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Inspiratory muscle training, with or without concomitant pulmonary rehabilitation, for chronic obstructive pulmonary disease (COPD) (Review)

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[Intervention Review]

Inspiratory muscle training, with or without concomitant pulmonary rehabilitation, for chronic obstructive pulmonary disease (COPD)

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ABSTRACT

Background

Inspiratory muscle training (IMT) aims to improve respiratory muscle strength and endurance. Clinical trials used various training protocols, devices and respiratory measurements to check the effectiveness of this intervention. The current guidelines reported a possible advantage of IMT, particularly in people with respiratory muscle weakness. However, it remains unclear to what extent IMT is clinically beneficial, especially when associated with pulmonary rehabilitation (PR).

Objectives

To assess the effect of inspiratory muscle training (IMT) on chronic obstructive pulmonary disease (COPD), as a stand-alone intervention and when combined with pulmonary rehabilitation (PR).

Search methods

We searched the Cochrane Airways trials register, CENTRAL, MEDLINE, Embase, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO, Physiotherapy Evidence Database (PEDro) ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform on 20 October 2021. We also checked reference lists of all primary studies and review articles.

Selection criteria

We included randomized controlled trials (RCTs) that compared IMT in combination with PR versus PR alone and IMT versus control/sham. We included different types of IMT irrespective of the mode of delivery. We excluded trials that used resistive devices without controlling the breathing pattern or a training load of less than 30% of maximal inspiratory pressure (PImax), or both.

Data collection and analysis

We used standard methods recommended by Cochrane including assessment of risk of bias with RoB 2. Our primary outcomes were dyspnea, functional exercise capacity and health-related quality of life.

Main results

We included 55 RCTs in this review. Both IMT and PR protocols varied significantly across the trials, especially in training duration, loads, devices, number/ frequency of sessions and the PR programs. Only eight trials were at low risk of bias.

PR+IMT versus PR

We included 22 trials (1446 participants) in this comparison. Based on a minimal clinically important difference (MCID) of −1 unit, we did not find an improvement in dyspnea assessed with the **Borg** scale at submaximal exercise capacity (mean difference (MD) 0.19, 95% confidence interval (CI) −0.42 to 0.79; 2 RCTs, 202 participants; moderate-certainty evidence).

We also found no improvement in dyspnea assessed with the**modified Medical Research Council dyspnea scale (mMRC)** according to an MCID between −0.5 and −1 unit (MD −0.12, 95% CI −0.39 to 0.14; 2 RCTs, 204 participants; very low-certainty evidence).

Pooling evidence for the **6-minute walk distance (6MWD)** showed an increase of 5.95 meters (95% CI −5.73 to 17.63; 12 RCTs, 1199 participants; very low-certainty evidence) and failed to reach the MCID of 26 meters. In subgroup analysis, we divided the RCTs according to the training duration and mean baseline PImax. The test for subgroup differences was not significant. Trials at low risk of bias (n = 3) demonstrated a larger effect estimate than the overall.

The summary effect of the **St George's Respiratory Questionnaire (SGRQ)** revealed an overall total score below the MCID of 4 units (MD 0.13, 95% CI −0.93 to 1.20; 7 RCTs, 908 participants; low-certainty evidence).

The summary effect of **COPD Assessment Test (CAT)** did not show an improvement in the HRQoL (MD 0.13, 95% CI −0.80 to 1.06; 2 RCTs, 657 participants; very low-certainty evidence), according to an MCID of −1.6 units.

Pooling the RCTs that reported **PImax** showed an increase of 11.46 cmH_2O (95% CI 7.42 to 15.50; 17 RCTs, 1329 participants; moderate-certainty evidence) but failed to reach the MCID of 17.2 cmH_2O. In subgroup analysis, we did not find a difference between different training durations and between studies judged with and without respiratory muscle weakness.

One abstract reported some **adverse effects** that were considered "minor and self-limited".

IMT versus control/sham

Thirty-seven RCTs with 1021 participants contributed to our second comparison. There was a trend towards an improvement when **Borg** was calculated at submaximal exercise capacity (MD −0.94, 95% CI −1.36 to −0.51; 6 RCTs, 144 participants; very low-certainty evidence). Only one trial was at a low risk of bias.

Eight studies (nine arms) used the **Baseline Dyspnea Index - Transition Dyspnea Index (BDI-TDI)**. Based on an MCID of +1 unit, they showed an improvement only with the 'total score' of the TDI (MD 2.98, 95% CI 2.07 to 3.89; 8 RCTs, 238 participants; very low-certainty evidence). We did not find a difference between studies classified as with and without respiratory muscle weakness. Only one trial was at low risk of bias.

Four studies reported the **mMRC**, revealing a possible improvement in dyspnea in the IMT group (MD −0.59, 95% CI −0.76 to −0.43; 4 RCTs, 150 participants; low-certainty evidence). Two trials were at low risk of bias.

Compared to control/sham, the MD in the **6MWD** following IMT was 35.71 (95% CI 25.68 to 45.74; 16 RCTs, 501 participants; moderate-certainty evidence). Two studies were at low risk of bias. In subgroup analysis, we did not find a difference between different training durations and between studies judged with and without respiratory muscle weakness.

Six studies reported the**SGRQ** total score, showing a larger effect in the IMT group (MD −3.85, 95% CI −8.18 to 0.48; 6 RCTs, 182 participants; very low-certainty evidence). The lower limit of the 95% CI exceeded the MCID of −4 units. Only one study was at low risk of bias.

There was an improvement in life quality with **CAT** (MD −2.97, 95% CI −3.85 to −2.10; 2 RCTs, 86 participants; moderate-certainty evidence). One trial was at low risk of bias.

Thirty-two RCTs reported **PImax**, showing an improvement without reaching the MCID (MD 14.57 cmH_2O, 95% CI 9.85 to 19.29; 32 RCTs, 916 participants; low-certainty evidence). In subgroup analysis, we did not find a difference between different training durations and between studies judged with and without respiratory muscle weakness.

None of the included RCTs reported **adverse events**.

Authors' conclusions

IMT may not improve dyspnea, functional exercise capacity and life quality when associated with PR. However, IMT is likely to improve these outcomes when provided alone.

For both interventions, a larger effect in participants with respiratory muscle weakness and with longer training durations is still to be confirmed.

PLAIN LANGUAGE SUMMARY

Are exercises for strengthening breathing muscles effective for people with chronic obstructive pulmonary disease?

Key messages

• Exercise combined with specific exercises to strengthen breathing muscles may not improve breathlessness, physical fitness and life quality. Strength of breathing muscles and endurance increased but not enough to make a difference to patients.

• Specific exercises to strengthen breathing muscles compared to no exercise may improve breathlessness, physical fitness and life quality. Strength of breathing muscles and endurance increased, but we don't know if this benefitted patients.

• We don't know whether exercise or specific exercises to strengthen breathing muscles is better for people with weakened breathing muscles who trained for several weeks.

• Future research should focus on people with weakened breathing muscles and studies should include more people.

What is chronic obstructive pulmonary disease (COPD)?

Chronic obstructive pulmonary disease (COPD) is a lung condition characterized by blockages in the airways, which cause shortness of breath and a cough. It appears after the long-term inhalation of irritating gases like cigarette smoke and chemicals. Training and strengthening the breathing muscles is thought to improve breathing and reduce air obstruction.

What exercise treatments do people with COPD use?

Health professionals use various exercises to help improve people's COPD.

• Some people undertake a program of general exercise and education to help reduce symptoms and improve their exercise capacity and life quality.

• Other people try to improve the strength and endurance of the breathing muscles through a series of breathing exercises using specific devices. This is called 'inspiratory muscle training' (IMT). The devices add resistance to breathing to strengthen the diaphragm and the intercostal muscles between the ribs - the muscles used for breathing. People may then be able to breathe in more air with each breath and be active for longer. The devices are also used by people with healthy lungs to improve their sports performance.

What did we want to find out?

We wanted to find out if exercise combined with IMT compared to exercise alone, and IMT compared to no exercise or sham IMT has a better effect on breathlessness, physical fitness and life quality. (A sham device has no effect on breathing muscles. It allows a fair test of the real devices, because people don't know which they are using.)

We also wanted to check whether IMT was associated with any unwanted effects.

What did we do?

We searched for studies that compared

• exercise combined with IMT with exercise alone; and

• IMT with no exercise or sham IMT.

We compared and summarized the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

Exercise plus IMT compared with exercise alone
We found 22 studies with 1446 participants, which lasted between 2 and 24 weeks. Exercise ranged from training only on a treadmill, with only a cycle, and a combination of exercises (training with a cycle and treadmill, muscle strengthening, stair climbing, and education). The duration and devices of IMT also varied across the studies.

We found that this combination:
• probably makes little to no difference to breathlessness (measured with different scales);
• has an unknown effect on physical fitness;

• may make little to no difference to life quality (measured with different scales);
• probably makes little to no difference to strength of breathing muscles.

