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Inspiratory muscle training in adults with chronic obstructive pulmonary disease: A systematic review

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Summary The purpose of this study was to conduct a systematic review to determine the effect of inspiratory muscle training (IMT) on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life for adults with chronic obstructive pulmonary disease (COPD).

A systematic review of the literature was conducted according the Cochrane Collaboration protocol using Medline and CINAHL. Nineteen of 274 extracted articles met the inclusion criteria and addressed comparisons of interest which included: IMT versus sham; IMT versus no intervention; low- versus high-intensity IMT; and two different modes of IMT. Thirteen meta-analyses were reported.

Results indicate that targeted resistive or threshold IMT was associated with significant improvements in some outcomes of inspiratory muscle strength (PI_{max} (cm H_2O)) and endurance (Inspiratory Threshold Loading (kPa)), exercise capacity (Borg Scale for Respiratory Effort (modified Borg scale), Work Rate maximum (Watts)), and dyspnea (Transition Dyspnea Index), whereas IMT without a target or not using threshold training did not show improvement in these variables. There was no conclusive evidence regarding quality of life measures.

IMT is effective for adults with COPD when using threshold or targeted devices that control or provide a target for training intensity.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a slow, progressive, incurable disease affecting the airways of the lungs resulting in loss of lung function[1] that places a substantial burden upon patients, their families and the health care system. In 1998/1999, 3.2% of Canadians were diagnosed with COPD while in 2001, 4.4% of Americans reported having COPD.[1,2] The prevalence of COPD is under-estimated however[1,2] since COPD is not usually diagnosed until symptoms are moderate to severe in nature.[3]

Individuals with COPD experience inspiratory muscle dysfunction due to the combined effects of increased work of breathing, hyperinflation, malnutrition, hypoxemia, hypercapnea and possible use of corticosteriods resulting in decreased inspiratory muscle strength and endurance.[4,5] Functionally, this presents as dyspnea and decreased exercise tolerance in individuals with COPD. Ramírez-Sarmiento et al.[6] have shown that inspiratory muscle training (IMT) is associated with improvement in inspiratory muscle strength and endurance, and with structural changes in the inspiratory muscle fibers. Therefore, improving inspiratory muscle strength and endurance is one management strategy that may help to relieve the sensation of dyspnea, thereby increasing the level of activity and improving quality of life for individuals with COPD.

The early literature on the use of IMT with individuals with COPD presents a mixed picture but generally is not supportive of this intervention. A meta-analysis published by Smith et al.[7] concluded that there was little evidence supporting the use of IMT in this population. However, the majority of studies included in this review did not control the pattern of breathing which could have resulted in a lower training resistance of IMT and Smith recommended further study. More recently, Lötters et al.[8] in 2002 published a second meta-analysis. While Lötters and colleagues supported the addition of IMT in pulmonary rehabilitation, this meta-analysis did not discuss the mode(s) and intensity of IMT used.

The purpose of this study was to examine the effects of IMT on inspiratory muscle strength and endurance, exercise capacity, dyspnea and quality of life in adults living with COPD. Specifically, this study compared the effect of: (1) IMT versus sham IMT; (2) IMT versus no intervention; (3) low intensity versus high-intensity IMT; and (4) different types (modes) of IMT.

Methods

A systematic review was conducted according to methods of the Cochrane Collaboration.[9]

Search strategy

Medline and CINAHL electronic databases were searched from their inception up to August 2003. Reference lists from pertinent articles and books were searched, personal contact was made with authors and targeted journals were hand-searched to identify any relevant articles.

Study criteria

Studies were required to meet the following inclusion criteria: (i) randomized controlled trial or randomized cross-over trial; (ii) published in English; (iii) with adult participants (18 years of age or older) with a diagnosis of stable COPD; (iv) that compared IMT to another comparison group. IMT was defined as any intervention(s) with the purpose of training the inspiratory muscles. The intervention could be administered in an institutional or home setting and may or may not have been supervised.

Defining no intervention

No intervention was defined as a control group that received standard medical management but had no IMT of any mode or intensity and no other intervention, i.e. patient education or breathing exercises.

Defining sham, low- and high-intensity IMT

In order to standardize across studies that defined sham IMT and low-intensity IMT at similar percentages of PI_{max}, we defined these loads using the tidal inspiratory pressure (PI) of individuals with COPD as reported by Bégin and Grassino.[10] Sham IMT was defined as that using the same type of device as the intervention group at an intensity less than or equal to the mean PI plus one standard deviation (SD). Since PI is directly proportional to the partial pressure of carbon dioxide in the arterial blood (PCO_2) of patients with COPD,[10] sham IMT for normocapneic individuals was defined as any intensity $\leqslant 8.3$ cm H_2O (i.e. mean PI+1 SD) and for individuals with moderate hypercapnia, as any intensity $\leqslant 11.5$ cm H_2O. Nine studies did not report the mean PCO_2 at baseline.[17,23,24,28–33] Seven of these studies reported sham as no or

minimal resistance[23,28–33] and two studies used a sham/low IMT intensity of 5[17] and 6.8[24] cm H_2O, respectively, which is less than our definition for sham in normcapneic individuals.

When a study included two groups using IMT where the intensity for both groups was greater than the mean PI+1 SD, and where there was a clear difference at the beginning of the study between the intensity of intervention for both groups based on the PI, the study was included in the low versus high subgroup comparison. As a result, the definitions of sham, low- and high-intensity IMT used in this systematic review may be different from the original authors' definitions of sham, low- and high-intensity IMT.

Different types of inspiratory muscle trainers—defining modes of IMT

Studies were classified into whether the intervention utilized: (i) targeted inspiratory resistive or threshold trainers; (ii) non-targeted inspiratory resistance trainers; or (iii) normocapneic hyperventilation trainers.

The threshold or targeted inspiratory resistive trainers ensure or facilitate attainment of training intensity during the training session. The Threshold®* trainer contains a calibrated spring-loaded valve that provides a constant, pre-determined training load that is maintained unless the participant drastically alters his/her breathing pattern. Targeted inspiratory resistive trainers incorporate a visual target for pacing breathing pattern that is placed inline with the inspiratory resistive trainer device. The most common target used is an incentive spirometer (e.g. Respirex®2†) however, other more complex targets have been utilized. Non-targeted inspiratory resistance trainers do not provide a target or means of controlling breathing pattern to ensure or facilitate the attainment of the training intensity. The most common commercial devices are the PFlex‡ and the IMT by DHD.§ Normocapneic or isocapneic hyperventilation or hyperpnea trainers include a visual target and use a rebreathing system and oxygen infusion set-up so that the participant maintains a constant level of PCO_2 and PO_2 during hyperventilation. Training intensity is set at a percentage of the maximum voluntary ventilation. Because normocapneic hyperventilation IMT devices require more equipment, they have primarily been used in research and are not readily available to clinicians.

*Threshold® trainers available from Respironics HealthScan Inc., 41 Canfield Rd., Cedar Grove, NJ, 07009-1201. 1-800-962-1266.

†Respirex®2 available from DHD 22-1000, Diemolding Healthcare Division, Canastota, NY, 13032.

‡P-Flex resistive trainer available from Respironics HealthScan Inc., 41 Canfield Rd., Cedar Grove, NJ, 07009-1201. 1-800-962-1266.

§Inspiratory muscle trainer available from DHD Medical Products, Diemolding Healthcare Division, Canastota, NY 13032.

Study inclusion and data abstraction

All abstracts retrieved from the literature search were reviewed independently by two reviewers (DB and KO). If one or both reviewer(s) believed the study met the inclusion criteria, the entire paper was independently reviewed by the same two reviewers to determine whether the study met the inclusion criteria. If there was any disagreement or uncertainty about including the study in the review, a third reviewer was asked to assess the study to determine final inclusion.

For the studies that met the inclusion criteria, data were abstracted independently by two reviewers (KO and LG, KO and JC, or, KO and DR) onto standard data abstraction forms. Abstracted data included: study citation, objectives, design, and duration; times at which participants were assessed; participant inclusion and exclusion criteria; characteristics of included participants (e.g. age, gender, severity of COPD); description of the IMT intervention (i.e. frequency, intensity, progression of intensity, duration, mode, level of supervision); description of control or other intervention group; number of participants at baseline and at study completion; types of outcomes used and their values at baseline and at study completion.

