Title: Inspiratory muscle training for improving inspiratory muscle strength and functional capacity in older adults: a systematic review and meta-analysis.

Abstract

Background: The ageing process can result in the decrease of respiratory muscle strength and consequently increased work of breathing and associated breathlessness during activities of daily living in older adults.

Objective: This systematic review and meta-analysis aims to determine the effects of inspiratory muscle training (IMT) in healthy older adults.

Methods: A systematic literature search was conducted across four databases (Medline/Pubmed, Web of Science, Cochrane Library and CINAHL) using a search strategy consisting of both MeSH and text words including older adults, inspiratory muscle training, and functional capacity. The eligibility criteria for selecting studies involved controlled trials investigating inspiratory muscle training via resistive or threshold loading in older adults (>60 years) without a long-term condition.

Results: Seven studies provided mean change scores for inspiratory muscle pressure and 3 studies for functional capacity. A significant improvement was found for maximal inspiratory pressure (PI_{max}) following training (n=7, 3.03 [2.44, 3.61], p=<0.00001) but not for functional capacity (n=3, 2.42 [-1.28, 6.12], p=0.20). There was no significant correlation between baseline PI_{max} and post-intervention change in PI_{max} values (n=7, *r*=0.342, p=0.453).

Conclusions: IMT can be beneficial in terms of improving inspiratory muscle strength in older adults regardless of their initial degree of inspiratory muscle weakness. Further research is required to investigate the effect of IMT on functional capacity and quality of life in older adults.

1.0 – Introduction

1.1 Background:

Respiratory function is reduced during the ageing process due to structural and physiological changes of the respiratory system [1]. These changes are characterised by decreased recoil pressure of the lung, respiratory muscle function and chest wall compliance [2]. During ageing we see a decrease in muscle mass, strength and function which can accelerate the decline in respiratory muscle strength in older adults assessed by maximal inspiratory pressure (PI_{max}) measurements [3]. Several studies in healthy older adults [4-6] have reported PI_{max} values as low as those reported in patients with lung or heart disease [6-8].

Decreased respiratory muscle strength leads to increased residual volume, functional residual capacity and consequently increased work of breathing and associated breathlessness during activities of daily living in older adults [9]. Therefore, exertional breathlessness in older adults may compromise an individual's daily functional capacity and quality of life [10].

Reduced respiratory muscle strength and functional capacity is often seen in patients with lung or heart disease [11, 12]. In these patients, an effective method to combat inspiratory muscle weakness is inspiratory muscle training (IMT). Several studies have been conducted investigating the effect of IMT in various respiratory [7, 13, 14] and cardiovascular disorders [8, 15, 16]. Previous meta-analyses have suggested that IMT can improve inspiratory muscle strength (reflected by an increase in maximal inspiratory pressure), six-minute walking distance (6MWD) and quality of life in chronic obstructive pulmonary disease (COPD) [17, 18] and chronic heart failure (CHF) [19].

Due to the age-related decline in respiratory muscle function, it is likely that IMT will also have a beneficial effect in an ageing population without a long-term condition. A recent systematic review has started to investigate IMT in healthy older adults with the authors suggesting a positive trend for IMT in improving inspiratory muscle strength [20]. It should be noted, however, that this review also included frail participants with comorbidities and extreme debilitation [21, 22] that could affect the magnitude of improvement in PImax. Accordingly, the present systematic review and meta-analysis focuses on the effects of IMT in healthy older adults without frailty or associated comorbidities given that in this population, reduced respiratory muscle strength is associated with a decline in pulmonary function [23], reduced physical performance [24], and constitutes an independent risk factor for myocardial infarction and cardiovascular mortality [25]. Thus, interventions that increase respiratory muscle function may have an important clinical impact in healthy older adults.

1.2 - Review objective:

To systematically review and perform a meta-analysis on the effects of inspiratory muscle training (IMT) for improving inspiratory muscle strength and functional capacity in healthy older adults.

2.0 – Methods:

2.1 - Search strategy:

This prospectively registered systematic review (CRD42019155163; https://www.crd.york.ac.uk/prospero/) followed the Cochrane Handbook for Systematic Reviews of Interventions [26] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. Electronic database (Medline/PubMed, Cochrane Library, Web of Science and CINAHL) were searched from August 2019 to February 2020.