IMT versus no training or sham device
We found 37 studies with 1021 participants, which lasted from 2 weeks to a year. IMT varied across the studies regarding devices, resistance, frequency and supervision.

We found out that IMT alone:
• may reduce breathlessness measured with one scale, but it is unclear if it has an effect when measured with two other scales;
• probably improves physical fitness;
• probably improves life quality when measured with one scale, but it is unclear if it has a benefit when measured with another one;
• may make little to no difference to strength of breathing muscles.

What are the limitations of the evidence?

The studies used different training durations, resistance, devices, number and frequency of sessions, and physical training programs. This makes it hard to draw firm conclusions. Overall our confidence in the conclusions is reduced because the studies were small, some participants may have been aware of which treatment they were receiving, and generally, there was some diversity in the studies.

How up to date is the evidence?

The evidence is up-to-date to 20 October 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Pulmonary rehabilitation plus inspiratory muscle training compared to pulmonary rehabilitation alone for people with chronic obstructive pulmonary disease

Pulmonary rehabilitation plus inspiratory muscle training compared to pulmonary rehabilitation alone for people with chronic obstructive pulmonary disease

Patient or population: people with chronic obstructive pulmonary disease (COPD)
Setting: community
Intervention: pulmonary rehabilitation (PR) + inspiratory muscle training (IMT)
Comparison: PR

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PR	Risk with PR +IMT				
Dyspnea assessed with Borg scale at submaximal exercise capacity Scale from 0 to 10 (worse) Follow-up: range 3 months to 4 months	The mean dyspnea was **4.65**	The mean dyspnea was **0.19 points higher** (0.42 lower to 0.79 higher)	-	202 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	The combination of PR+IMT probably results in little to no difference in dyspnea measured with Borg at submaximal exercise capacity compared to PR alone, considering an MCID of −1 unit
Dyspnea assessed with mMRC Scale from 0 to 4 (worse) Follow-up: range 1 month to 2 months	The mean dyspnea ranged from **−0.8 to −0.33**	MD **0.12 lower** (0.39 lower to 0.14 higher)	-	204 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b]	The evidence is very uncertain about the effect of the combination of PR+IMT on dyspnea measured with the mMRC compared to PR alone, considering an MCID between −0.5 and −1 unit
Functional exercise capacity assessed with 6MWD Follow-up: range 2 weeks to 6 months	The mean functional exercise capacity was **304.72** meters[c]	MD **5.95 meters higher** (5.73 lower to 17.63 higher)	-	1199 (12 RCTs)	⊕⊖⊖⊖ Very low[d,e]	The evidence is very uncertain about the effect of the combination of PR+IMT on the 6MWD compared to PR alone, considering an MCID of 26 meters

Health-related quality of life assessed with SGRQ total score Scale from 0 to 100 (worse) Follow-up: range 3 weeks to 6 months	The mean health-related quality of life was **14.9**[c]	MD **0.13 higher** (0.93 lower to 1.2 higher)	-	908 (7 RCTs)	⊕⊕⊖⊖ Low[f]	The combination of PR+IMT may result in little to no difference in health-related quality of life measured with the SGRQ compared to PR alone, considering an MCID of −4 units
Health-related quality of life assessed with CAT Scale from 0 to 40 (worse) Follow-up: range 3 weeks to 6 months	The mean health-related quality of life ranged from **−3.42 to −3**	MD **0.13 higher** (0.8 lower to 1.06 higher)	-	657 (2 RCTs)	⊕⊖⊖⊖ Very low[g,h]	The evidence is very uncertain about the effect of the combination of PR+IMT on health-related quality of life measured with the CAT compared to PR alone, considering an MCID of about −1.6 units
Inspiratory muscle strength assessed with PImax Follow-up: range 3 weeks to 6 months	The mean inspiratory muscle strength was **67.37** cmH_2O[c]	MD **11.46 cmH_2O higher** (7.42 higher to 15.50 higher)	-	1329 (17 RCTs)	⊕⊕⊕⊖ Moderate[d]	The combination of IMT+PR probably slightly increases inspiratory muscle strength (PImax) compared to PR alone, without reaching the MCID of 17.2 cmH_2O

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CAT:** COPD [chronic obstructive pulmonary disease] Assessment Test; **IMT:** inspiratory muscle training; **MD:** mean difference; **mMRC:** modified Medical Research Council dyspnoea scale; **MCID:** minimum clinically important difference; **PImax:** Maximal Inspiratory Pressure; **PR:** pulmonary rehabilitation; **RCT:** randomized controlled trial; **SGRQ:** St George's Respiratory Questionnaire; **6MWD:** six-minute walk distance

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423482112637765988.

[a]Downgraded by one level for imprecision due to small sample size (rule of thumb: at least 400 participants).
[b]Downgraded by two levels for risk of bias because all the trials are at high risk of bias.
[c]Including change and endpoint scores.

[d]Downgraded by one level for risk of bias because most of the evidence is from studies at high risk of bias and with some concern.
[e]Downgraded by two levels for inconsistency due to considerable statistical heterogeneity (I^2 statistic), confidence intervals not overlapping, and significant variations in the direction of the effects.
[f]Downgraded by two levels for risk of bias due to a considerable bias across the studies in the measurement of the outcome (lack of blinding) and all the trials are at high risk of bias and some concern.
[g]Downgraded by two levels for risk of bias due to considerable bias across the studies in the measurement of the outcome (lack of blinding) and most of the evidence is from studies at high risk of bias and some concern.
[h]Downgraded by one level for inconsistency due to considerable statistical heterogeneity and confidence intervals not overlapping .

Summary of findings 2. Inspiratory muscle training compared to control or sham for people with chronic obstructive pulmonary disease

Inspiratory muscle training compared to control or sham for people with chronic obstructive pulmonary disease

Patient or population: people with chronic obstructive pulmonary disease (COPD)
Setting: community
Intervention: inspiratory muscle training (IMT)
Comparison: control or sham

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control or sham	Risk with IMT				
Dyspnea assessed with Borg scale at submaximal exercise capacity Scale from 1 to 10 (worse) Follow-up: range 5 weeks to 4 months	The median dyspnea was **1.5**	MD **0.94 lower** (1.36 lower to 0.51 lower)	-	144 (6 RCTs)	⊕⊖⊖⊖ Very low[a,b]	IMT may improve dyspnea measured with Borg scale at submaximal exercise capacity compared to control/sham but the evidence is very uncertain, considering an MCID of −1 unit (only the lower limit of the 95% CI exceeded the MCID)
Dyspnea assessed with BDI-TDI: focal score (TDI) Scale from −9 to +9 (better) follow-up: range 2 months to 6 months	The median dyspnea was **1.2**	MD **2.98 higher** (2.07 higher to 3.89 higher)	-	238 (8 RCTs)	⊕⊖⊖⊖ Very low[b,c]	IMT may improve dyspnea measured with the BDI-TDI (Focal score) compared to control/sham but the evidence is very uncertain, considering an MCID of +1 unit
Dyspnea assessed with mMRC Scale from 0 to 4 (worse)	The median dyspnea was **0.62**	MD **0.59 lower** (0.76 lower to 0.43 lower)	-	150 (4 RCTs)	⊕⊕⊖⊖ Low[b,d]	IMT may improve dyspnea measured with the modified mMRC compared to con-

Follow-up: range 8 months to 8 months						trol/sham, considering an MCID between −0.5 and −1 unit
Functional exercise capacity assessed with 6MWD Follow-up: range 2 weeks to 12 months	The mean functional exercise capacity was **298.4** meters	MD **35.71 meters higher** (25.68 higher to 45.74 higher)	-	501 (16 RCTs)	⊕⊕⊕⊖ Moderate[d]	IMT probably improves functional exercise capacity measured with the 6MWD compared to control/sham, considering an MCID of 26 meters
Health-related quality of life assessed with SGRQ total score Scale from 0 to 100 (worse) Follow-up: range 2 months to 12 months	The median health-related quality of life was **23.61**	MD **3.85 lower** (8.18 lower to 0.48 higher)	-	182 (6 RCTs)	⊕⊖⊖⊖ Very low[e,f]	IMT may improve health-related quality of life measured with the SGRQ compared to control/sham but the evidence is very uncertain, considering an MCID of −4 units (only the lower limit of the 95% CI exceeded the MCID)
Health-related quality of life assessed with CAT Scale from 0 to 40 (worse) Follow-up: mean 2 months	The mean health-related quality of life ranged from **−0.5 to 0.3**	MD **2.97 lower** (3.85 lower to 2.1 lower)	-	86 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]	IMT probably improves health-related quality of life measured with CAT compared to control/sham, considering an MCID of about −1.6 units
Inspiratory muscle strength assessed with PImax Follow-up: range 2 weeks to 12 months	The mean inspiratory muscle strength was **51.23** cmH_2O	MD **14.57 cmH_2O higher** (9.85 higher to 19.29 higher)	-	916 (32 RCTs)	⊕⊕⊖⊖ Low[d,g,h]	IMT may increase inspiratory muscle strength (PImax) slightly compared to control/sham considering the MCID of 17.2 cmH_2O

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

BDI-TDI: Baseline Dyspnea Index - Transition Dyspnea Index;**CI:** confidence interval; **CAT:** COPD Assessment Test; **IMT:** inspiratory muscle training; **MD:** mean difference; **mMRC:** modified Medical Research Council dyspnoea scale; **MCID:** minimum clinically important difference; **PImax:** Maximal Inspiratory Pressure; **PR:** pulmonary rehabilitation; **RCT:** randomized controlled trial; **SGRQ:** St George's Respiratory Questionnaire; **6MWD:** six-minute walk distance

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423482164894599533.