The outcome measures assessed for this systematic review included, but were not limited to, inspiratory muscle strength (e.g. maximum inspiratory pressure—PI_{max}, maximum voluntary ventilation), inspiratory muscle endurance (e.g. sustained inspiratory pressure, inspiratory threshold loading), exercise capacity (e.g. 6 or 12 min walk tests—6MWT/12MWT, Borg scale for effort), dyspnea (e.g. Transition Dyspnea Index—TDI), quality of life (e.g. Chronic Respiratory Disease Questionnaire—CRQ) and lung volumes and/or spirometry (e.g. forced vital capacity—FVC, forced expiratory volume in 1 s—FEV_1).

Methodological quality of the studies was also assessed by two reviewers (DB and KO) for each of the included studies using the criteria by Jadad et al.[11] for randomization, double-blinding and withdrawals/drop-outs. In addition, groups were assessed as to whether they were similar at baseline and whether an intention-to-treat analysis was performed. Per protocol analysis occurred when

only participants who adhered to the research protocol were analyzed.[12,13] A description of the methodological quality of the studies was completed rather than generating a formal methodological score.[9]

In instances where there was insufficient data available in the articles, or further clarification was required, authors from the original articles were contacted requesting further information.

Data analysis

Subgroups analyses were performed on targeted inspiratory resistive or threshold trainers for the following comparisons: (1) IMT versus sham IMT; (2) IMT versus no intervention; (3) low-intensity versus high-intensity IMT; and (4) targeted inspiratory resistive IMT versus threshold IMT. One further subgroup comparison included non-targeted inspiratory resistive IMT versus sham IMT.

Meta-analyses were performed using the RevMan Version 4.2.2[14] software to perform the statistical analysis. Outcomes were analyzed as continuous outcomes using the random effects model to calculate the weighted mean difference and 95% confidence intervals. $P<0.05$ was considered significant for overall effect and $P<0.1$ was considered significant for heterogeneity.[15] Sensitivity analyses were performed in the presence of significant heterogeneity in which studies were systematically removed from the analyses to determine the robustness of the findings. In instances of statistical heterogeneity, potential reasons for heterogeneity were discussed and a rationale was provided for whether combining studies made practical sense, as suggested by Lau et al.[15] Where no comparisons were possible to permit a meta-analysis, a qualitative analysis of the studies was completed.

Results

Description of included studies

The search strategy retrieved a total of 274 citations of which 19[6,16–33] were judged to meet the inclusion criteria and addressed subgroup comparisons of interest (Fig. 1). Ten studies compared targeted inspiratory resistive or threshold IMT versus sham IMT (Table 1). One study compared targeted inspiratory resistive IMT versus no intervention, one compared both targeted inspiratory resistive IMT and threshold IMT versus no intervention as well as comparing these two

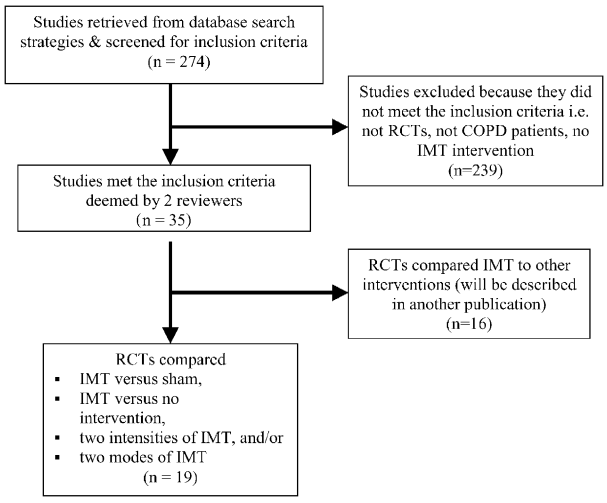


Figure 1 Flow diagram indicating number of studies retrieved from the search strategies, and the number of studies excluded and included in this systematic review.

modes of IMT, and one compared low versus high IMT (Table 2). Six studies compared non-targeted inspiratory resistive IMT versus sham IMT (Table 3). Four articles required a third reviewer to determine final study inclusion and in each case were deemed to not meet the inclusion criteria.

Participants of included studies

Participants in the included studies were adults with COPD with an average age ranging from 61 to 70 years and an average FEV_1 ranging from 24% to 52% predicted. Less than 30% of the study participants were females.

Methodological quality of studies

All 19 included studies were described as randomized, however only 3 described the actual randomization process.[26,27,31]

Seven of the 19 included studies were described as double-blinded in which both participants and outcome assessors were blind to the intervention and allocation of participants within groups.[19–21,23,24,27,30] Single blinding occurred in 10 of the 19 studies, in which participants were unaware of the intervention they received due to the use of sham IMT.[6,16–18,22,28,29,31–33] Blinding was not specified in two of the 19 studies in which IMT was compared with no intervention.[25,26]

Twelve of the 19 included studies reported on participants who withdrew from the study, or were non-compliant with the intervention. Two of these 12 studies reported no withdrawals,[18,29] whereas

Table 1 Characteristics of studies included in the systematic review: targeted inspiratory resistive IMT or threshold IMT versus sham IMT.

Study	Method	Sample size (N = at baseline; W = % withdrawal)	Patient characteristics (mean age in years; % male upon completion of study)	Severity of COPD (FEV_1% predicted or FEV_1/FVC; mean PCO_2 at baseline)	Mode of IMT and supervision	Monitoring of breathing pattern	Time, intensity and progression of IMT	Frequency and duration of IMT	Intensity of sham IMT (cm H_2O)	Outcomes assessed
Belman et al.[16]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$, $W = 15.0\%$	64 years, 59% male	FEV_1/FVC = 0.33, 39 mm Hg	Targeted inspiratory resistance trainer; daily log and supervision once per week in lab	Controlled at 12.5 breaths per minute	15 min per session @ a maximum pressure tolerated	2X per day, 7 days per week for 6 weeks	7.5–10	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, Pulmonary function tests/spirometry
Harver et al.[17]	RT; IMT versus sham	$N = 23$, $W = 17.4\%$	63 years, 84% male	FEV_1 38% predicted, PCO_2 NR	PFlex adapted to give targeted visual feedback; Not supervised. Biweekly phone calls to home.	Spontaneous breathing pattern	15 min per session @ 5–35 cm H_2O/l s. Participants encouraged to increase to a new training level (PFlex setting) every 7–10 days	2X per day, 7 days per week for 8 weeks	5 cm H_2O/l s	Inspiratory muscle strength, dyspnea, Pulmonary function tests/spirometry
Heijdra et al.[18]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$, $W = 0\%$	62 years, 75% male	FEV_1 36% predicted, 45 mm Hg	Targeted inspiratory resistance trainer; PT checked in once per week with participants	3 s inspiration, 4 s expiration monitored by target of incentive spirometry	15 min per session @ 60% PI_{max}, intensity adjusted weekly to maintain PI_{max} of 60%	2X per day, 7 days per week for 10 weeks	5.7 (10% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, Pulmonary function tests/spirometry
Kim et al.[19]	RT; IMT versus sham	$N = 112$, $W = 40.2\%$	65 years, 76% male	FEV_1 40% predicted, 42 mm Hg	Threshold load trainer; Diary and nurse called participants at home to monitor progress, provide coaching, encourage adherence	Noseclips	15–30 min per session @ 30% PI_{max}. Intensity increased monthly to sustain 30% PI_{max}	1X per day, 7 days per week for 24 weeks	"barely perceptible and too light to influence strength" (p. 358)	Inspiratory muscle strength, inspiratory muscle endurance, Exercise capacity, Dyspnea
Larson et al.[20]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 45$, $W = 51.1\%$	63 years, 91% male	FEV_1 32% predicted, 41 mm Hg	Threshold load trainer; daily log and telephone call once per week	NR	15 min (week 1), 30 min (week 2–8) @ 30% PI_{max}, progression of intensity: NR	1X per day, 7 days per week for 8 weeks	8 (15% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance, Exercise capacity, quality of life