The final search strategy included relevant MeSH Terms, Text Words and Publication Types relating to the population (e.g. "aged" and "older adults"), the intervention (e.g. "inspiratory muscle training" and "breathing exercises"), the outcomes (e.g. "exercise tolerance", "quality of life" and "maxim* inspiratory") and the design (e.g. "random*", "clinical trial" and "experimental study"). These terms were constructed and grouped by Boolean logic with no restrictions on publication date. The full PubMed search strategy can be found in Appendix 1.

2.2 – Inclusion and exclusion criteria:

MeSH Terms/Text Words including "frail elderly", "frail" and "frailty" were included in the search strategy due to the finding that, during pre-scoping, these keywords were associated with older populations with weaker inspiratory muscles undertaking IMT programmes [28]. The MeSH Term "breathing exercises" was also included as, during pre-scoping, it was found to be associated with inspiratory muscle training in some studies [6, 28-30]. Studies were considered eligible if they fulfilled the pre-determined participants, interventions, comparisons and outcomes (PICOS) criteria (Appendix 2).

Initial screening of titles and abstracts and assessment of full texts were performed independently by two authors (blinded for review) who were blinded to each other's decisions. Any disagreements between the authors were sent to a third author (blinded for review).

2.3 – Data extraction:

Data was extracted in terms of the following subheadings. 1) author information (first author and year of publication), 2) participant characteristics (age, gender, baseline maximal inspiratory pressure; PI_{max}), 3) mode of IMT and supervision, 4) time, intensity and progression of IMT, 5) frequency and duration of IMT, 6) control and 7) outcomes assessed.

2.4 – Quality assessment:

The PEDro quality scale was used to assess internal and external validity of the included studies [31]. Two authors (blinded for review) independently reviewed each included study on the following domains of the PEDro scale: eligibility criteria, random allocation, concealed allocation, baseline similarity, blinding of subjects, therapist and assessor, measures obtained from more than 85% of subjects initially allocated to groups, full intention to treat, group comparison, and point measures and measures of variability. PEDro scale scores 9-11 were considered excellent, 6-8 good, 4-5 fair and ≤3 poor [31] . No study was excluded based on poor quality.

2.5 – Data analysis:

Meta-analyses of the studies were performed using the software Review Manager (RevMan V5.3; Cochrane Collaboration, Oxford, UK). Outcomes were continuous and change scores with standard deviations were used to obtain effect size reported as standard mean differences with 95% confidence intervals. The heterogeneity of studies were assessed by the I^2 value, and were classified as might not be important (0-40%), moderate heterogeneity (30-60%), substantial heterogeneity (50-90%), and considerable heterogeneity (75-100%) [26]. A small minimum clinically important difference (MCID) in functional capacity was observed if participants in the IMT groups improved their 6MWD by above 20m and a substantial MCID if the improvement was over 50m [32]. A random-effects model was used for the meta-analyses as variation in methods were found between included studies beyond random sampling. Pearson's correlation analysis was performed in order to determine the association between baseline PI_{max} and change in PI_{max} following IMT within included studies. The level of significance for all analyses was set at $p < 0.05$.

3.0 – Results:

The databases yielded 986 studies (Figure 1). Following the removal of 181 duplicates and screening of 805 titles/abstracts, 19 articles remained for full-text screening of which 11 were excluded. Overall, 8 studies were included in this systematic review with one of these studies [5] excluded from the meta-analysis due to insufficient data reported (Table 1). The full characteristics of included studies can be found in Appendix 3.

