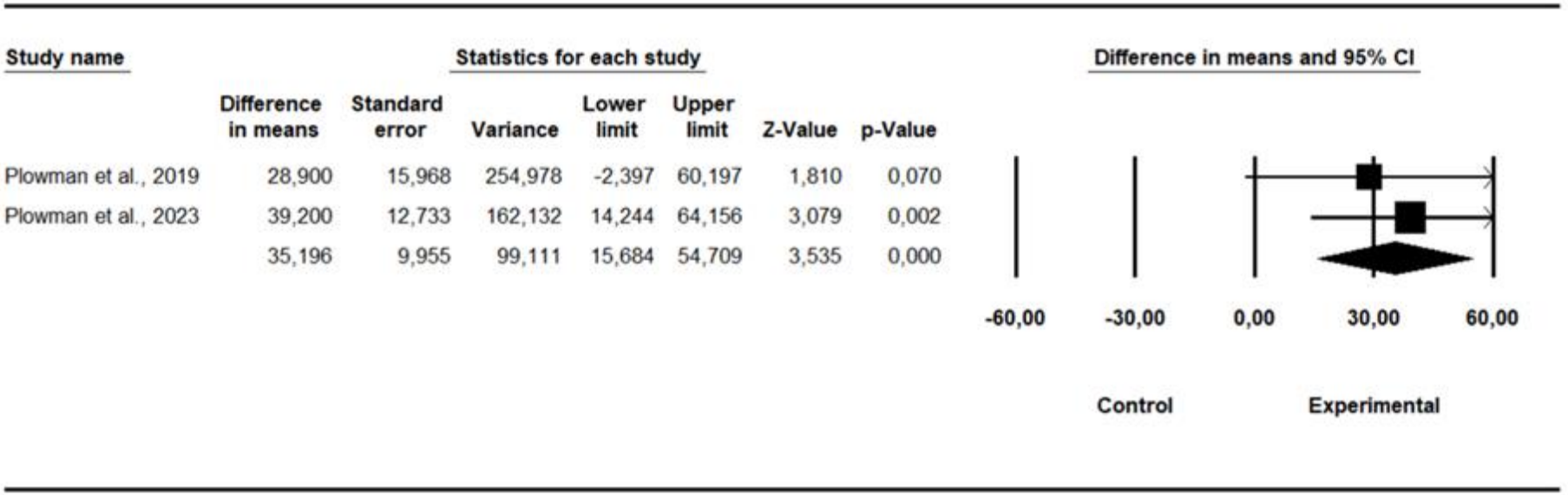

Figure 3 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on maximal expiratory pressure, cmH_2O (*n*=98).