Lisboa et al.[21]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$, $W = NR$	62 years, 65% male	FEV_1 38% predicted, 41 mm Hg	Threshold load trainer; Not supervised	NR	30 min per session @30% PI_{max}. Intensity adjusted every week to ensure PI_{max} remained at target level	1X per day, 6 days per week for 10 weeks	5 (10% PI_{max} at baseline)	Inspiratory muscle strength, Exercise capacity, Dyspnea, Pulmonary function tests/spirometry
Patessio et al.[22]	RT; IMT versus sham	$N = 16$, $W = NR$	63 years, 100% male	FEV_1 52% predicted, 42 mm Hg	Targeted inspiratory resistance trainer (resistance trainer with visual feedback); NR	Spontaneous breathing pattern	15 min per session @50% PI_{max}, Progression of intensity NR	4X per day, 7 days per week for 8 weeks	No inspiratory resistance	Inspiratory muscle strength, inspiratory muscle endurance, Dyspnea, Pulmonary function tests/ spirometry
Sánchez-Riera et al.[23]	RT; IMT versus sham	$N = 20$, $W = 0\%$	67 years, 90% male	FEV_1 40% predicted, PCO_2 NR	Targeted inspiratory resistance trainer; Not supervised	Controlled at 8 breaths per min with metronome	15 min per session @30% PI_{max}, modified every 6 wks to maintain 30% PI_{max} (target load began at 6 cm H_2O and increased every 2 min by 2 cm H_2O)	2X per day, 6 days per week for 24 weeks	No inspiratory resistance	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, quality of life, Dyspnea
Villafranca et al.[24]	RT; high versus low IMT (redefined as IMT versus sham for this review)	$N = 20$, $W = NR$	62 years, 65% male	FEV_1/ FVC = 0.39, PCO_2 NR	Threshold load trainer; Not supervised	NR	15 min per session @ 30% PI_{max}. Intensity adjusted each week to ensure PI_{max} remained at target level	2X per day, 6 days per week for 10 weeks	6.8 (10% PI_{max} at baseline)	Inspiratory muscle strength, inspiratory muscle endurance
Ramírez-Sarmiento et al.[6]	RT; IMT versus sham	$N = 14$, $W = 0\%$	66 years, 100% male	FEV_1 24% predicted, 45 mm Hg	Threshold load trainer; supervised by personnel	NR	30 min per session @ 60% maximum sustained inspiratory pressure (SIP). Intensity adjusted dependent on participant tolerance	1X per day, 5 days per week for 5 weeks	No inspiratory resistance	Inspiratory muscle strength, inspiratory muscle endurance, Exercise capacity, Pulmonary function tests/spirometry

IMT—inspiratory muscle training; *N*—number; %—percent; FEV_1—forced expiratory volume in 1 s; FVC—forced vital capacity; PCO_2—arterial partial pressure of carbon dioxide; mm Hg—millimeters of mercury; cm H_2O—centimeters of water; RT—randomized trial; @—at; X—times; NR—not reported; PI_{max}—maximum inspiratory pressure; min—minutes; s—second; PT—physical therapist.

Table 2 Characteristics of studies included in the systematic review: IMT versus no intervention and low intensity IMT versus high intensity IMT.

Study	Method	Sample size (N = at baseline; W = % withdrawal)	Patient characteristics (mean age in years; % male upon completion of study)	Severity of COPD (FEV_1% predicted or FEV_1/FVC)	Mode of IMT and supervision	Monitoring of breathing pattern	Time, intensity and progression of IMT	Frequency and duration of IMT	Outcomes assessed
Reid and Warren[25]	RT; IMT versus no intervention versus treadmill	$N = 12$, $W = 0\%$	66 years, 83% male	NR	Inspiratory resistance trainer; supervised by PT	Monitored with metronome at 16 breaths per min	30 min per session @ unknown intensity. Increased level of resistance until able to tolerate 5 min.	1X per day, 5 days per week for 6 weeks	Inspiratory muscle strength, exercise capacity, Pulmonary function tests/ spirometry
Hsiao et al.[26]	RT; Target IMT versus Threshold IMT versus no intervention	$N = 42$, $W = 28.6\%$	70 years, 87% male	FEV_1 51% predicted	Threshold load trainer and Target inspiratory resistance trainer; daily log (home based IMT program)	Noseclips	15 min per session @ 50% PI_{max}. Intensity adjusted every 2 weeks at lab to ensure intensity maintained at 50% PI_{max}.	2X per day, 5 days per week for 8 weeks	Inspiratory muscle strength, inspiratory muscle endurance, exercise capacity, quality of life, Dyspnea
Preusser et al.[27]	RT; Low intensity versus high intensity IMT	$N = 22$, $W = 9.1\%$	66 years, 36% male	FEV_1 34% predicted	Threshold load trainer; Supervised	NR	5 min (week 1)–18 min (week 12) @ 52% PI_{max} (HIGH) and @ 22% PI_{max} (LOW). Intensity adjusted every 4 weeks to maintain target intensity.	1X per day, 3 days per week for 12 weeks	Inspiratory muscle strength, inspiratory muscle endurance, Exercise capacity

IMT—inspiratory muscle training; N—number; %—percent; FEV_1—forced expiratory volume in 1 s; FVC—forced vital capacity; RT—randomized trial; NR = not reported; min–minutes; @—at; X–times; PI_{max}—maximum inspiratory pressure; PT—physical therapist.

Table 3 Characteristics of studies included in the systematic review: non-targeted inspiratory resistive IMT versus sham IMT.

Study	Method	Sample size (N = at baseline; W = % withdrawal)	Patient characteristics (mean age in years; % male upon completion of study)	Severity of COPD (FEV_1% predicted or FEV_1/FVC)	Mode of IMT and supervision	Monitoring of breathing pattern	Time, intensity and progression of IMT	Frequency and duration of IMT	Intensity of sham IMT (cm H_2O)	Outcomes assessed
Bjerre-Jepsen et al.[28]	RT; IMT versus sham	$N = 28$, $W = NR$	62 years, % male NR	$FEV_1/FVC = 0.39$	Face mask with variable inspiratory resistance; Not supervised	Not controlled	15 min per session @ unknown intensity (resistance participants could not manage to breathe through for 2 min). Intensity progressed every 2 weeks.	3X per day, 7 days per week for 6 weeks	No inspiratory resistance	Exercise capacity
Falk et al.[29]	RT; IMT versus sham	$N = 27$, $W = 0\%$	64 years, 59% male	FEV_1 29% predicted	Inspiratory resistance trainer; Checked by PT every 2 weeks to see if apparatus used correctly and to increase intensity	NR	Up to 10 min (2–10 min) per session @ resistance that participants could breathe for 2 min without discomfort. Intensity increased every 2 weeks as able to tolerate for 2 min without discomfort.	3X per day, 7 days per week for 12 weeks	No inspiratory resistance	Inspiratory muscle endurance, Dyspnea, Pulmonary function tests/spirometry
Guyatt et al.[30]	RT; IMT versus sham	$N = 133$, $W = 38.3\%$	66 years, 71% male	$FEV_1/FVC = 0.40$	PFlex inspiratory muscle trainer; Not supervised. Training sessions prior to study with nurse at weekly intervals	NR	10 min per session @ setting on PFlex. Began at lowest resistance level and if tolerated, intensity was increased to next level each week.	5 X per day, 7 days per week for 24 weeks	"Minimal resistance" (p. 598)	Inspiratory muscle strength, Inspiratory muscle endurance, Exercise capacity, quality of life
Jones et al.[31]	RT; IMT versus sham versus exercise	$N = 30$, $W = 30.0\%$	61 years, 57% male	NR	Inspiratory resistance trainer; watched every 2 weeks at lab	NR	15 min per session @ unknown intensity (resistance that produced fatigue of breathlessness after 15 min of breathing) progression of intensity NR	2X per day, 7 days per week for 10 weeks	No inspiratory resistance	Exercise capacity, Dyspnea, Pulmonary function tests/ spirometry
McKeon et al.[32] Inspiratory muscle strength, exercise capacity	RT; IMT versus sham	$N = 18$, $W = NR$	68 years, % male NR	FEV_1 36% predicted	Inspiratory resistance trainer; spouses asked to supervise and then asked to sign diary directly after intervention	Not controlled—"normal rate"	15 min per session @ approximately 4-4.5 mm resistance	3X per day, 7 days per week for 6 weeks	No inspiratory resistance	
Richardson et al.[33]	RT; IMT versus sham	$N = 21$, $W = 23.8\%$	68 years, 81% male	FEV_1 35% predicted	Inspiratory resistance trainer; not supervised	Not controlled (breathing pattern not monitored)	30 min per session @ unknown intensity. Intensity increased depending on resistance able to tolerate for 5 min.	1X per day, 5 days per week for 6 weeks	"Minimal resistance"	Inspiratory muscle strength, Inspiratory muscle endurance

IMT—inspiratory muscle training; N—number; %—percent; FEV_1–forced expiratory volume in 1 s; FVC—forced vital capacity; RT—randomized trial; @—at; X–times; NR = not reported; min—minutes; PT—physical therapist.

withdrawal rates among the other studies ranged from 9% to 51%.[6,16,17,19,20,26,27,30,31,33] Seven studies reported that loss of interest or non-compliance was a reason for withdrawal.[6,17,19,20,26,30,31] Other reasons for withdrawal included: pulmonary health problems,[6,17,19,20] other illnesses[16,19,20,30,31,33] including surgery[27] and admission to hospital,[26] work, family or transportation issues,[19,33] homelessness,[27] social reasons,[31] and change in medications.[26] The remaining 7 of the 19 studies did not report on withdrawal rates.