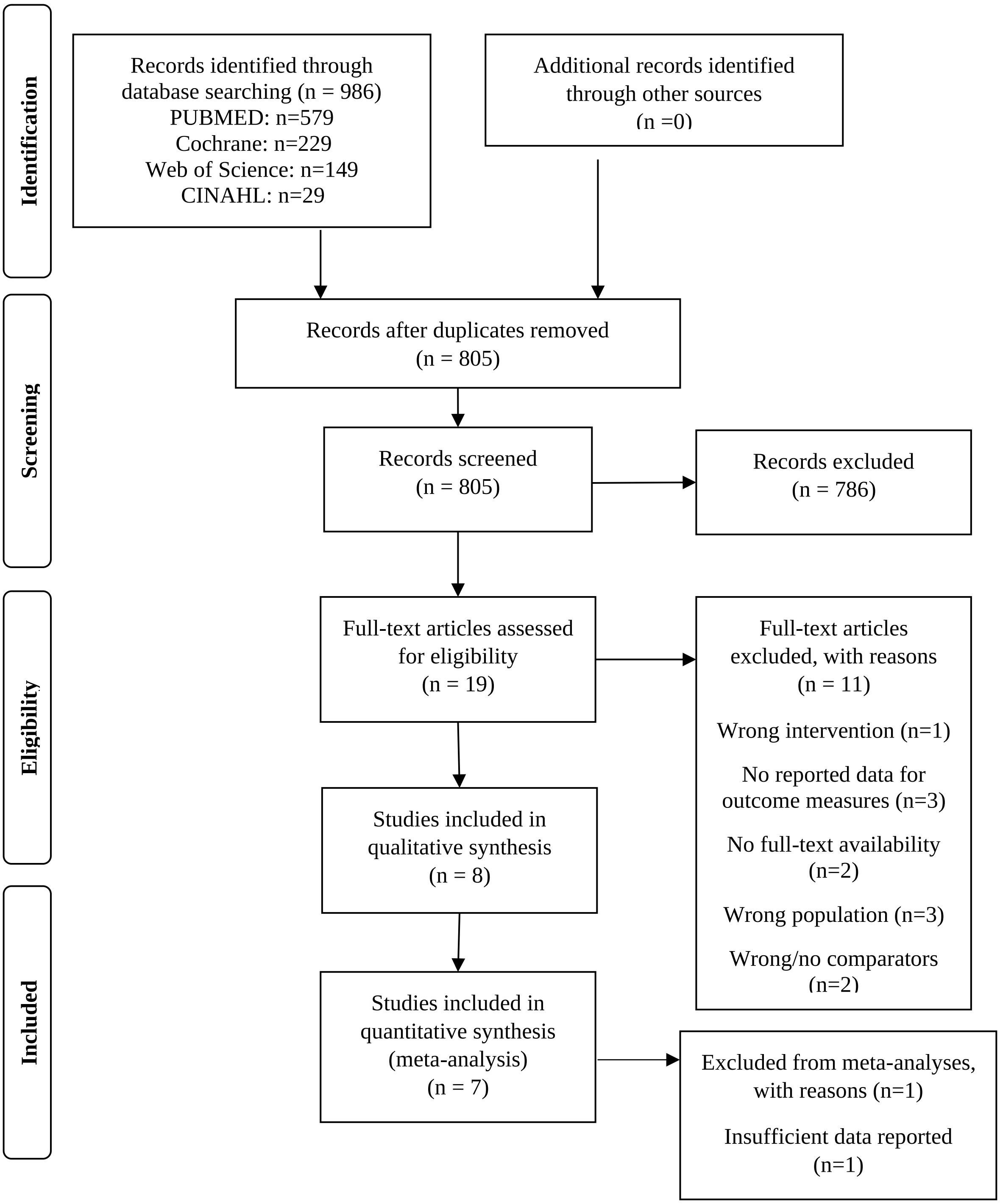

Figure 1. PRISMA flow diagram of studies through database search and selection process; n=number.

Table 1. Characteristics of included studies

Author	Year	N (I/C)	Age, years; mean (SD)	Gender (M/F)	Baseline PI_{max} (cmH2O)	Mode of IMT and supervision	Time, intensity and progression of IMT	Frequency and duration of IMT
Albuquerque et al. [5]	2013	13/13	IMT: 68.5 (64.7 -76) CG: 67.5 (62.7-71.5)	IMT: 6/7 CG: 5/8	IMT: 55 (45-71.2) CG: 75 (67.5-95)	Threshold loading device (Threshold), 1/5 sessions supervised a week	8-10 sets of 5-6 reps at 40-70% PI_{max}	5 sessions a week for 6 weeks
Aznar-Lain et al. [4]	2007	9/9	IMT: 68.5 ± 6.3 CG: 67.8 ± 7.5	IMT: 2/7 CG: 2/7	IMT: 54.1 ± 9.2 CG: 67.8 ± 14.4	Threshold loading device (Respironics), supervision not reported	8-10 sets of 5-6 reps at 50-80% PI_{max}, 1-minute rest between sets	5 sessions per week (3 during week 1) for 8 weeks
Ferraro et al. [28]	2019	23/23	IMT: 75 ± 6 CG: 72 ± 5	IMT: 9/14 CG: 9/14	IMT: 76.0 ± 27.4 CG: 72.8 ± 40.9	Threshold loading device (POWERbreathe), unsupervised, home-based	30 breaths, 50% PI_{max}, able to increase resistance when 30 breaths were achievable with ease	Twice daily, 8 weeks
Huang et al. [6]	2011	24/24	IMT: 70.6 ± 4.8 CG: 70.8 ± 9.1	IMT: 2/22 CG: 2/22	IMT: 59.1 ± 19.2 CG: 58.8 ± 19.1	Threshold loading device, 3/5 sessions supervised a week	4 sets of 6 breaths. Load adjusted to maintain 75% PI_{max} every week	5 sessions per week for 6 weeks
Mills et al. [29]	2015	17/17	IMT: 69 ± 3 CG: 68 ± 3	IMT: 9/8 CG: 11/6	IMT: 82 ± 27 CG: 96 ± 27	Threshold loading device (POWERbreathe), unsupervised	30 breaths, 50% PI_{max}, able to increase resistance when 30 breaths were achievable with ease	Twice daily, 8 weeks