[a]Downgraded by two levels for risk of bias because most of the evidence is from studies at high risk of bias and some concern, there is an issue with blinding, and high risk of bias studies show different estimates to studies at low risk of bias and some concern.
[b]Downgraded by one level for imprecision due to small sample size (rule of thumb: less than 400).
[c]Downgraded by two levels for risk of bias due to considerable bias across the studies in the measurement of the outcome (lack of blinding) and most of the evidence is from studies at high risk of bias and some concern.
[d]Downgraded by one level for risk of bias because most of the evidence is from studies at high risk of bias and with some concern.
[e]Downgraded by two levels for risk of bias because most of the evidence is from studies at high risk of bias and some concern, and high risk of bias studies show different estimate to studies at low risk of bias and some concern.
[f]Downgraded by two levels for imprecision due to small sample size (rule of thumb: less than 400) and because the 95% CI includes benefit and harm.
[g]We did not downrate inconsistency although substantial statistical heterogeneity because the studies are on one side of the line of no effect. So we are more confident about the direction of the effect.
[h]Downgraded by one level for publication bias because the funnel plot and the number of studies give rise to serious suspicions about publication bias.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a respiratory condition that includes bronchitis and emphysema. Chronic bronchitis is defined by the presence of a productive cough for at least three months per year for two consecutive years, during which other causes of cough have been excluded (GOLD 2022). Emphysema is damage to the portion of the lungs responsible for gas transfer called alveoli (Berg 2016). COPD is a significant public health issue, especially in low- and middle-income countries, where nearly 90% of deaths from COPD occur (WHO 2020). COPD was the third leading cause of global deaths in 2016 with about 3 million deaths (WHO 2018), and it is expected to remain in the third ranking until 2030 (WHO 2013).

The main risk factors for COPD are tobacco smoking, second-hand smoking, air pollution, and exposure to fuel oil fumes (GOLD 2022). COPD is characterized by a non-reversible airflow obstruction in the lungs. Exposure to irritants stimulates mucus production and damages cilia that clear away mucus and dirt; this causes air to be trapped inside airways, leading to hyperinflation (GOLD 2022; Ramos 2014). Airflow obstruction in emphysema is due to the loss of elastin, which increases lung compliance and decreases elastic recoil (Costanzo 2019). In other words, the lungs lose their ability to return spontaneously to their resting position after inhalation. COPD is a cause of disability as it affects people's ability to breathe normally and has systemic, severe, and long-term effects (Agustí 2005). Post-bronchodilator spirometry is the primary test to measure airflow obstruction. It confirms airflow limitation if the ratio between forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) is less than 70% (GOLD 2022).

Clinically, the most common symptoms are dyspnea, chronic cough, wheezing, and sputum production. Dyspnea — also known as shortness of breath or breathlessness — is the most common symptom reported by patients with COPD and is associated with a deterioration in their quality of life and physical activity (Anzueto 2017). Dyspnea results from multiple mechanisms, such as air trapping and dynamic hyperinflation, and it is associated with a significant load on the respiratory muscles (Padula 2006; O'Donnell 2007). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests a therapeutic strategy based on medical history, clinical symptoms, and life quality (ABCD stages) (GOLD 2022).

Description of the intervention

Inspiratory muscle training (IMT), also known as respiratory or ventilatory muscle training, aims to improve inspiratory muscle strength and endurance through a series of breathing exercises. It was developed in the late 1970s (Andersen 1979; Belman 1980; Leith 1976), and it has been used in people with respiratory diseases such as COPD and asthma. IMT focuses on enhancing the performance of respiratory muscles and on improving respiratory symptoms and exercise capacity (Padula 2006).

There are three main categories of IMT devices: threshold loading devices, passive and electronic flow resistive devices, and isocapnic hyperpnea devices (Belman 1994). Other devices exist, and they are reported in Menzes 2018. Most threshold trainers have an adjustable spring-loaded valve to set the resistance level from 9 cm of water (cmH_2O) to 41 cmH_2O (or from 7 cmH_2O to 41 cmH_2O) and allow changes in resistance by 2 cmH_2O (Menzes 2018). The threshold pressure is independent of the breathing pattern (Geddes 2005). The passive-resistive trainer contains holes of different diameters: the biggest hole provides the lowest resistance, whereas the narrowest hole offers the highest resistance (McConnell 2004; Menzes 2018). The respiratory load can be selected by turning the dial towards the chosen hole. However, unlike the threshold device, passive-resistive trainers depend on the inspiratory flow (Wu 2017). The electronic resistive device is similar to the passive-resistive trainer, and it has the advantage of dynamically adapting the flow resistance (Menzes 2018). Isocapnic hyperpnea trainers are based on low load and high respiratory flow (60% to 90% of maximal voluntary ventilation (MVV)) so that respiratory muscles contract at a higher speed (for an extended time) (McConnell 2004). That device contains a rebreathing bag to maintain physiological rates of CO_2, so patients breathe both fresh air and some of the expired CO_2. In addition to multiple devices of IMT, protocols for this therapy differ between teams in terms of frequency, duration, and supervision (Langer 2015).

Various measures are used to evaluate respiratory muscle strength (Laveneziana 2019). Maximal static inspiratory mouth pressure (PImax) is the most commonly used technique to assess the strength of the diaphragm and other inspiratory muscles (Pessoa 2014). It is calculated through a mouthpiece connected to a manometer, either at residual volume or at functional residual capacity (Laveneziana 2019). However, this technique requires the co-operation of patients. Other approaches to assess inspiratory muscle strength exist, such as sniff nasal inspiratory pressure (SNIP) based on a pressure sensor attached to a catheter placed in the nostril (Maillard 1998), phrenic nerve electric transcutaneous stimulation, and phrenic nerve magnetic stimulation (Caruso 2015).

How the intervention might work

Unlike inspiration, expiration is a passive process. In people with COPD, elastin in the lungs can be reduced, leading to incomplete expiration; this means air is trapped in the airways and leads to hyperinflation (Papandrinopoulou 2012). Static and dynamic distention caused by hyperinflation explains, in part, the pathophysiology of respiratory muscle dysfunction in COPD (O'Donnell 2006). Indeed, inspiratory muscles (the diaphragm, intercostal muscles, and the sternocleidomastoid muscle (SCM)) are exposed to an important load generated from hyperinflation and high airway resistance (Caron 2011). In the early stages of COPD, inspiratory muscles try to adapt to these circumstances. For example, type II muscle fibers of the diaphragm switch into type I, which are highly resistant to fatigue (Clanton 2009). There is also an increase in blood capillaries (Doucet 2004) as well as the oxidative capacity (since type I fibers have high mitochondrial density and enzymes that support the oxidative pathway, so the ability to use oxygen will be increased) (Ottenheijm 2008). At an advanced stage of the disease, oxidative stress, gas exchange abnormalities, and the changes in the chest cavity overcome adaptation mechanisms and the diaphragm will be in a position of impaired mechanical advantage. It loses up to 60% of its muscle tissue and becomes shorter and more horizontal, leading to ineffective mechanical function (Caron 2011; Ottenheijm 2008; Salito 2015). A study showed that IMT induced structural and anatomical changes in external intercostal muscles by changing the distribution of type I fibers and increasing the size of type II fibers

(Ramirez Sarmiento 2002). Overall, inspiratory muscle weakness is associated with dyspnea and respiratory failure, despite the ability of the diaphragm to adapt itself to hyperinflation (Bégin 1991; Caron 2011). IMT may improve the strength and endurance of these muscles.

In COPD, it is difficult to work on expiration flow and volume due to mechanical changes. However, it is possible to work on inspiration since it is an active process. In other words, strengthening of the inspiratory muscles increases the inspiratory flow (so there will be an increase in the tidal volume (TV)), decreases the inspiratory time, and improves the expiratory time (Beaumont 2018; Charususin 2016).