Fourteen of the 19 included studies reported that comparison groups were similar at baseline.[6,16–18,26,28–33] Three studies did not report on group similarity at baseline.[19,21,25] Two studies had older participants,[20] participants with lower arterial oxygen,[20] or fewer males[27] in the sham group.

Intention-to-treat was performed in two of the 19 included studies that reported no drop-outs[18,29] and was inferred in 11 of the 19 studies, because group participants appeared to be analyzed based on the groups to which they were originally randomized.[16,21–25,27,28,31–33] In the remaining 6 studies, intention-to-treat analysis was not performed, but rather a per protocol analysis was conducted whereby participants who were non-compliant with the intervention were excluded from the analysis.[6,17,19,20,26,30]

Targeted inspiratory resistive or threshold IMT versus sham IMT

Ten studies compared targeted inspiratory resistive or threshold IMT versus sham IMT[6,16–24] (Table 1). Five of the ten meta-analyses conducted using these studies (Table 4) demonstrated a statistically significant overall effect in favor of targeted inspiratory resistive IMT or threshold IMT. Inspiratory muscle strength, as reflected by PI_{max}, improved by 12.3 cm H_2O (95% CI: 7.5, 17.1, $P<0.00001$, $n=233$). Inspiratory threshold loading, a measure of inspiratory muscle endurance, increased by 1.0 kPa (95% CI: 0.3, 1.7, $P=0.005$, $n=74$). Exercise capacity measures improved: the Borg score for respiratory effort decreased by 2.3 points (95% CI: −3.1, −1.5, $P<0.00001$, $n=40$) and work rate maximum improved by 13.8 watts (95% CI: 4.2, 23.3, $P=0.005$, $n=34$). Dyspnea as indicated by TDI improved by 3.4 points (95% CI: 1.9, 5.0, $P<0.00001$, $n=59$). Of these five meta-analyses, however, three were statistically significant for heterogeneity (PI_{max}, inspiratory threshold loading, TDI). Two other meta-analyses that did not show an overall effect (respiratory muscle endurance time, maximum oxygen consumption) were also statistically significant for heterogeneity. In these instances, sensitivity analyses were conducted to determine the robustness of findings. Where applicable, results of the sensitivity analyses and potential reasons for heterogeneity are discussed in the comments section in Table 4.

Two of the studies[20,23] included outcomes related to quality of life but a meta-analysis was not possible since both studies used different measures. No changes were reported in the Profile of Mood States, the Health Perceptions Questionnaire or Sickness Impact Profile[20] whereas a large clinically significant change in the CRQ was reported after IMT[23](1.3–1.6 points for each scale relative to the typical responsiveness estimate of 0.5/7 point change on any CRQ scale).[34]

Targeted inspiratory resistive or threshold IMT versus no intervention

A non-significant improvement in PI_{max} was shown in the meta-analysis comparing targeted inspiratory resistive IMT alone versus no intervention (Table 5), whereas a statistically significant increase in PI_{max} of 14.1 cm H_2O was shown by the meta-analysis that compared targeted inspiratory resistive or threshold IMT compared to no intervention (95% CI: 1.3, 26.9, $P=0.03$, $n=27$) (Table 6).

Low IMT versus high IMT

In the one study[27] comparing low- versus high-threshold IMT, both groups showed significant improvements in the incremental threshold loading test, inspiratory muscle endurance and the 12 MWT. The high IMT group also showed improvement in PI_{max}.

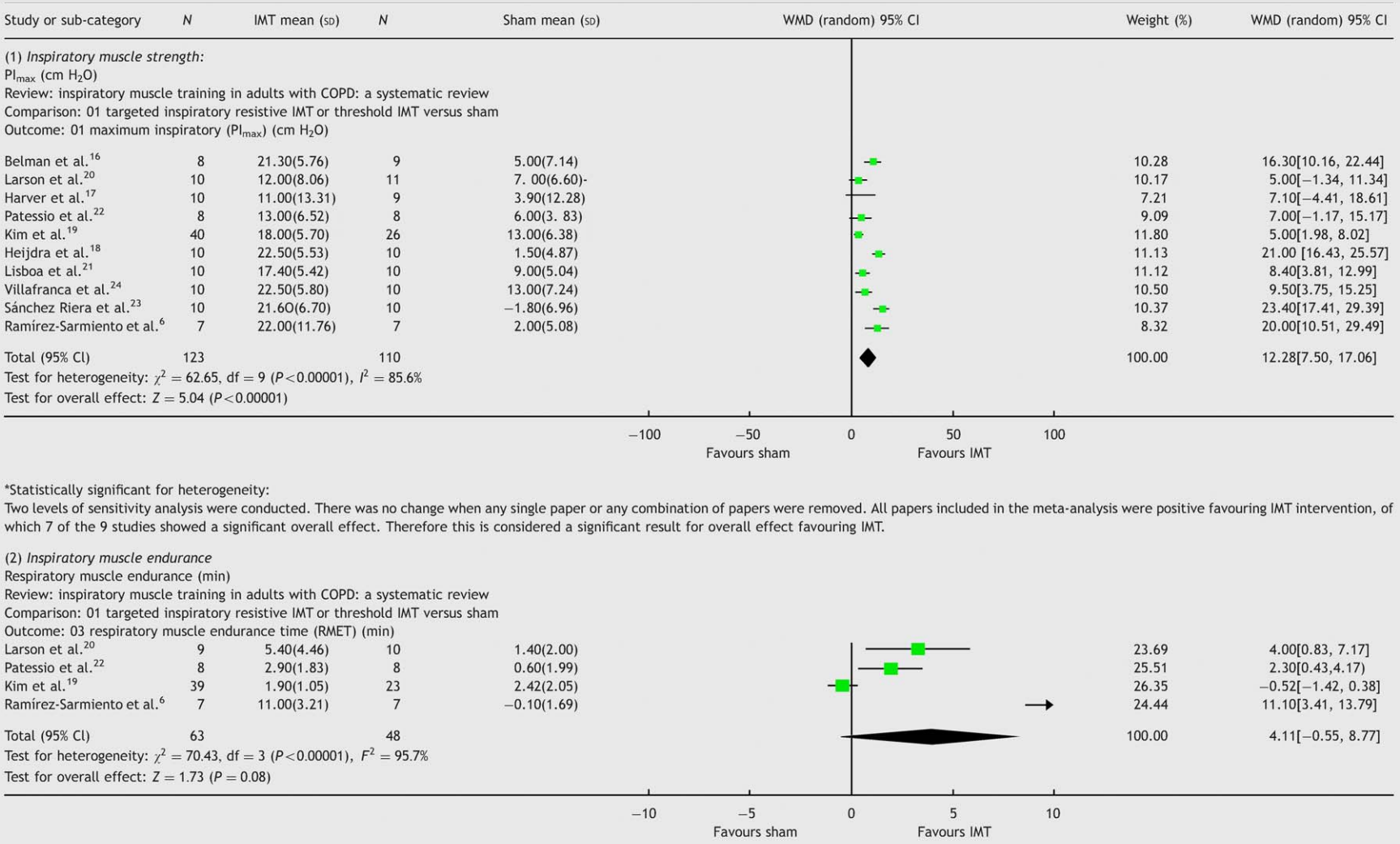
Threshold IMT versus targeted inspiratory resistive IMT

The one study[26] that compared threshold to targeted inspiratory resistive IMT using a home-based training protocol showed similar significant improvements in PI_{max}, respiratory muscle endurance time and the 6 MWT test for both types of training.