Rodrigues et al. [33]	2018	11/8	IMT: 64 ± 3 CG: 64 ± 4	IMT: 0/11 CG: 0/8	IMT: 84 ± 18 CG: 80 ± 16	Threshold loading device (POWERbreathe, 1/5 sessions supervised a week	30 repetitions, 50% PI_{max}. Load adjusted to maintain 50% PI_{max} once a week	5 sessions per week for 5 weeks
Souza et al. [34]	2014	12/10	IMT: 68.3 ± 5.2 CG: 68.3 ± 5.3	IMT: 0/12 CG: 0/10	IMT: 73.3 ± 12.2 CG: 79.4 ± 18.4	Threshold loading device (Respironics), supervised once per week	8 cycles of 2-minutes work at 40% PI_{max}, 1-minute rest	Twice daily, 7 weeks
Watsford & Murphy [30]	2008	13/13	IMT: 64.8 ± 2.5 CG: 64.0 ± 2.9	IMT: 0/13 CG: 0/13	IMT: 69 ± 20 CG: 74 ± 14	Inspiratory and expiratory threshold loading (Powerlung), unsupervised	Hypertrophy sessions: 3 sets of 10 reps at 10RM. Endurance sessions: 40 breaths at 40RM. Strength sessions: 5 sets of 5 reps at 5RM	12 sessions per week, 6 days, 8 weeks. Hypertrophy - 8 sessions per week, endurance - 2 sessions, strength - 2 sessions

Footnote: 6MWT, six-minute walk test; BMI, body mass index; CG, control group; IMT, inspiratory muscle training; PI_{max}, maximal inspiratory pressure; PE_{max}, maximal expiratory pressure; MVPA, moderate to vigorous physical activity; MVV, maximal voluntary ventilation; PAL, physical activity levels; QoL, quality of life; RM, repetition maximum; VO_2 peak, peak oxygen uptake.

3.1 – Characteristics of included subjects:

The included studies comprised of 239 participants and had a mean age of 68.2 years (range 64-75) and an average baseline PI_{max} of 72.3cmH_2O (59-89cmH_2O). Participants were healthy older adults with no reported diseases that could influence inspiratory muscle strength.

3.2 – Quality assessment:

The risk of bias of included studies can be found in Appendix 4. The mean PEDro score for included studies was 6.4 and ranged from 4 to 9 (fair to excellent), suggesting a fairly low risk of bias towards the main outcome measures. The most frequent omissions in the quality of study design or reporting included: allocation of participants to groups was not concealed [4-6, 28-30, 33], the therapist applying treatment was not blinded [4-6, 28-30, 33, 34] and assessors were not blinded [6, 29, 30]. Furthermore, two studies did not randomise participants to intervention or control groups [5, 6].

3.3 – Interventions:

All studies used a threshold inspiratory loading device with the addition of one study using a device that delivered both inspiratory and expiratory threshold loading [30]. Training protocols used inspiratory pressures that ranged from 30% to 80% PI_{max}, with the majority of studies using training intensities of 30-60% PI_{max} [28, 29, 33, 34]. The shortest duration of inspiratory muscle training was 5 weeks [33] and the longest was 8 weeks [4, 28-30]. At least one supervised training a week was reported in four out of the eight included studies [5, 6, 33, 34]. SHAM-IMT was used in the control condition of six studies [4, 5, 28, 29, 33, 34], with the control groups within the remaining studies either not participating in any training protocol [30] or was not reported [6].

3.4 – Outcome measures:

All studies (n=8) used maximal inspiratory pressure (PI_{max}; cmH_2O) to reflect inspiratory muscle strength as an outcome measure [4-6, 28-30, 33, 34]. Three studies used the distance covered during a six-minute walk test (6MWD; meters) to reflect functional capacity [6, 29, 33].