Why it is important to do this review

The clinical symptoms most often reported by patients with COPD are dyspnea, a decline in exercise capacity and an impairment in their quality of life (Spruit 2013). It is recommended to start pulmonary rehabilitation (PR) as soon as possible, ideally either during hospitalisation or soon after discharge from the hospital (Spruit 2013). Current guidelines recommend an optimal duration of eight weeks for a PR program (Rochester 2015). Usually, PR consists of physiotherapy, nutritional and psychosocial care, patient therapeutic education, and upper and lower limb training (Beaumont 2015; Spruit 2013).

The American Thoracic Society (ATS) reported that IMT may be beneficial as a stand-alone intervention and when added to PR in patients with respiratory muscle weakness (Spruit 2013). However, the potential effects of combining IMT and PR are still unclear. Indeed, some recent randomized controlled trials (RCTs) did not find significant improvements in patients with severe COPD (Beaumont 2018; Charususin 2018), and most of the published clinical trials and meta-analyses recommended further investigation (Beaumont 2018a; Gosselink 2011; Langer 2015; Lötters 2002). Furthermore, there is a lack of certainty in the linear relation between PImax, FEV1, and clinical outcomes. In other words, many RCTs showed that IMT improves PImax, but the extent to which this improvement is clinically significant (i.e. the minimal clinically important difference) has not yet been proved (Beaumont 2018; Schultz 2018). The benefits of unsupervised IMT are also unclear (Langer 2015).

Although many meta-analyses have been published on different modes and modalities of IMT (Geddes 2005; Geddes 2008; Gosselink 2011; Lötters 2002; O'Brien 2008; Smith 1992), several questions remain unanswered. For example, the optimum duration of a training program has not been established, nor has the effect of IMT on dyspnea and quality of life. There is also a need to investigate its additional effect when added to PR. Moreover, the published meta-analyses are a few years old, and there are now other studies to be included. A recent clinical trial (Langer 2015), showed that factors other than inspiratory muscle weakness might influence the performance of IMT, such as the variety of protocols, and it is worth exploring these.

OBJECTIVES

To assess the effect of inspiratory muscle training (IMT) on chronic obstructive pulmonary disease (COPD) as a stand-alone intervention and when combined with pulmonary rehabilitation (PR).

METHODS

Criteria for considering studies for this review

Types of studies

We included published randomized controlled trials (RCTs), as full-text articles or abstracts, as well as unpublished RCTs. We included abstracts if they reported at least the number of participants in each group, the duration of the intervention, and the training load. We accepted trials with more than two arms. We excluded observational studies, quasi-RCTs and cross-over trials since no washout period for IMT has been established.

Types of participants

We included people with COPD diagnosed according to international standards (GOLD 2022), at any stage of the disease. We placed no restrictions on age, duration, setting, or the kind of pulmonary rehabilitation. We planned to include RCTs with different conditions for the same intervention of interest as long as we could obtain the data of participants with COPD separately.

We classified COPD according to GOLD 2022 stages based on the predicted value of Forced Expiratory Pressure in 1 Second (FEV1):

- GOLD 1 - mild: FEV1 ≥ 80% predicted
- GOLD 2 - moderate: 50% ≤ FEV1 < 80% predicted
- GOLD 3 - severe: 30% ≤ FEV1 < 50% predicted
- GOLD 4 - very severe: FEV1 < 30% predicted

Types of interventions

The review consists of two comparisons, as follows.

- IMT plus PR versus PR
- IMT versus no treatment or sham

First, we included trials that explored the benefit of combining IMT and PR compared to PR only. PR consists of, but is not limited to, exercise training, physiotherapy, therapeutic education, and nutritional and psychosocial care (McCarthy 2015). We included different types of IMT irrespective of the mode of delivery: resistance training (high load, low frequency) or endurance training (low load, high frequency), device (i.e. threshold loading, resistive flow device, isocapnic hyperpnea). We made no restrictions on the duration, supervision (home-based or in a healthcare setting), or timing (during hospitalization or later) of the intervention. We excluded studies where the training was conducted only once per week (face-to-face or distance sessions), regardless of the total duration of the clinical trial. The minimum accepted training load was 30% of PImax or more (Hill 2010). We also excluded trials that used a resistive device without controlling the breathing pattern. If a study conducted an incremental training load that started less than 30% of PImax, we considered only the follow-up from which the load was equal to our threshold.

According to the proportion of supervised sessions, we defined supervision as:

- under 20%: unsupervised;
- 20% to 70%: partially supervised; and
- above 70%: fully supervised.

For the second comparison, we compared IMT with control or sham. We defined sham training as using a resistance of less than 30% of PImax. We accepted control groups if they did not receive any intervention or received an intervention other than exercise training to blind participants (e.g. therapeutic education). We made the exception for breathing exercises if participants in the control group did not receive more than one type of training (e.g. diaphragmatic breathing, pursed lips breathing), and the purpose was not to compare it with IMT.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies.

Primary outcomes

Dyspnea: the essential scale for our primary analysis is the Borg scale (Borg 1982). We only included the Borg score when it was measured at isotime. We analysed all the scales reported by the trials as long as they were validated, and when possible, we combined them in a meta-analysis. The other included scales were: Baseline and Transition Dyspnea Indexes (BDI-TDI) (Mahler 2005), and Modified Medical Research Council (mMRC) (Bestall 1999).

Functional exercise capacity: this can be assessed through multiple tests. We did not exclude studies based on the test used. However, for our analysis, we considered that the most important measurement is the six-minute walk distance (6MWD) (Holland 2014). Therefore, we included it in the summary of findings table and considered it for subgroup analysis. We included other tests and reported them either in qualitative or quantitative analysis.

Health-related quality of life: we accepted any scales as long as they were validated. This includes the St. George's Respiratory Questionnaire (SGRQ) (Jones 1992), the chronic respiratory questionnaire (CRQ) (Wijkstra 1994) and the COPD assessment test (CAT) (Jones 2009).

Secondary outcomes

Inspiratory muscle strength: measured by maximal static inspiratory mouth pressure (PImax) (Laveneziana 2019).

Laboratory exercise tests: we were primarily interested in the maximal oxygen uptake (VO_2peak), which could be measured through:

- incremental cycle ergometer test;
- endurance cycle ergometer test;
- treadmill test.

Respiratory muscle endurance:

- **Respiratory muscle endurance pressure (P_{thmax}):** measured by incremental load testing (Laveneziana 2019). It is the maximally tolerated pressure when breathing against a continuously increasing load.
- **Respiratory muscle endurance time (T_{lim}):** measured by constant load testing (Laveneziana 2019). It is the time an individual can maintain breathing against a fixed load. It can be carried out either through a threshold/resistive or isocapnic hyperpnea device.
- **Maximal voluntary ventilation (MVV):** this is the total volume of expired air between 12 seconds to 15 seconds of deep and fast respiration. MVV is usually compared to predicted MVV (calculated through the forced expiratory volume at 1 second) (Wood 2017).

Respiratory function:

- forced expiratory volume at 1 second (FEV1)
- residual volume

Adverse events: as defined by the trial authors.

We collected outcomes irrespective of the time frame and summary statistics (change from baseline or final values), with a preference for change score. For each trial, we analysed only the outcomes listed above and not all the outcomes reported in the trial. However, we included all the tests and measurements used for the same outcome.

Search methods for identification of studies

Electronic searches

We searched for all published and unpublished RCTs regarding IMT for COPD, in consultation with the Cochrane Airways Information Specialist. We did not apply restrictions on language or publication status (i.e. published, ongoing, or unpublished).

We searched the following databases for relevant trials in October 2020 and we updated our literature search on 23 August 2021 and on 20 October 2022.

- Cochrane Airways Trials Register (Cochrane Airways 2022), via the Cochrane Register of Studies, all years to date (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Register of Studies, all years to date (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- MEDLINE Ovid SP ALL, 1946 to 12 October 2020 (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- Embase Ovid SP, 1974 to week 41 2020 (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- PsycINFO Ovid SP, 1967 to October week 1 2020 (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO, 1937 to 13 October 2020 (searched 13 October 2020, 23 August 2021 and 20 October 2022)
- Physiotherapy Evidence Database (PEDro), 1999 onwards (searched 13 October 2020, 23 August 2021 and 20 October 2022)

We searched the following trials registries.

- US National Institutes of Health Ongoing Trials Register, ClinicalTrials.gov(searched 13 October 2020, 23 August 2021 and 20 October 2022)
- World Health Organization International Clinical Trials Registry Platform(searched 13 October 2020, 23 August 2021 and 20 October 2022)

The database search strategies are listed in Appendix 1. The search strategy was developed in MEDLINE by the Cochrane Airways Information Specialist in collaboration with the authors and peer-

reviewed by another Cochrane Information Specialist using the PRESS checklist (McGowan 2016). The MEDLINE search strategy was then adapted appropriately for each database.

All databases and trial registries were searched from their inception to the present, with no restriction on language or type of publication. Hand-searched conference abstracts and grey literature were identified through the Cochrane Airways Trials Register and CENTRAL. When possible, A native-language speaker translated studies written in a language other than English.