Non-targeted inspiratory resistive IMT versus sham IMT

For the six studies comparing non-targeted inspiratory resistive IMT versus sham IMT[28–33] (Table 3), only one meta-analysis was possible. Inspiratory muscle strength (Table 7) as measured by PI_{max}

Table 4 Meta-analyses results comparing targeted inspiratory resistive IMT or threshold IMT versus sham IMT.



*Statistically significant for heterogeneity:
Two levels of sensitivity analysis were conducted. There was no change when any single paper or any combination of papers were removed. All papers included in the meta-analysis were positive favouring IMT intervention, of which 7 of the 9 studies showed a significant overall effect. Therefore this is considered a significant result for overall effect favouring IMT.

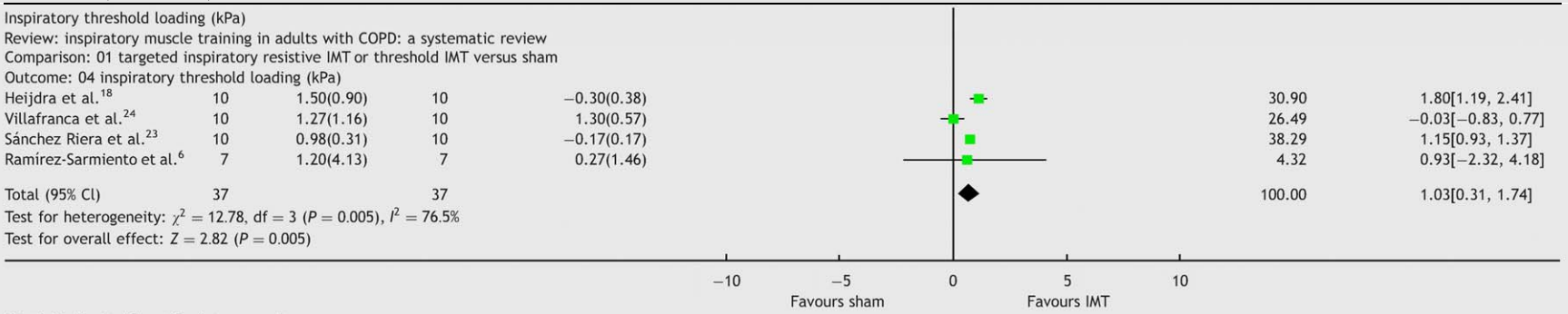
*Statistically significant for heterogeneity:
The overall effect is not significant. Sensitivity analysis showed no change in the heterogeneity results when one study at a time was removed, thus the investigators chose to report on the meta-analysis including all four studies. Three of the four studies favoured IMT.

Table 4 (*continued*)

Inspiratory threshold loading (kPa)
Review: inspiratory muscle training in adults with COPD: a systematic review
Comparison: 01 targeted inspiratory resistive IMT or threshold IMT versus sham
Outcome: 04 inspiratory threshold loading (kPa)

Heijdra et al.[18]	10	1.50(0.90)	10	−0.30(0.38)	30.90	1.80[1.19, 2.41]
Villafranca et al.[24]	10	1.27(1.16)	10	1.30(0.57)	26.49	−0.03[−0.83, 0.77]
Sánchez Riera et al.[23]	10	0.98(0.31)	10	−0.17(0.17)	38.29	1.15[0.93, 1.37]
Ramírez-Sarmiento et al.[6]	7	1.20(4.13)	7	0.27(1.46)	4.32	0.93[−2.32, 4.18]
Total (95% CI)	37		37		100.00	1.03[0.31, 1.74]

Test for heterogeneity: $\chi^2 = 12.78$, df = 3 ($P = 0.005$), $I^2 = 76.5\%$
Test for overall effect: $Z = 2.82$ ($P = 0.005$)

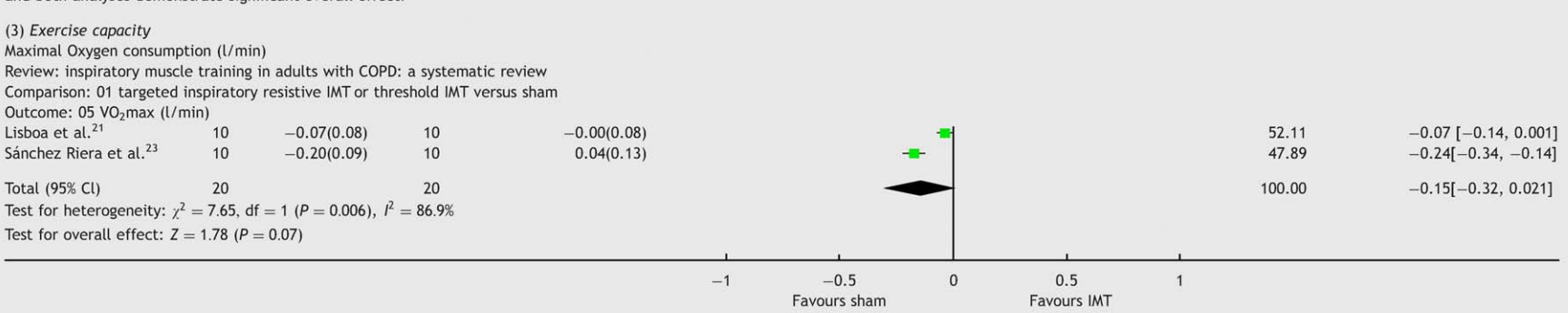


*Statistically significant for heterogeneity:
There is a significant overall effect favouring IMT. Sensitivity analysis was conducted. Heterogeneity results became not significant when Villafranca et al.[24] was removed from the analysis. This resulted in a WMD of 1.38 with 95% CI of 0.86,1.90. Investigators have chosen to report on the meta-analysis that includes all four possible studies because it is more conservative to support the results of the meta-analysis when all four papers are included and both analyses demonstrate significant overall effect.

(3) *Exercise capacity*
Maximal Oxygen consumption (l/min)
Review: inspiratory muscle training in adults with COPD: a systematic review
Comparison: 01 targeted inspiratory resistive IMT or threshold IMT versus sham
Outcome: 05 VO_2max (l/min)

Lisboa et al.[21]	10	−0.07(0.08)	10	−0.00(0.08)	52.11	−0.07 [−0.14, 0.001]
Sánchez Riera et al.[23]	10	−0.20(0.09)	10	0.04(0.13)	47.89	−0.24[−0.34, −0.14]
Total (95% CI)	20		20		100.00	−0.15[−0.32, 0.021]

Test for heterogeneity: $\chi^2 = 7.65$, df = 1 ($P = 0.006$), $I^2 = 86.9\%$
Test for overall effect: $Z = 1.78$ ($P = 0.07$)