3.5 - Meta-analysis of included studies:

3.5.1 – Inspiratory muscle strength:

Seven studies [4, 6, 28-30, 33, 34] with 212 participants provided mean change scores for pooling. The meta-analysis showed a positive effect of inspiratory muscle training on maximal inspiratory pressure (n=7, 3.03 [2.44, 3.61], $p < 0.001$; Figure 2). The average increase in maximal inspiratory pressure in the intervention was 26.3±4.9cmH_2O compared to a 3.7±4.1cmH_2O in the control. The meta-analysis showed moderate heterogeneity (I^2=47%). No significant correlation was found between baseline PI_{max} and post-intervention change in PI_{max} expressed as absolute values (n=7, r=0.342, p=0.453; Figure 3) and percentage change from baseline (n=7, r=-0.490, p=0.264; Figure 4).

3.5.2 – Six-minute walk distance:

Three studies [6, 29, 33] with 101 participants provided mean change scores for pooling. Inspiratory muscle training showed no significant effect on the distance covered during a six-minute walk test (n=3, 2.42 [-1.28, 6.12], p=0.20; Figure 2), however it can be considered to result in a small MCID [32]. The average increase in 6MWD following IMT was 24.7±22.1m in the intervention groups compared to 9±8.6m in the control groups. The meta-analysis showed considerable heterogeneity (I^2=97%).