Searching other resources

We checked the reference lists of all primary studies and reviews for additional references. We searched for relevant manufacturers' websites for device information. We searched on PubMed for errata or retractions from included studies published in full-text and, when possible, reported the date this was done within the review.

Data collection and analysis

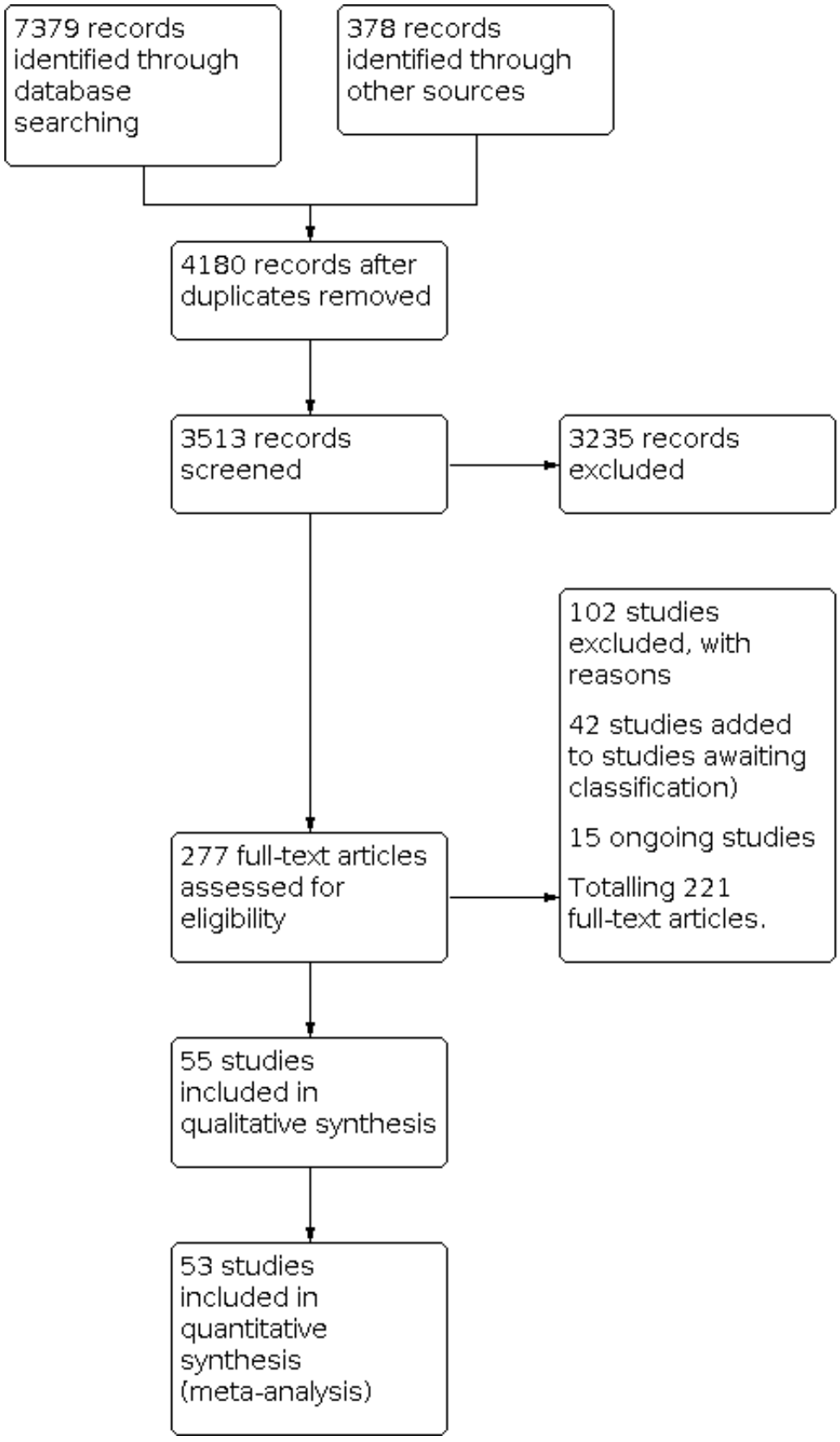
Selection of studies

Two review authors from complementary disciplines (OA and WF) independently screened the titles and abstracts of the search results using Covidence, and they coded them as 'include' (eligible or potentially eligible/unclear) or 'exclude'. We retrieved full-text study reports of all potentially eligible studies, and two review authors (OA and WF) independently screened them for inclusion while also recording the reasons for excluding ineligible studies. We retrieved the full text of potentially relevant reports and removed duplicate records using Covidence.

When appropriate, we contacted the study authors to request further information. We also contacted the manufacturer of the IMT device when we did not understand the concept of training. We resolved disagreements through discussion, without the need for a third review author. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and the 'Characteristics of excluded studies' table (Moher 2009).

Figure 1.



Data extraction and management

Two review authors (OA and AK) used a data collection form that we piloted on at least one study in the review to extract characteristics from included studies. We extracted the data using Covidence and an Excel spreadsheet. We planned to record any missing information as unclear or not described. Each form included the following information.

- General information: study ID, author contact detail, and the person who is completing the form
- Methods: aims of the study, study design, total study duration
- Participants: inclusion criteria, exclusion criteria, total number randomized, number randomized per group, mean age, age range, sex, COPD stage, clusters (if applicable), number missing, reasons for missing participants, number of participants moved from one group to another, reasons moved, baseline imbalances, and subgroup analysis
- Intervention/comparison groups: type of group, type of intervention, type of control, duration, supervision, setting, device, intensity, frequency, type of training (strength/endurance)
- Outcomes: primary and secondary outcomes, baseline characteristics, and time points
- Notes: funding for studies and notable conflicts of interest of trial authors

Two review authors (OA and AK) independently extracted outcome data from included studies. We noted in the Characteristics of included studies tables if outcome data were not reported in a usable way or if some of the data were missing. We resolved disagreements by reaching a consensus or by involving a third review author (SK). If we identified multiple reports from the same study, we would extract data from all reports directly into a single data collection form. One review author (OA) transferred data into the Review Manager 5 file (Review Manager 2020). We double-checked that data had been entered correctly by comparing data presented in the systematic review against the study reports. A second review author (WF) spot-checked study characteristics for accuracy against the study report.

Assessment of risk of bias in included studies

Two review authors (OA and TL) assessed the risk of bias independently for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We resolved any disagreements by discussion or by involving another review author (SK). We assessed the risk of bias according to the following domains.

- Bias arising from the randomization process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We used RoB 2 to assess risk of bias in randomized studies (Sterne 2019). We used the RoB 2 Excel tool to complete the risk of bias assessment. We used RevMan Web to generate traffic light plots of the domain-level judgments for each outcome (RevMan Web 2022).

Our effect of interest was the assignment to the intervention at baseline and our main outcomes were those listed in the summary of findings tables. We judged each outcome as being at low risk, some concerns, or high risk according to the RoB 2 algorithm. We provided a quote from the study report, together with a justification for our judgment, in the risk of bias table.

Where information on risk of bias relates to unpublished data or correspondence with a trial author, we noted this in the risk of bias table. To detect reporting bias, we compared the study protocol with the published report, and we contacted the study authors to identify missing or partially reported data. If more than 10 studies were included in the meta-analysis, we created a funnel plot to explore publication bias. None of the included studies was a cluster-RCT.

We incorporated the risk of bias assessment in the Results section of the review and it was also part of the GRADE assessment of the certainty of evidence (along with precision, directness, consistency, and publication bias). When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome. Our primary analysis included all the studies without taking the risk of bias judgments into account.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the 'Differences between protocol and review' section of this systematic review.

Measures of treatment effect

All of our outcomes were continuous data. We calculated a mean difference (MD) with 95% confidence intervals (CIs) where studies used the same scale, and the standardised mean difference (SMD) with 95% CIs where studies used different scales to measure the same concept. We interpreted SMD analysis following the rule of thumb based on Cohen's d effect size (Cohen 1988):

- 0.2 represents a small effect;
- 0.5 represents a medium effect;
- 0.8 represents a large effect.

Depending on how studies reported ordinal data, we analysed the scales as continuous (since all of them were longer than five). We presented all results with a 95% CI.

We undertook a meta-analysis when it was meaningful. That is to say, it made sense to combine the data, and the populations, interventions and outcomes were similar enough to be pooled in the same forest plot. If both change-from-baseline and end-point scores were available for continuous data, we used change-from-baseline, unless there was a low correlation between measurements in individuals.

If adjusted analyses were available (analysis of variance (ANOVA) or analysis of covariance (ANCOVA)), we used these as a preference in our meta-analyses. If the adjusted MD was reported, we included it in the meta-analysis using the Generic Inverse Variance method unless adjusted and unadjusted analyses were similar.