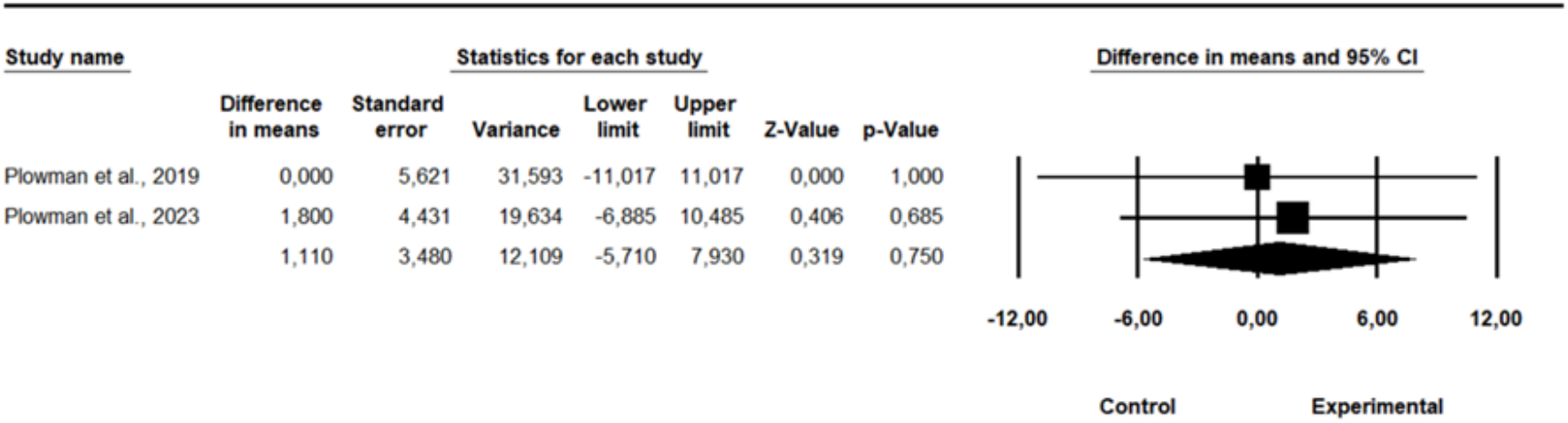

Figure 4 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on forced vital capacity, percentage of the predicted (*n*=98).

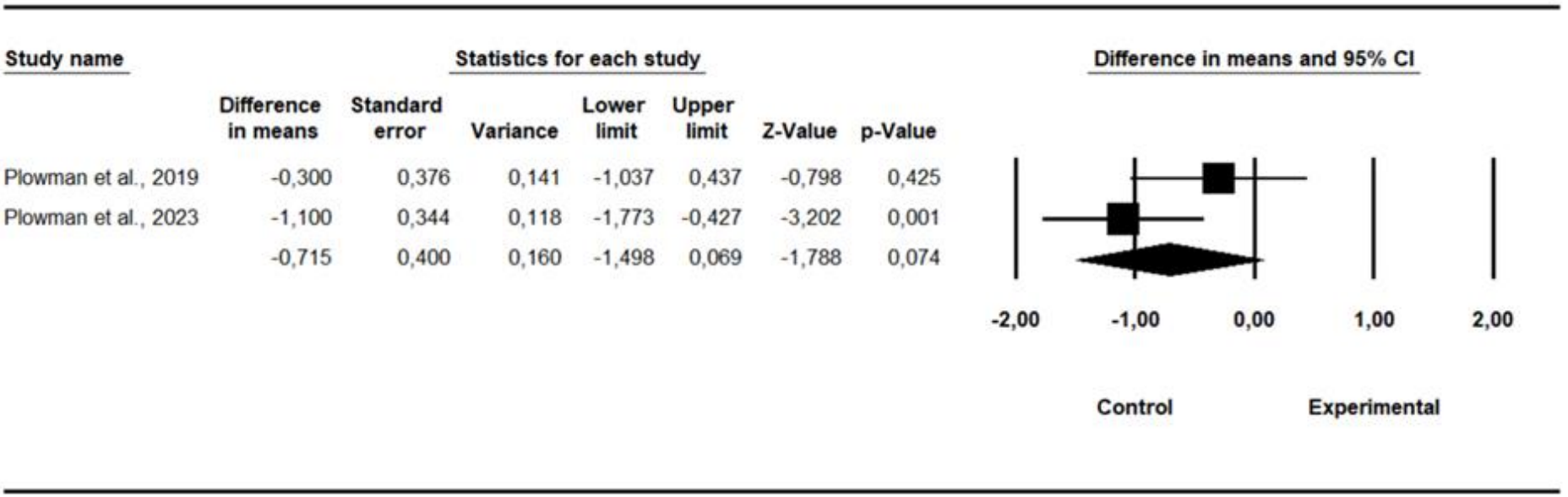

Figure 5 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on peak inspiratory flow, L/s (*n*=98).