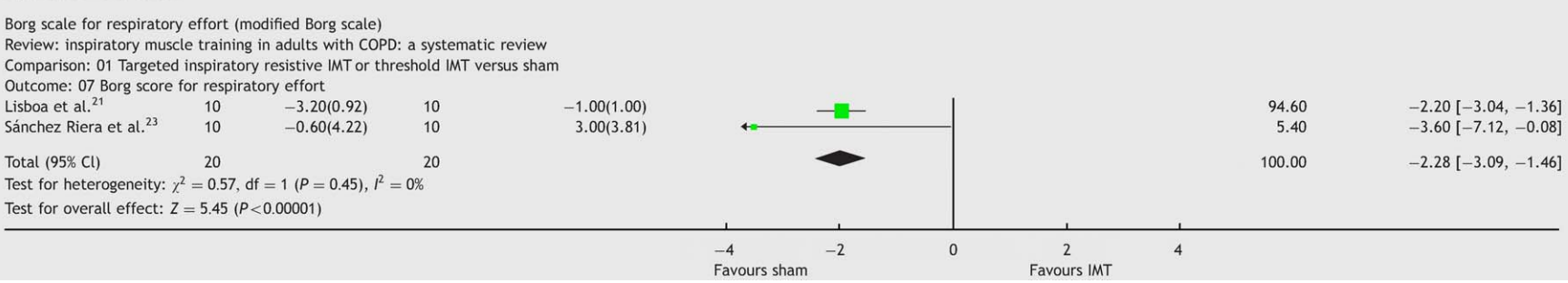


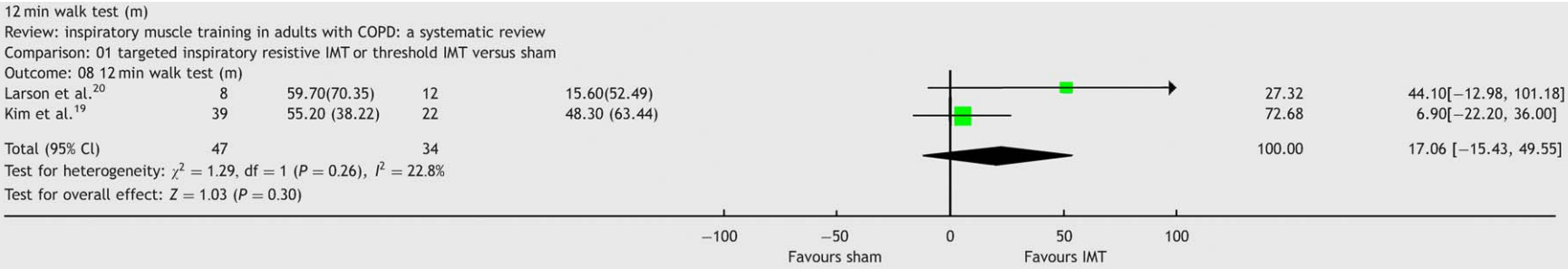
*Statistically significant for heterogeneity:
The overall effect is not significant. Since the same two studies were combined in the meta-analysis for the Borg Scale for Respiratory Effort and was not significant for heterogeneity, the investigators support the finding of no significant overall effect.

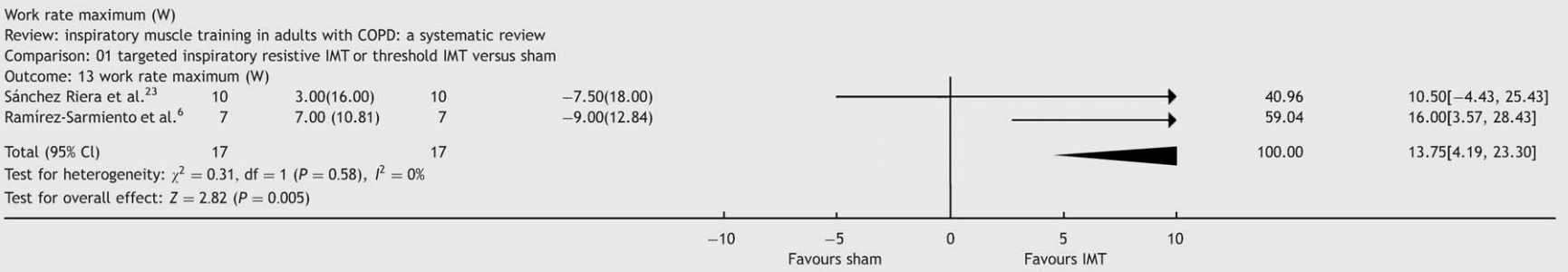
Borg scale for respiratory effort (modified Borg scale)
Review: inspiratory muscle training in adults with COPD: a systematic review
Comparison: 01 Targeted inspiratory resistive IMT or threshold IMT versus sham
Outcome: 07 Borg score for respiratory effort

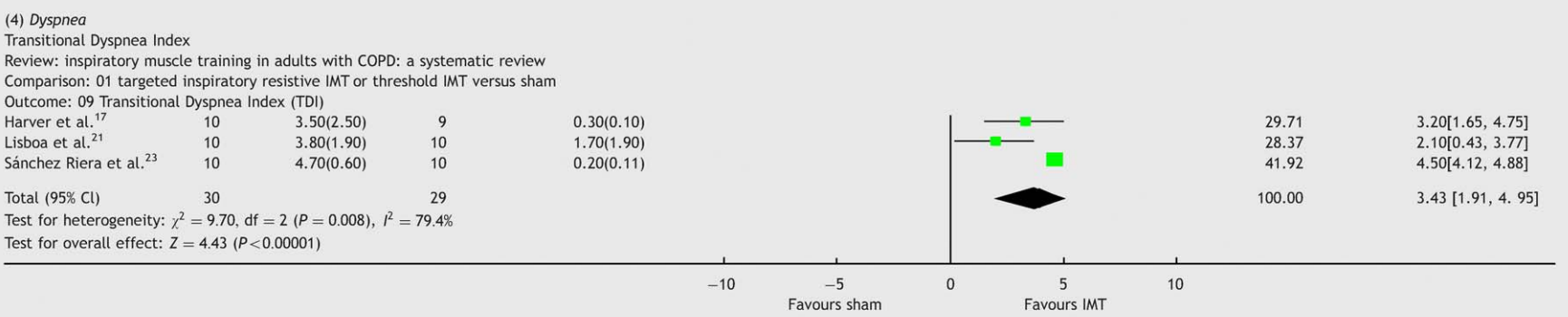
Lisboa et al.[21]	10	−3.20(0.92)	10	−1.00(1.00)	94.60	−2.20 [−3.04, −1.36]
Sánchez Riera et al.[23]	10	−0.60(4.22)	10	3.00(3.81)	5.40	−3.60 [−7.12, −0.08]
Total (95% CI)	20		20		100.00	−2.28 [−3.09, −1.46]

Test for heterogeneity: $\chi^2 = 0.57$, df = 1 ($P = 0.45$), $I^2 = 0\%$
Test for overall effect: $Z = 5.45$ ($P < 0.00001$)









*Statistically significant for heterogeneity:
Sensitivity analysis was completed by removing one study at a time. When Sánchez Riera et al. [23] was removed, heterogeneity was not significant and the WMD decreased to 2.69 with 95% CI of 1.55,3.82. When Lisboa et al.[21] was removed, heterogeneity was not significant and the WMD increased to 4.08 with 95% CI of 2.88,5.27. The meta-analysis with all three papers demonstrates a positive overall effect and the sensitivity analysis confirms it as being significant favouring IMT.

Table 4 (*continued*)