Unit of analysis issues

- **Cluster-RCTs and dichotomous outcomes:** were not included in the review.

- **Repeated observations on participants:** if studies reported outcomes at multiple time points, we chose the longest follow-up period to keep consistent with the studies. We divided the duration of follow-up into categories to explore possible differences in the effect estimate. More information is in 'Subgroup analysis and investigation of heterogeneity'.
- **Studies with more than two groups:** we included only the relevant arms.
- **Two comparisons from the same study within the same meta-analysis:** we combined the active arms or halved the control group to avoid double-counting.

Dealing with missing data

We requested missing or unclear numerical data from study authors (such as for conference abstracts; randomization, the training load). We did not use imputation because most of the data were available, and it was not possible to receive the participants' data. For studies that reported only the overall effect estimate without providing data for each intervention group, we used the generic inverse variance method to meta-analyse them.

We used the methods recommended by McGrath 2020 to convert median to mean.

When the data were presented only graphically, and in case we could not get numerical information from the study authors, we used WebPlotDigitizer to extract them from the graphs.

Assessment of heterogeneity

We assessed statistical heterogeneity through visual inspection by detecting overlapping confidence intervals in the forest plot. We used the Chi^2 test with a P value of 0.05 to indicate the statistical significance and the I^2 test (Higgins 2003), to explore statistical heterogeneity (we considered a value over 50% to represent substantial heterogeneity). We performed subgroup analysis to investigate heterogeneity. We also discussed clinical heterogeneity (e.g. COPD stages) and methodological heterogeneity (e.g. duration of the intervention, number of sessions per week, the total number of sessions, the training load).

Assessment of reporting biases

We created funnel plots to explore possible small-study and publication biases for functional exercise capacity (6MWD) and respiratory muscle strength (PImax) since they were included in the summary of findings table and more than 10 trials explored these outcomes.

Data synthesis

We expected the included studies to have many variables that could influence the pooled effect estimate. Therefore, we used a random-effects model for the analysis. We ran a meta-analysis when it was appropriate; that is, where it made sense to combine different effect estimates and the studies were homogeneous enough to allow reliable interpretation of the analysis.

Ordinal outcomes were meta-analysed as continuous data following the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). Two authors (OA and AK) analysed the data using RevMan 5 (Review Manager 2020), and RevMan Web (RevMan Web 2022).

Subgroup analysis and investigation of heterogeneity

We carried out the following subgroup analyses.

- Duration of intervention: short-term (less than four weeks), medium-term (between four weeks and seven weeks and six days), long-term (eight weeks and longer).
- Respiratory muscle strength (PImax): studies with participants with respiratory muscle weakness (the mean baseline PImax of the participants was less than or equal to 60 cmH_2O) or without respiratory muscle weakness (the mean baseline PImax of the participants was greater than 60 cmH_2O).

We used the following outcomes in the subgroup analyses.

- Dyspnea: Baseline Dyspnea Index-Transition Dyspnea Index (BDI-TDI)
- Functional exercise capacity: 6-minute walk distance (6MWD)
- Respiratory muscle strength (PImax)

We included within-study data when available. We used the formal test for subgroup interactions in RevMan Web (RevMan Web 2022).

Sensitivity analysis

We performed the following sensitivity analyses.

- We removed from the primary analysis studies judged to be at high risk of bias and some concerns.
- We compared the results of the random-effects and fixed-effet models for the BDI-TDI, the 6MWD, the SGRQ and PImax.

We considered studies to be at high risk of bias overall if we judged at least one of the domains to be high risk.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables (Summary of findings 1, Summary of findings 2) including the following outcomes.

- Dyspnea: Borg scale, mMRC and BDI-TDI
- Functional exercise capacity: 6MWD
- Health-related quality of life: SGRQ, COPD Assessment Test (CAT)
- Inspiratory muscle strength: PImax

We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data for the prespecified outcomes. Our time point was the end of the study. We used the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021), and the GRADE Handbook, using GRADEpro GDT software. We justified all decisions to downgrade the quality of studies using footnotes and we made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

Details are available in Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies tables.

Results of the search

We identified from the literature search 7379 records through database searching and 378 from other sources (International Clinical Trials Registry Platform (ICTRP); Epistemonikos).

After removing duplicates and screening titles and abstracts, we checked the eligibility of 277 studies through full-text review (see Figure 1). Searching the reference lists of past published systematic reviews did not reveal further eligible records. In the end, we included 55 studies in this review, of which six RCTs had more than two arms. Of the 55 studies, 53 contributed data to meta-analyses.

When contact details were available, we contacted the study authors for clarification. We classified 42 studies as 'awaiting classification' because of insufficient data (although we contacted study authors) or because we couldn't find the abstract (only the title was available in Covidence), and 15 as ongoing studies.

One study in Chinese (ZhouL 2016), and one in Spanish (Bustamante 2007), were translated into English by native speakers (see Acknowledgements). One study in Japanese (Okura 2020) was translated into English using Google Translate.

Included studies

Comparison 1: pulmonary rehabilitation plus inspiratory muscle training versus pulmonary rehabilitation

Population

We included 22 RCTs with 1446 participants in this comparison. We classified the COPD stages according to post-bronchodilator forced expiratory volume in one second (FEV1) (GOLD 2022). They ranged from mild to moderate (Tout 2013), moderate to severe (Abedi Yekta 2019; Berry 1996; Dekhuijzen 1991; Larson 1999; Magadle 2007; Majewska-Pulsakowska 2016; Schultz 2018; Wang 2017), mild to very severe (Paneroni 2018), moderate to very severe (Beaumont 2015; Charususin 2018; Fanfa Bordin 2020; Mador 2005; Tounsi 2021), and severe to very severe (Beaumont 2018; Dellweg 2017; Weiner 1992; Weiner 2000). Three studies did not report COPD stage.

The number of participants in the intervention group (PR+IMT) was 742. The mean age ranged from 51.33 to 70.8 years, and the mean body mass index (BMI) ranged from 21.31 to 28.8 kg/m^2. The number of participants in the control group (PR only) was 704. The mean age ranged from 53.5 to 70.8 years, and the mean BMI ranged from 22.4 to 29.68 Kg/m^2. In the studies that reported gender, there were around 763 men and 482 women.

Intervention

Pulmonary rehabilitation

The rehabilitation programs varied across the studies. They ranged from training with only a treadmill (Abedi Yekta 2019), with only a cycle ergometer (Larson 1999), and a combination of training protocols in the remaining studies (training with cycle and treadmill, limb muscles strengthening exercises, stair climbing, and therapeutic patient education programs). Five studies monitored training intensity according to heart rate: 50% (Weiner 1992), 60% (Abedi Yekta 2019; Fanfa Bordin 2020), 80% (Dekhuijzen 1991) and 85% (Larson 1999). One study (Tounsi 2021) individualized the training program based on 60% to 80% of the average speed achieved during the six-minute walk test.

Inspiratory muscle training

Two studies trained their participants for two days a week (Abedi Yekta 2019; Tout 2013), six studies for three days a week (Fanfa Bordin 2020; Mador 2005; Magadle 2007; Wang 2017; Weiner 1992; Weiner 2000), eight studies reported five days a week (Beaumont 2015; Beaumont 2018; De Farias 2019; Dekhuijzen 1991; Dellweg 2017; Larson 1999; Majewska-Pulsakowska 2016; Paneroni 2018), and four studies trained their participants for the whole week (Berry 1996; Charususin 2018; Schultz 2018; Tounsi 2021). Two studies (Masanga 2011; Sykes 2005) did not provide details about the training. The number of weeks ranged from two weeks (Paneroni 2018) to 24 weeks (Magadle 2007).

The training was unsupervised in one study (Majewska-Pulsakowska 2016), partially supervised in three studies (De Farias 2019; Larson 1999; Schultz 2018), and fully supervised in the remaining studies.

Three trials performed endurance training, using SpiroTiger (De Farias 2019; Paneroni 2018), and normocapnic hyperpnea (Mador 2005), respectively. The other RCTs conducted strength training with Powerbreathe devices, Threshold IMT device, and Respifit S-Unit. Five studies did not change the training loads during the study, ranging from 30% to 80% of PImax. In the other RCTs, the training load increased from 15% to 60% of PImax (Weiner 2000), from 30% to 60% of PImax (Abedi Yekta 2019; Larson 1999; Majewska-Pulsakowska 2016; Schultz 2018; Sykes 2005; Tout 2013), from 50% to 80% of PImax (Berry 1996; Tounsi 2021; Weiner 1992), from 35% to 80% (De Farias 2019), from 50% to 60% (Beaumont 2018), from 50% to 84% of PImax (Charususin 2018), and from 66% to 85% of Maximal Voluntary Ventilation (MVV) (Paneroni 2018).

In Magadle 2007 and Weiner 2000, participants received respectively three months and six months of PR before being allocated to continue with PR alone or to receive IMT.