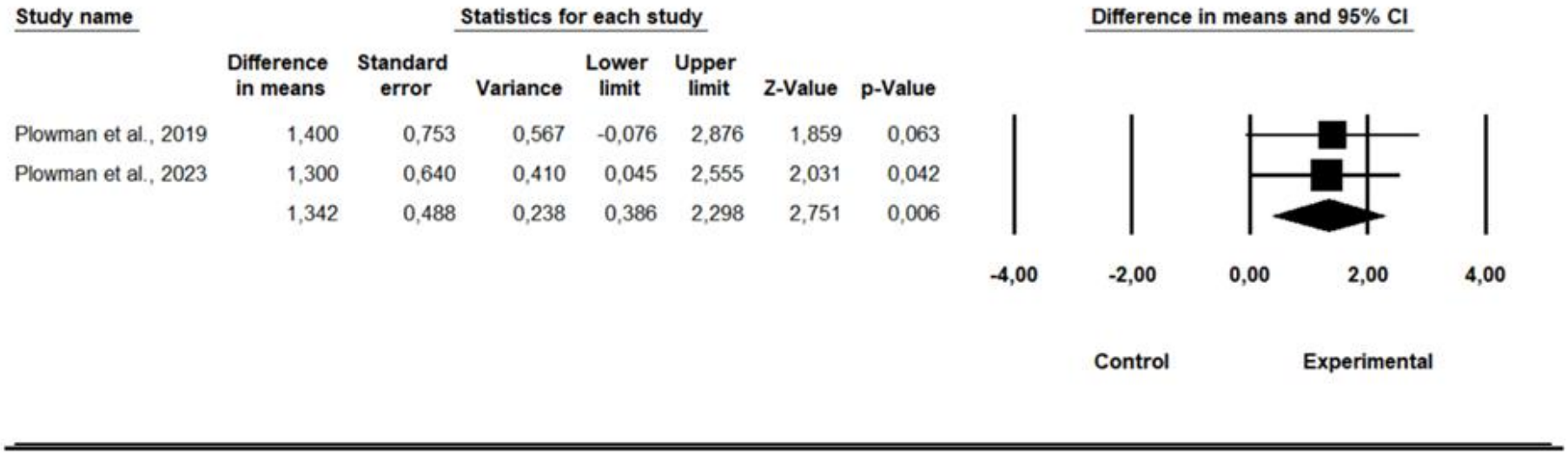

Figure 6 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on peak expiratory flow, L/s (*n*=98).

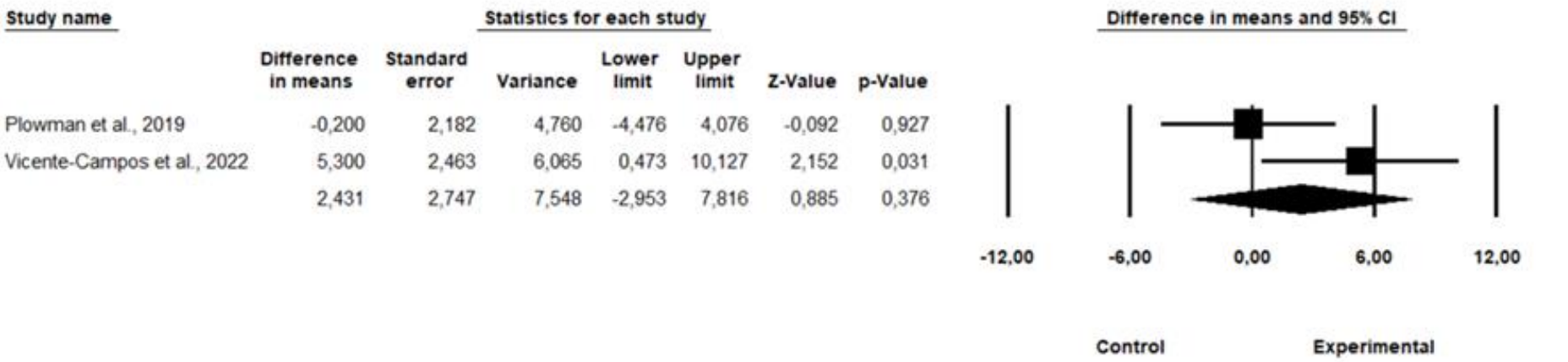

Figure 7 - Mean difference (95% CI) of effect of respiratory strength training versus no/placebo intervention on functional status (*n*=93).