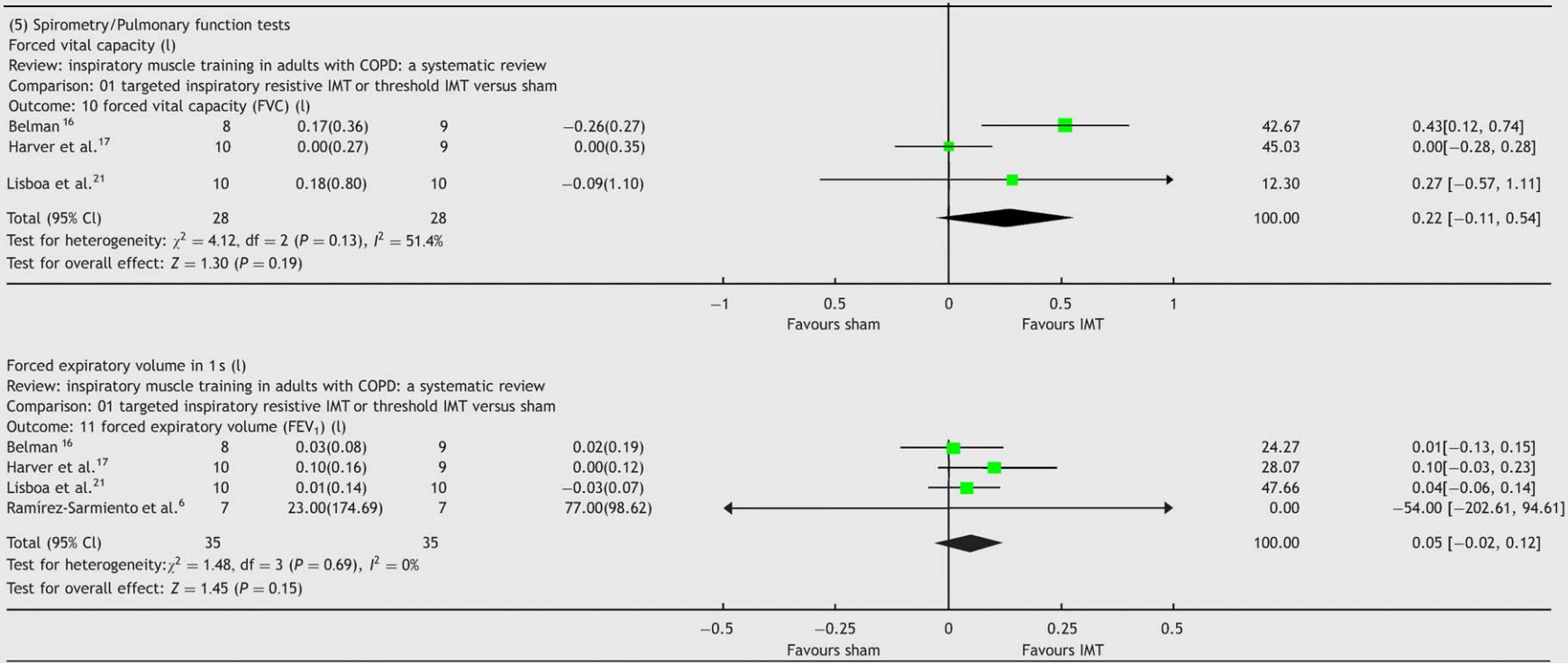


Table 5 Meta-analysis results comparing targeted inspiratory resistive IMT versus no intervention.

Study or sub-category	*N*	IMT mean (SD)	*N*	No intervention mean (SD)	WMD (random) 95% CI	Weight (%)	WMD (random) 95% CI
(1) Inspiratory muscle strength							
PI_{max} (cm H_2O)							
Review: inspiratory muscle training in adults with COPD: a systematic review							
Comparison: 06 targeted inspiratory resistive IMT or threshold IMT versus no intervention							
Outcome: 01 maximum inspiratory pressure (PI_{max}) (cm H_2O)—targeted inspiratory resistive IMT versus no intervention							
Reid and Warren[25]	5	8.00(28.60)	2	11.00(6.40)		24.56	−3.00[−29.59, 23.59]
Hsiao et al.[26]	10	24.40(15.00)	10	10.60(13.40)		75.44	13.80[1.33, 26.27]
Total (95% CI)	15		12			100.00	9.67[−4.50, 23.85]
Test for heterogeneity: $\chi^2 = 1.26$, df = 1 ($P = 0.26$), $I^2 = 20.4\%$							
Test for overall effect: $Z = 1.34$ ($P = 0.18$)							

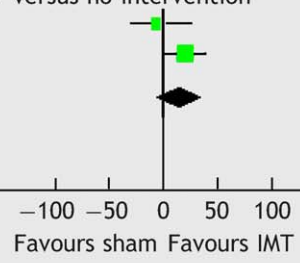


Table 6 Meta-analysis results comparing targeted inspiratory resistive IMT or threshold IMT versus no intervention.

Study or sub-category	*N*	IMT mean (SD)	*N*	No intervention mean (SD)	WMD (random) 95% CI	Weight (%)	WMD (random) 95% CI
(1) Inspiratory muscle strength							
PI_{max} (cm H_2O)							
Review: inspiratory muscle training in adults with COPD: a systematic review							
Comparison: 06 targeted inspiratory resistive IMT or threshold IMT versus no intervention							
Outcome: 02 maximum inspiratory pressure (PI_{max}) (cm H_2O)—targeted insp. Resist. or threshold IMT versus no intervention							
Reid and Warren[25]	5	8.00(28.60)	2	1.00(6.40)		23.20	7.00[−19.59, 33.59]
Hsiao et al.[26]	10	26.80(19.40)	10	10.6.(13.40)		76.80	16.20 [1.59, 30.81]
Total (95% CI)	15		12			100.00	14.07 [1.26, 26.87]
Test for heterogeneity: $\chi^2 = 0.35$, df = 1 ($P = 0.55$), $I^2 = 0\%$							
Test for overall effect: $Z = 2.15$ ($P = 0.03$)							
Test for heterogeneity: $\chi^2 = 0.35$, df = 1 ($P = 0.55$), $I^2 = 0\%$							
Test for overall effect: $Z = 2.15$ ($P = 0.03$)							

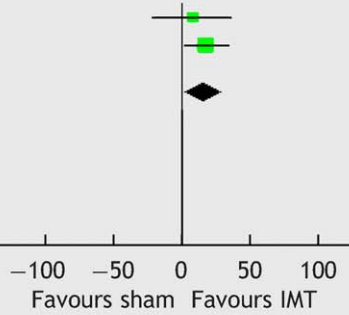
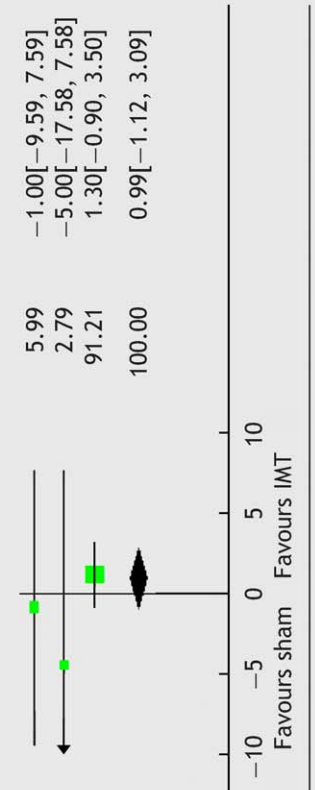


Table 7 Meta-analysis results comparing non-targeted inspiratory resistive IMT versus sham IMT.

Study or sub-category	N	IMT mean (SD)	N	Sham mean (SD)	WMD (random) 95% CI	Weight (%)	WMD (random) 95% CI
(1) Inspiratory muscle strength							
PI_{max} (cm H_2O)							
Review: inspiratory muscle training in adults with COPD. a systematic review							
Comparison: 02 non-targeted inspiratory resistive IMT versus sham							
Outcome: 01 maximum inspiratory pressure (PI_{max}) (cm H_2O)							
McKeon et al.[32]	10	3.00(8.56)	8	4.00(9.76)		5.99	−1.00[−9.59, 7.59]
Richardson et al.[33]	6	−2.00(13.37)	4	3.00(6.76)		2.79	−5.00[−17.58, 7.58]
Guyatt et al.[30]	43	1.50(4.97)	39	0.20(5.18)		91.21	1.30[−0.90, 3.50]
Total (95% CI)	59		51			100.00	0.99[−1.12, 3.09]
Test for heterogeneity: $\chi^2 = 1.15$, df = 2 ($P = 0.56$), $I^2 = 0\%$							
Test for overall effect: $Z = 0.92$ ($P = 0.36$)							



showed a non-significant trend towards an increase in PI_{max} for participants in the IMT group compared to participants in the sham group.

Only one of the six studies[29] reported significant differences between the IMT and sham groups which included decreased dyspnea, decreased functional residual capacity, decreased respiratory rate at rest and during exercise, and increased endurance time on a cycle ergometer with the use of IMT.

Three studies[30–32] concluded that IMT provided no additional improvement for individuals with COPD compared to sham IMT and one[28] found improvement in stair-climbing ability in both the intervention and control groups but concluded that IMT did not contribute to the improvement observed.

The final study in this grouping[33] stated that the majority of the participants in the study were not training at a sufficient level because the researchers did not control the pressure generation and breathing pattern during the training sessions.

Discussion

This systematic review demonstrated that the mode of IMT is important in order to achieve a significant improvement of inspiratory muscle strength, endurance and exercise capacity in adults with COPD. Targeted inspiratory resistive or threshold IMT when compared with sham IMT significantly improves some outcomes of inspiratory muscle strength (PI_{max}), inspiratory muscle endurance (inspiratory threshold loading) and exercise capacity (Borg score for respiratory effort, work rate maximum), and decreases dyspnea (TDI) (Table 4). It had no effect on respiratory muscle endurance, maximal oxygen consumption, 12 min walk test, FVC or FEV_1. On the other hand, non-targeted inspiratory resistive IMT when compared with sham IMT showed no effect on inspiratory muscle strength (PI_{max}) (Table 7) and only one of six studies[29] using non-targeted inspiratory resistive IMT reported significant outcomes favoring IMT. No conclusions could be drawn regarding the effect of any mode of IMT on quality of life outcomes.