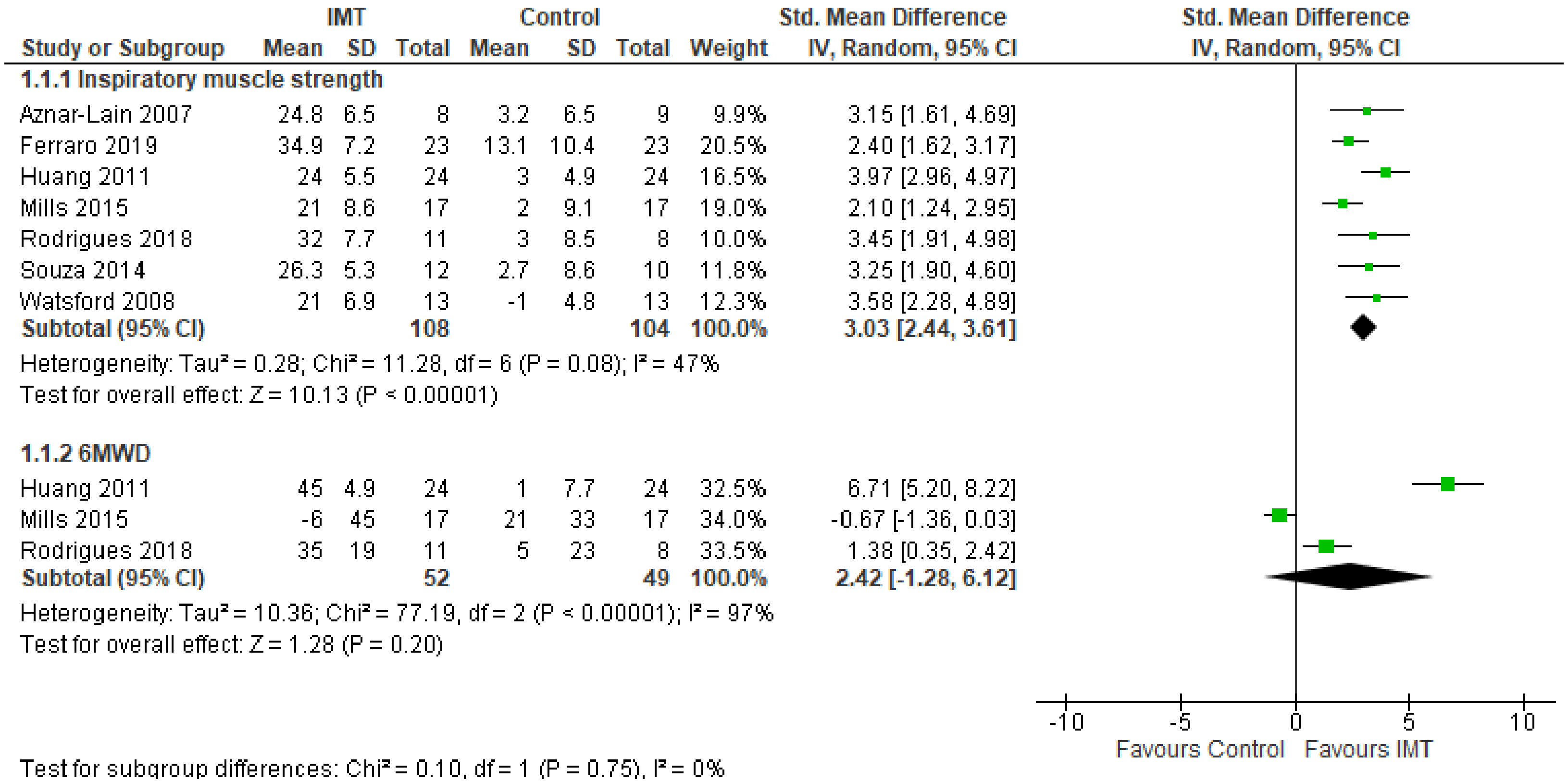

Figure 2. Mean difference (95% CI) from baseline of the effect of inspiratory muscle training on inspiratory muscle strength (measured by maximal inspiratory pressure; n=7) and six-minute walk test distance (n=3) compared to control.

Footnote: SD, standard deviation, IMT, inspiratory muscle training, 6MWD, six-minute walk distance, CI, confidence interval.

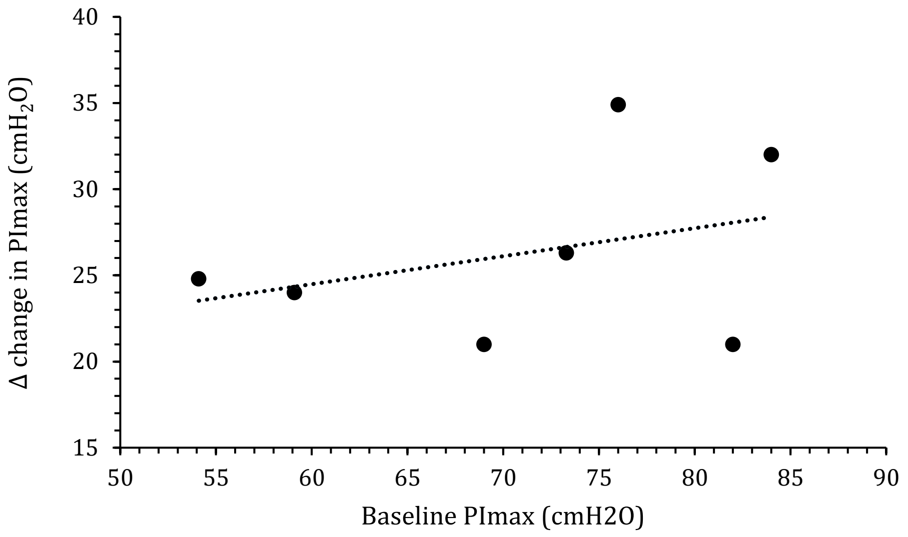

Figure 3. The relationship between baseline maximal inspiratory pressure (PI_{max}) values and delta (Δ) changes in PI_{max} following training (n=7).

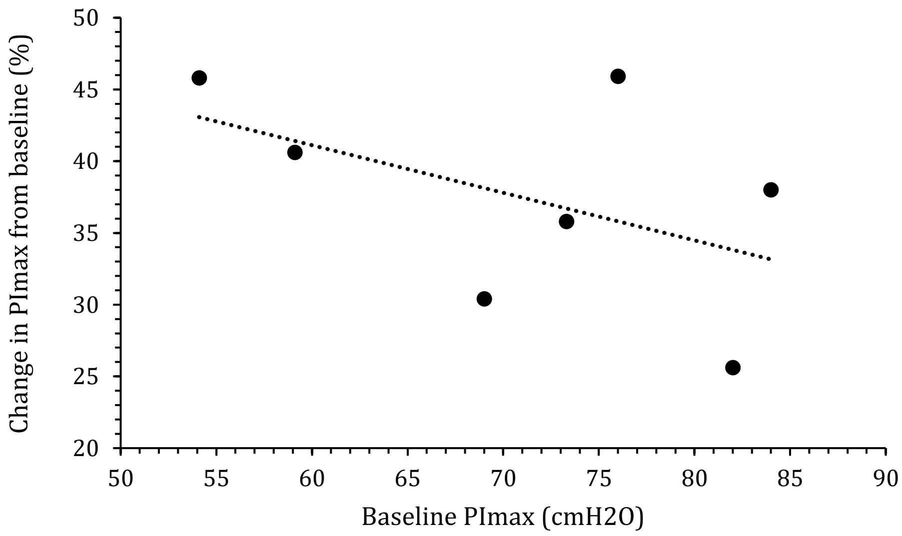

Figure 4. The relationship between baseline maximal inspiratory pressure (PI_{max}) values and percentage changes in PI_{max} from baseline following training (n=7).