Comparisons

All the studies focused on our main comparison (PR+IMT vs PR), and there were no indirect comparisons. Three RCTs (Abedi Yekta 2019; Larson 1999; Majewska-Pulsakowska 2016), had four arms, including both comparisons. One trial had three arms (De Farias 2019). We included the appropriate comparison separately.

Primary outcomes

Dyspnea: two studies explored dyspnea with the Borg scale at isotime and the Modified Medical Research Council (mMRC) scale, one study (Schultz 2018), with BDI-TDI, and two studies (Beaumont 2015; Beaumont 2018), reported the Multidimensional Dyspnea Profile (MDP).

Functional exercise capacity: 12 studies measured functional exercise capacity with the 6MWD, three studies used the 12-

minute walk distance (12MWD), three studies used exercise time, and five studies used maximal exercise capacity (Wmax). For the latter measurement, Charususin 2018 calculated Wmax by asking participants to cycle at a load of 20 watts (w) and then increasing it by 10 w/min until symptom limitation. Mador 2005 followed a similar protocol starting at no load until the participant could no longer continue cycling for 30 seconds. Dekhuijzen 1991 increased the load by 10% of the predicted Wmax, which was measured through the following formula: "Wmax predicted = 1.7x weight (kg) + 40x FEV,(L)-25". Wang 2017 chose an incremental load of 5 w/min or 10 w/min.

Health-related quality of life (HRQoL): seven studies assessed HRQoL with the SGRQ, three studies used the Chronic Respiratory Disease Questionnaire (CRQ), two studies used the COPD Assessment Test (CAT), and one study used the Clinical COPD Questionnaire (CCQ).

Secondary outcomes

Inspiratory muscle strength (PImax): 17 studies reported PImax. Eight of these studies measured it at residual volume.

Laboratory exercise test (VO_2peak): five trials measured VO_2peak . All studies except for Berry 1996 reported VO_2peak in L/min. So we used the mean weight of each group in Berry 1996 to convert from mL/kg/min to L/min.

Respiratory muscle endurance strength (P_{thmax}): two studies measured P_{thmax} (Larson 1999; Weiner 1992).

Respiratory muscle endurance time (T_{lim}) was measured by asking participants to breathe until exhaustion against a load of 30% of PImax (Paneroni 2018), 50% to 60% of PImax (Charususin 2018), 70% of PImax (Dekhuijzen 1991), 70% of MVV (Mador 2005), and 70% to 75% of MVV (Paneroni 2018).

FEV1: six studies reported FEV1 as percentage of predicted and liters. Three studies (Berry 1996; Paneroni 2018; Wang 2017), reported MVV, and one study (Charususin 2018), reported residual volume

Only one abstract (Masanga 2011), reported adverse events.

For both our primary and secondary outcomes, we did not include data from Sykes 2005 in our primary analysis.

Comparison 2: inspiratory muscle training versus control/sham

Population

We included 37 RCTs with 1021 participants in this comparison. As in comparison 1, we classified COPD stages according to post-bronchodilator FEV1 (GOLD 2022). They ranged from moderate (Leelarungrayub 2017), severe (Lisboa 1997, Weiner 2003; Weiner 2006), mild to severe (Bavarsad 2015), mild to very severe (Dacha 2019), moderate to severe (Abedi Yekta 2019; Belman 1988; Bustamante 2007; Harver 1989; Hsiao 2003; Koppers 2006; Larson 1999; Majewska-Pulsakowska 2016; Petrovic 2012; Saka 2021; Sanchez Riera 2001; Scherer 2000; Wu 2017; Xu 2018), moderate to very severe (Berton 2015; Chuang 2017; Heijdra 1996; Langer 2018; Nikoletou 2016; Saher 2021), and severe to very severe (Beckerman 2005; Covey 2001; Hill 2006; Hill 2007; Kim 1993; Larson 1988; Preusser 1994; Ramirez Sarmiento 2002; ZhouL 2016).

The number of participants in the IMT group was 526. The mean age ranged from 51.8 to 70.4 years, and the mean BMI ranged from 19.25 to 29 kg/m^2. For studies that reported gender, there were in total 268 men and 129 women. The number of participants in the control group (control/sham) was 495. The mean age ranged from 54.2 to 71.1 years, and the mean BMI ranged from 18.54 to 28.8 kg/m^2. For studies that reported gender, there were 269 men and 132 women

Intervention

Inspiratory muscle training

Participants trained from two days a week (Abedi Yekta 2019), to the whole week (Beckerman 2005; Berton 2015; Bustamante 2007; Dacha 2019; Harver 1989; Kim 1993; Koppers 2006; Langer 2018; Larson 1988; Petrovic 2012; Xu 2018). The duration of the intervention ranged from two weeks (Saher 2021) to a year (Beckerman 2005), and the total duration of training ranged from four hours (Abedi Yekta 2019) to 144 hours (Beckerman 2005).

Eight studies conducted training with resistive devices. Three studies (Belman 1988; Harver 1989; Wu 2017), used Pflex (Respironics Inc, Pittsburgh, PA, USA) device, one study (Leelarungrayub 2017), used Portex (Smith Medical ASD), one study (Hsiao 2003), used Respirex (Respirex®2, DHD 22-1000, Diemolding Healthcare Division, Canastota, NY, USA), two studies (Heijdra 1996; Sanchez Riera 2001), used INSPIRx (Intertech Resources Inc; Ft. Myers, FL; Respirecare Medical Inc., The Hague, the Netherlands), and one study (Bavarsad 2015), used Respivol (Medinet, Milano, Italy).

Participants underwent endurance training with Normocapnic Hyperpnea in two RCTs (Koppers 2006; Scherer 2000), and both endurance and strength training in one RCT (Petrovic 2012), using Respifit S (Mauerbach, Austria). The remaining 25 studies conducted IMT with either Threshold IMT or Powerbreathe devices.

Two trials trained their participants 'as tolerated' (Belman 1988; Bustamante 2007), and one trial (Bavarsad 2015), used an incentive spirometer device at a load equal to or more than the inspiratory volume. The training load increased from 30% to 60% of PImax in six trials (Abedi Yekta 2019; Covey 2001; Larson 1999; Majewska-Pulsakowska 2016; Nikoletou 2016; Saher 2021), 30% to 45% in one trial (Xu 2018), from 15% to 60% of PImax in two trials (Weiner 2003; Beckerman 2005), from 9% to 100% in one trial (Leelarungrayub 2017), from 50% to 100% of PImax in two trials (Hill 2006; Langer 2018) and approximately from 50% to 133% in one trial (15 to 40 cmH_20) (Chuang 2017) The remaining 23 studies chose a fixed load that ranged from 30% to 80% of PImax.

The training was fully supervised in eight studies, partially supervised in two studies, and unsupervised in 20 studies. Six studies did not report details of supervision (Harver 1989; Hill 2007; Petrovic 2012; Saher 2021; Weiner 2003; Weiner 2006).

Control/sham

Twenty-two studies used a sham IMT while 15 studies did not provide any intervention to the control group. One study (Cutrim 2019), provided diaphragmatic breathing at a rate of 15 to 20 breaths/min for both the intervention and the control groups. Participants in the control group underwent therapeutic patient education and pursed lips breathing (Covey 2001), and therapeutic patient education (Larson 1999).

Comparison

All the studies focused on our main comparison (IMT versus control/sham), and there were no indirect comparisons. Two studies (Hsiao 2003; Wu 2017), had three arms, including two intervention groups (each group used a different device or protocol) and a control group. When two arms from the same study were included in a forest plot, we halved the number of participants in the control group.

As for comparison 1, we extracted the appropriate arms from Abedi Yekta 2019, Larson 1999 and Majewska-Pulsakowska 2016.

Primary outcomes

Dyspnea: six studies measured dyspnea with the Borg scale at isotime. Eight studies assessed dyspnea with BDI-TDI and four studies with the mMRC.

Functional exercise capacity: 16 studies measured functional exercise capacity with the 6MWD, three studies with 12MWD, seven studies with Wmax, five studies with exercise time, and two studies with the shuttle walk test (SWT). Hill 2006 and Koppers 2006 measured Wmax by increasing the work rate by 10% per minute; Larson 1999 asked the participants to warm up by pedalling for 3 minutes at 10 w followed by 2 minutes at 20 w, and then they started the graded cycle at 30 w; and Lisboa 1997 increased the load by 75 kpm every 2 minutes. Sanchez Riera 2001, and Wu 2017 increased the work rate by 10 w/min after one minute of unloaded pedalling.

To measure exercise time, Berton 2015 asked the participants to cycle at 75% of Wmax; Koppers 2006 set the load at 50% of PImax; Scherer 2000) measured it on a treadmill set to 80% of the incline and to 100% of the speed reached at VO_2peak; and Wu 2017 considered it as the time to reach Wmax.