In the meta-analyses comparing targeted inspiratory resistive or threshold IMT to no intervention, inspiratory muscle strength (PI_{max}) improved when either mode (type) of IMT (targeted or threshold) were included in meta-analysis (Table 6), whereas there was no improvement in this outcome with targeted inspiratory resistive IMT alone in meta-analysis (Table 5). This finding was likely due to the

larger sample size of one study,[26] resulting in heavier weighting of this study when combining the studies in the meta-analysis.

Two systematic reviews have been conducted on this topic previously.[7,8] Neither one, however, stratified the studies based on the mode of IMT used in the intervention group(s), nor, the type of intervention used in the control group(s) (e.g. sham, no intervention). Although Smith et al.[7] identified the type (mode) of training, all of the studies were combined in their meta-analysis and they did not describe or consider the type of intervention used in the control groups. This may explain their conclusion that there is little support for IMT for individuals with COPD. On the other hand, Lötters et al.[8] addressed the issue of controlling the training loads by including studies with training intensities $\geqslant$30% PI_{max}, but again neither the mode(s) of IMT nor the type of intervention(s) used in the control groups was described. Lötters and colleagues concluded "that IMT alone significantly improves inspiratory muscle strength and endurance, whereas the sensation of dyspnea significantly decreases."[8, p. 574]

There are several issues to consider when interpreting the results of our study. Our review is based on a small number of trials ($n = 19$), which involved relatively small numbers of participants (range of 12–133 participants). Moreover, six of the meta-analyses combined only two studies. Although the use of standard mean difference would permit the inclusion of a greater number of studies with different outcomes within a meta-analysis, this is not recommended by the Cochrane Reviewer's Handbook[9] as this would eliminate the units of outcome being analyzed, thus making it difficult to interpret the results for use within clinical practice. The meta-analyses were also limited due to differences in the modes of IMT used, and the types of outcomes assessed within the individual studies. As a result, meta-analyses could not be performed for outcomes of HRQL.

Statistical heterogeneity was present in five of the meta-analyses. Reasons for heterogeneity in this review may include variance between studies pertaining to the type of participants, frequency, intensity, mode and duration of the intervention, and whether or not the intervention was supervised. In instances where there was statistical heterogeneity, a random effects model was used, sensitivity analyses performed, and individual studies were examined to explain heterogeneity and to determine whether to proceed with the analysis.

Included studies consisted of predominately male participants (comprising approximately 70% of the total participants), limiting our ability to interpret results for females living with COPD. The longest study lasted for 24 weeks, with an average duration of 10.5 weeks, which limited our ability to determine long-term outcomes of IMT for persons with COPD.

Finally, limitations in this systematic review may exist because of bias. There is potential for publication bias, either because only published studies were included in this systematic review or because there may be a tendency in the literature to have more positive studies published in relation to smaller less significant ones. This may have resulted in an over-estimation of IMT effect. Funnel plots, an aid to detecting publication bias, were not included in this paper since they are difficult to interpret when combining less than 10 studies.[9] There is also potential for observer bias (due to lack of double-blinding particularly for the assessors of outcomes, and for those studies that did not include sham IMT), for migration bias (due to large withdrawal rates), and for selection bias (differences in comparison groups at baseline in some studies might have resulted in confounders being distributed unevenly between some groups). Withdrawal rates among included studies ranged from 0% to 51%, with non-compliance highlighted as being a reason for withdrawal in many of the included studies ($n = 7$). The lack of intention to treat analysis within individual studies impacts our ability to determine the effectiveness of IMT versus its efficacy.

The results of this systematic review have implications for future research. Current research is limited to individuals with stable COPD and does not consider whether there may be an optimal time to prescribe IMT regarding the course of COPD, the severity of COPD or in relation to acute exacerbations of COPD. Furthermore, it would be important to confirm the effectiveness of IMT in both genders. While this systematic review demonstrates positive effect related to the use of targeted inspiratory resistive or threshold IMT in people with COPD, further research is warranted to determine if there is: an optimal mode of IMT (threshold, targeted inspiratory resistive or some other combination of inspiratory resistive and high volume loading); an optimal training intensity; and if IMT significantly improves HRQL and other functionally based outcomes that will have direct implications for both the person with COPD and health care utilization, given the dearth of research on the effect of IMT in these outcomes.

Clinical implications

The inspiratory muscles, like other skeletal muscles, undergo adaptation in response to overload

stimuli during exercise training[35,36] resulting in changes in muscle strength and endurance as well as exercise performance. However, for a training effect to be achieved, the appropriate mode must be prescribed.[36,37] Use of targeted inspiratory resistive or threshold modes of IMT ensures that the training intensity is achieved and maintained during the exercise protocol whereas the non-targeted inspiratory resistive mode does not.

For a training effect, the frequency, duration and intensity of exercise must also be considered. Standard guidelines suggest a training frequency of 1–2 times per day for a total duration of 20–30 min, 3–5 days per week.[37] While Ramírez-Sarmiento et al.[6] demonstrated functional improvement and adaptive cellular changes in the inspiratory muscles after 5 weeks of training, training must be maintained for the cellular training effects to be sustained.[38] Recognizing that in individuals with COPD, the inspiratory muscles are at risk for fatigue and injury,[36,39] Reid et al.[40] recommend the following parameters for IMT in COPD: an initial training interval of as short as 3–5 min, progressing to two 15 min or one 30 min session(s) per day, 4–6 days per week at a training intensity of 40–70% PI_{max} indefinitely.

In the subgroup comparison of targeted inspiratory resistive or threshold IMT versus sham, most protocols trained for 30 min per day in one or two sessions[6,16–21,23,24] and one study[22] trained for 15 min four times a day for a total of 60 min. The number of sessions ranged from 5 to 7 days per week. The training intensity varied from 30% PI_{max} [19–21,23,24] to 60% PI_{max}.[18] However, an intensity of as low as 22% demonstrated positive results when the training sessions were supervised.[27]

When prescribing IMT for individuals with COPD, the clinician must consider the individual's co-morbidities, motivation, level of dyspnea, and severity of disease. The clinician should choose training parameters that will improve the strength and endurance of the inspiratory muscles with the least amount of risk to the patient.[40] We recommend the following guidelines when using IMT in this population. IMT should be carried out for at least a total of 30 min daily but can be spread over more than one session per day. Training should occur at least 5 days per week. While gains may be measurable after as short as 5 weeks, IMT should become part of the individual's routine exercise program. The minimal training intensity necessary to obtain training effect is less clear and may depend on the type of supervision provided. It could start as low as 22% PI_{max} and be progressed to as high as 60% PI_{max} using a targeted inspiratory resistive or threshold trainer.

Targeted inspiratory resistive IMT is as effective as threshold IMT for adults with COPD,[26] but the devices have pros and cons that deserve consideration by clinicians and patients when selecting the preferred device. Hsiao and colleagues[26] found that the targeted trainer provided visual feedback enhancing the participant's motivation and was less expensive, but it was more difficult to ensure participants were exercising at their target intensity. On the other hand, they reported that the threshold trainer provided consistent training intensity, though there could be problems in providing a precise intensity at pressures less than 9 cm H_2O. Participants found it difficult to keep the threshold trainer dry and clean in the high-humidity environment in Taiwan where the study was conducted.

There are two more factors that may deserve consideration when selecting the mode of IMT to use. With the threshold trainer, the training intensity is set on the device. If the person does not generate a high enough pressure to achieve the training intensity, the valve does not open and the person is unable to inspire. With targeted inspiratory resistive trainer, the device provides a target. The person can succeed in meeting the target or not but, either way, still receives an inspiratory breath. Secondly, the targeted inspiratory resistive trainer has a short ramping up and ramping down of pressure intensity with each inspiration whereas threshold trainer produces a square waveform with each inspiration.

Conclusion

This systematic review has shown that targeted inspiratory resistive or threshold IMT significantly improves inspiratory muscle strength and endurance, and decreases dyspnea for adults with stable COPD. Since only some outcomes of exercise capacity were improved with these modes of IMT, further research is needed. Non-targeted inspiratory resistive IMT is not shown to provide any conclusive benefit. At present, the choice between using either targeted inspiratory resistive or threshold IMT rests upon clinical considerations. Training protocols must include sufficient frequency, intensity and duration of IMT and supervision may have an effect on outcomes.

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