4.0 – Discussion:

The present systematic review and meta-analysis suggests that specific IMT can significantly increase inspiratory muscle strength, reflected by an increase in maximal inspiratory pressure (cmH_2O). This meta-analysis showed an effect size of 3.03 (2.44, 3.61) and can be categorised as a huge positive effect [35]. There was no significant change in six-minute walk distance (6MWD) following IMT, however, the improvement observed in this meta-analysis could be considered clinically meaningful as participants improved by over 20m [32]. This meta-analysis also showed a large effect size (2.42 [-1.28, 6.12]). Due to the lack of statistical significance, high heterogeneity (I^2=97%), and small number of included studies (n=3), more research is needed to determine the true effect of IMT on functional capacity in healthy older adults.

4.1 – Interpretation of findings:

Previous meta-analyses investigating the effect of IMT have typically reported average increases in PI_{max} in COPD patients by 13 cmH_2O [18], 11.6 cmH_2O [17] and 16 cmH_2O [36], as well as increase in PI_{max} by 20 cmH_2O [19] in chronic heart failure (CHF) patients. The present study suggests that IMT is also beneficial in improving inspiratory muscle strength in older adults without a long-term condition, reflected by an average increase of $26.3\pm4.9 cmH_2O$ within the experimental groups compared to a non-significant average change of $3.7\pm 4.1 cmH_2O$ within the control groups.

The mechanisms of improved PI_{max} following IMT are likely due to structural and functional adaptations to the training stimulus, including strength, speed of shortening and power output [37]. In this case, the majority of studies used a moderate training load of 30-60% PI_{max}, which has been shown to elicit improvements in both maximal shortening velocity and PI_{max} [37, 38]

secondary to hypertrophy of inspiratory muscles [39, 40]. The present review provides evidence that hypertrophy is related to the improvement in PI_{max} as two included studies [29, 34] reported increases in diaphragm thickness following IMT.

The average improvement in functional capacity, reflected by an increase of 24.7±22.1m, following IMT in older adults within the present meta-analysis did not reach statistical significance. Previous research has used both distribution- and anchor-based methods to determine a small minimum clinically important difference (MCID) of 20m and a substantial MCID of 50m for the 6MWD in community-dwelling older adults [32], suggesting that the improvement observed in this meta-analysis may be clinically meaningful. Mills and colleagues [29] suggested that the observed lack of improvement in functional capacity was due to participants having a higher predicted baseline 6MWD (102-103%) [41] compared to the lower values of 90% in the healthy older group in the study by Huang et al. [6]. Baseline 6MWD values were in line with predicted values for healthy older adults [41]. Rodrigues et al. [33], suggested that the improvement in functional capacity is likely due to a greater improvement in PI_{max} compared to that observed previously [29]. Furthermore, the greater increase in distance covered (44m) observed by Huang et al. [6] could be related to the participants in the IMT group having lower baseline PI_{max} values (59.1 ± 19.2cmH_2O) compared to Rodrigues et al. [33] (84 ± 18cmH_2O) and Mills et al. [29] (82 ± 27cmH_2O). It should be noted that the control group used in Huang et al. [6] consisted of participants with COPD and not older adults without COPD, however baseline values for age, PI_{max}, and 6MWD were similar between groups.

Unfortunately, quality of life could not be included as an outcome measure within this meta-analysis due to different questionnaires used between included studies, along with insufficient data reported. Albuquerque et al. [5] found that IMT had no significant effect on any of the medical outcomes study short form-36 (SF-36) scales, whereas Huang et al. [6] reported a significant increase in the physical component score following IMT. Mills et al. [29] used the Older Person's Quality of Life Questionnaire (OPQOL-35) but did not find any significant changes following the training programme.

IMT has been shown to improve various other outcome measures in older adults, including: increased diaphragm thickness [29, 34], moderate-vigorous physical activity levels [4], time to exhaustion exercise tests [4], peak oxygen uptake (VO_2 peak) [4], balance [28], maximal expiratory pressure peak inspiratory flow rate (PIFR) [28, 29], cardiac autonomic modulation [33], and dyspnoea scores [6]. However, some studies report conflicting results including no significant effect of IMT on physical activity levels [29] and dyspnoea levels [21]. IMT that induces significant improvements in PI_{max} can also reduce breathlessness in COPD [42] and CHF patients [43], however, when Huang and colleagues [6] investigated the relationship between the difference in PI_{max} and the difference in dyspnea scores following IMT in healthy older adults , no significant correlation was observed. The authors suggested that this was due to a ceiling effect as participants reported relatively high baseline dyspnea scores.