Table 1. Characteristics of included trials (*n*= 5).

Study	Participants	Comparison	Parameters	Outcome measures*
Cheah et al. (2009)	*n* = 19 Age = 54 (10) Sex = 12 Men / 7 Women Time since diagnostic (months) = 32 (20)	IMT X Placebo	**Experimental group:** IMT (Threshold IMT), with load progression of 15 to 60%. 10 minutes, 3x/day, 7x/week, 12 weeks. **Control group:** Training with the device without load.	Maximal inspiratory pressure, maximal expiratory pressure, forced vital capacity and functional status (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised).
Pinto et al. (2012)	*n* = 26 Age = 57 (9) Sex = 18 Men / 6 Women Time since diagnostic (months) = 12 (6)	IMT X Placebo	**Experimental group:** IMT (Threshold IMT), with load progression of 30 to 40%. 10 minutes, 2x/day, 7x/week, 16 weeks. **Control group:** Training with the device with the minimal load.	Maximal inspiratory pressure, maximal expiratory pressure, forced vital capacity, peak expiratory flow and functional status (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised).
Plowman et al. (2019)	*n* = 48 Age = 62 (10) Sex = 29 Men / 19 Women Time since diagnostic (months) = 19 (11)	EMT X Placebo	**Experimental group:** EMT (Threshold PEP), with a load of 50%. 25 repetitions, 5x/week, 8 weeks. **Control group:** Training with the device without load.	Maximal expiratory pressure, forced vital capacity, peak inspiratory flow, peak expiratory flow and functional status (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised).
Plowman et al. (2023)	*n* = 45 Age = 63 (11) Sex = 27 Men / 18 Women	RMT X Placebo	**Experimental group:** IMT (Threshold IMT) + EMT (EMST 150), with a load of 30%. 25 repetitions for the IMT, and 25 repetitions for the EMT, 5x/week, 12 weeks.	Maximal inspiratory pressure, maximal expiratory pressure, forced vital capacity, peak

	Time since diagnostic (months) = Not reported		**Control group:** Training with the device without load.	inspiratory flow and peak expiratory flow.
Vicente - Campos et al. (2022)	*n* = 20 Age = 50 (9) Sex = Not reported Time since diagnostic (months) = Not reported	IMT X Nothing	**Experimental group:** IMT (POWERbreathe), with load progression of de 40 to 60%. 15 repetitions, 2x/day, 5x/week, 8 weeks. **Control group:** Nothing.	Maximal inspiratory pressure and functional status (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised).

IMT = Inspiratory muscle training; EMT = Expiratory muscle training; RMT = Respiratory muscle training.
* Only outcome measures of interest were extracted.

Table 2. PEDro criteria and scores for the included papers (*n*=5).

Criteria	Cheah et al, 2009	Pinto et al, 2012	Plowman et al, 2019	Plowman et al, 2023	Vicente - Campos et al, 2022
Random allocation	Y	Y	Y	Y	N
Concealed allocation	Y	N	N	N	N
Groups similar at baseline	Y	Y	Y	Y	Y
Participant blinding	Y	Y	Y	Y	N
Therapist blinding	N	N	N	Y	N
Assessor blinding	N	Y	Y	Y	Y
<15% dropouts	Y	Y	Y	Y	Y
Intention-to-treat analysis	Y	N	N	Y	Y
Between-group difference	Y	Y	Y	Y	Y
Point estimate and variability	Y	Y	Y	Y	Y
Total	**8**	**7**	**7**	**9**	**6**

N = No; Y = Yes