A recent systematic review investigated the effects of IMT in an older population [20]. Due to a large heterogeneity in participant characteristics, however, the authors did not perform a meta-analysis on their included studies. Two studies [21, 22] that were included in the review conducted by Seixas et al. [20] were excluded from the present systematic review and meta-analysis due to a considerable amount of the participants having comorbidities that could significantly affect inspiratory muscle strength. Furthermore, the participants were significantly older than in the remaining studies (84.5 years compared to 68.2 years) and had lower baseline PI_{max} values (33.6cmH_2O compared to 73.3 cmH_2O). The lack of improvement in PI_{max} following IMT within these two studies (6.7 and 2.8cmH_2O) contradicts previous literature which has suggested that patients with pronounced inspiratory muscle weakness (PI_{max} <60cmH_2O) show a better response to IMT in terms of inspiratory muscle strength and functional capacity in COPD [18] and CHF [44]. In the present review, correlation analysis of included studies showed no significant association between baseline inspiratory muscle strength and the post-IMT change in PI_{max} (Figure 3) and percentage change in PI_{max} from baseline (Figure 4), suggesting that IMT is beneficial in older adults regardless of their initial degree of inspiratory muscle weakness. Accordingly, IMT would be beneficial even in older adults with a wide range of inspiratory muscle weakness.

Cebria I Iranzo et al. [21, 22] suggested that the lack of improvement following the training programme is likely due to the extreme debilitation and institutionalisation of the older adults [21]. Furthermore, a significant improvement in PI_{max} following IMT was only observable when compared to the decreased values within the control group [22]. This suggests that IMT in frail older adults with sarcopenia may be beneficial in preventing the age-related decline in respiratory muscle strength, which is evident within this population [45].

The study conducted by Albuquerque et al. [5] was also excluded from the meta-analysis due to the data expressed as median and interquartile range (IQR). Nevertheless, this study showed significant improvements in inspiratory muscle strength and functional capacity following a six-week IMT programme compared to the SHAM-IMT control.

4.2 - Quality of the evidence:

The quality of the included studies ranged from fair to excellent on the PEDro quality scale (Appendix 4). As most of the studies involved mainly unsupervised training sessions, the lack of a blinded therapist in all included studies is unlikely to significantly increase the risk of bias in the present meta-analysis. However, the lack of reported intention to treat [4-6, 28-30, 33, 34] and concealed allocation [4-6, 28-30, 33] in the majority of included studies reduced the overall quality of the evidence.

4.3 – Strengths and limitations:

This is the first meta-analysis to investigate the effects of IMT during healthy ageing and was conducted in line with both the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines. The main limitations of this systematic review and meta-analysis include the considerable heterogeneity along with the lack of reported intention to treat analysis and concealed allocation to groups. The high heterogeneity in the 6MWD meta-analysis is likely due to the variation of methods and participant characteristics between studies, such as the intensity, frequency and duration of IMT along with baseline PI_{max} values. Future research should aim to standardise methods of IMT in this population to reduce heterogeneity. Furthermore, since three studies [30, 33, 34] were performed in older women only, sex differences could have affected the absolute values for baseline PI_{max}, however, as absolute change scores were used when pooling the data (Figure 2.), and to show the relationship between baseline and post-intervention changes (Figure 3.) this is unlikely to have affected our results.

4.4 - Implications for improving inspiratory muscle strength:

By administering IMT to healthy older adults, it may be possible to prevent or delay the decline in inspiratory muscle strength in this population with inexpensive equipment and without requiring significant time. Evidence suggesting that respiratory muscle strength may be at the beginning of a causal chain leading to decreased pulmonary function and mortality [23] highlights the clinical importance of interventions, such as IMT, that can improve or maintain respiratory muscle strength in healthy older adults.

5.0 – Conclusion:

Overall, this systematic review and meta-analysis provides evidence that IMT can be beneficial in an older population without the presence of a long-term condition; however, due to the high heterogeneity and large variation of methods it is difficult to draw concrete conclusions. There is a need for future studies to investigate the effect of IMT on functional capacity and quality of life in healthy older adults, and to determine whether IMT can reduce breathlessness and improve daily physical activity levels, which are associated with mortality in this population [46, 47].

Conflicts of interest:

The authors declare that there are no conflicts of interests.

Declaration of sources of funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

6.0 - References

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