Health-Related Quality of Life (HRQoL): six studies assessed HRQoL with the SGRQ, five studies used CRQ, two studies used CAT, two studies used SF-36 (Chuang 2017; Nikoletou 2016), and one study used the CCQ (Leelarungrayub 2017).

Secondary outcomes

Inspiratory muscle strength (PImax): 32 studies reported PImax. Fourteen studies measured it at residual volume, 10 studies at functional residual capacity, one study reported both measurements, and the remaining studies did not report the measurement method.

Laboratory exercise test (VO_2peak): 11 studies reported VO_2peak.

Respiratory muscle endurance pressure (P_{thmax}): five studies (Hill 2006; Koppers 2006; Preusser 1994; Ramirez Sarmiento 2002; Weiner 2003), followed the protocol of Nickerson 1982. One study (Larson 1999), started with an initial load of 30% of PImax and increased by 5.7 cmH_2O until exhaustion.

Respiratory muscle endurance time (T_{lim}): 10 studies reported T_{lim}. Langer 2018, Nikoletou 2016 and Petrovic 2012 asked the participants to breathe as long as possible against 50% to 60% of PImax, and Hill 2006 and Ramirez Sarmiento 2002 asked them to breathe against 80% of PImax. Bustamante 2007 set the load at 66% of PImax, Hsiao 2003 at 70%, and Scherer 2000 at 66% or 75% of MVV.

MVV: two studies measured MVV (Belman 1988; Harver 1989)

Residual volume: two studies measured residual volume (Ramirez Sarmiento 2002; Hill 2006).

Forced expiratory volume at 1 second (FEV1): 10 studies reported FEV1 in %Pred, and 12 studies in litrs.

Adverse events: none of the included studies reported adverse events.

Excluded studies

We excluded 133 studies after the full-text review. For further details, please refer to Characteristics of excluded studies.

Risk of bias in included studies

We present the risk of bias assessment for each outcome, including all domain judgments and support for judgments, in a spreadsheet (Ammous 2022). We generated traffic light plots in most forest plots of our primary outcomes and for PImax in the secondary outcomes.

Comparison 1. Pulmonary rehabilitation plus inspiratory muscle training versus pulmonary rehabilitation

- **Dyspnea:** one study was at low risk of bias for dyspnea (Borg and mMRC; Charususin 2018), while three others were at high risk of bias. Larson 1999 had issues with intention to treat (ITT) analysis (the number of participants that were not analyzed could impact the results), missing data could depend on its true value and participants were not blinded. Both Beaumont 2018 and Wang 2017 did not blind participants.
- **Functional exercise capacity:** three studies were at low risk of bias for functional exercise capacity (6MWD; Beaumont 2018; Charususin 2018; Dellweg 2017). Most studies that we judged at some concern did not provide sufficient details about allocation concealment, excluding participants from the analysis (less than 5%) and only the journal article was available. We considered one study at high risk of bias because missingness is likely to depend on its true value (Paneroni 2018), and another study because of a lack of details about the randomization process (Tout 2013).
- **Health-related quality of life:** no study was at low risk of bias for the SGRQ and CAT. The main issue across the studies was the lack of blinding. One study was at low risk of bias for CRQ (Charususin 2018), and the two others were at high risk of bias because of issues with ITT analysis (Larson 1999) and lack of blinding (Mador 2005).
- **Inspiratory muscle strength:** six studies were at low risk of bias (PImax; Beaumont 2018; Charususin 2018; Dellweg 2017; Fanfa Bordin 2020; Schultz 2018; Tounsi 2021). Most studies were at some concern because of a lack of details about allocation concealment and only the journal article was available. Two studies were considered at high risk of bias (Larson 1999; Paneroni 2018), because missingness is likely to depend on its true value and one study because of a lack of details about the randomization process (Tout 2013).

Comparison 2. Inspiratory muscle training versus control/sham

- **Dyspnea**: one study was at low risk of bias for dyspnea (Borg; Langer 2018), two studies were at high risk of bias because participants were not blinded (Larson 1988; Petrovic 2012), and the others were at some concern because lack of details about allocation concealment. Similarly, only Langer 2018 was at low risk of bias for BDI-TDI. We judged Harver 1989 at high risk of bias because the authors did not mention the reasons behind missing data, Weiner 2003 because the data in the graph were different from the text and Wu 2017 because participants were not blinded. For mMRC, from the four included studies, two studies were at low risk of bias (Langer 2018; Xu 2018), one study at some concern because lack of details about allocation concealment (Saka 2021), and one study at high risk of bias because participants were not blinded (ZhouL 2016).
- **Functional exercise capacity:** two studies were at low risk of bias (6MWD; Cutrim 2019; Xu 2018). Four studies were at high risk of bias because of issues with ITT analysis (Beckerman 2005; Hsiao 2003; Ramirez Sarmiento 2002; Saher 2021), lack of details about missing data (Leelarungrayub 2017), and the data in the graph were different from the text (Weiner 2003). The remaining studies were at some concern because of the lack of details about allocation concealment.
- **Health-related quality of life:** only Xu 2018 was at low risk of bias for the SGRQ and CAT. Most of the studies that reported the SGRQ were at some concern because of the lack of details about allocation concealment (Berton 2015; Saka 2021), lack of details in the trial register (Saka 2021), and no information about whether adjusted analysis was planned in advance (Berton 2015). All the studies that reported CRQ were at high risk of bias (mainly because participants were not blinded) and some concern (lack of details about allocation concealment and issues with the reported results).
- **Inspiratory muscle strength:** only three studies were at low risk of bias (PImax; Cutrim 2019; Langer 2018; Xu 2018). All the remaining studies did not provide enough details about allocation concealment and studies at high risk of bias had issues with ITT analysis or missingness, or both.

Overall risk of bias

The main issues we found across the studies were the lack of details about allocation concealment (randomization process), lack of blinding (measurement of the outcome, although we considered using a sham IMT equal to blinding participants), and only journal articles were available (selection of the reported results).

Effects of interventions

See: **Summary of findings 1** Pulmonary rehabilitation plus inspiratory muscle training compared to pulmonary rehabilitation alone for people with chronic obstructive pulmonary disease; **Summary of findings 2** Inspiratory muscle training compared to control or sham for people with chronic obstructive pulmonary disease

Comparison 1: pulmonary rehabilitation plus inspiratory muscle training versus pulmonary rehabilitation

See: Summary of findings 1

Primary outcomes

Dyspnea

Borg scale

Two studies used the Borg scale at isotime to evaluate dyspnea. Considering a MCID of −1 unit (Ries 2005), there was no improvement in dyspnea with an overall effect estimate (MD 0.19, 95% CI −0.42 to 0.79; I^2 = 0%; 2 studies, 202 participants; Analysis 1.1). We judged only one study (Charususin 2018), to be at low risk of bias, which revealed a similar effect estimate. One study (Sykes 2005), reported greater improvement in dyspnea at "heavy load" in the IMT+ exercise group but did not report numerical data.

Using GRADE, we downgraded the certainty of the evidence for Borg by 1 point due to serious concerns regarding imprecision.

mMRC scale

We did not find any improvement in dyspnea using the mMRC scale (MD −0.12, 95% CI −0.39 to 0.14; I^2 = 0%; 2 studies, 204 participants; Analysis 1.2). The MCID is estimated to be between −0.5 to −1 unit (Araújo 2017; Cazzola 2015).

We downgraded the certainty of evidence to very low due to very serious concerns with risk of bias and serious concerns with imprecision.

BDI-TDI and MDP

There was no significant difference between the two arms in the studies that reported the BDI-TDI (Schultz 2018), and the MDP (Beaumont 2015; Beaumont 2018).

Functional exercise capacity

6MWD

We pooled the 12 studies that reported the 6MWD test in a meta-analysis that showed no evidence of a difference between groups (MD 5.95, 95% CI −5.73 to 17.63; I^2 = 61%; 12 studies, 1199 participants; Analysis 1.3). The mean and upper bounds of the 95% CI were lower than the MCID of 26 meters indicating that the mean change was not clinically relevant (Puhan 2011). Sykes 2005 narratively reported a better 6MWD in the intervention group.

We had very low confidence in the results due to serious concerns with risk of bias and very serious concerns with inconsistency.

We conducted a subgroup analysis according to the duration of the intervention (short, medium and long-term interventions). The test for subgroup differences was not significant (Chi^2 = 0.30, df = 2 (P = 0.86), I^2 = 0%, Analysis 1.4).

In the following subgroup analysis, we divided the studies according to their baseline PImax and the test for subgroup differences was not significant (Chi^2 = 1.94, df = 1 (P = 0.16), I^2 = 48.3%, Analysis 1.5).

One study (Wang 2017), reported a subgroup analysis for intervention group participants with or without respiratory muscle weakness, with greater improvement in 6MWD for the weakened respiratory muscle group.

In sensitivity analysis, keeping just the studies at low risk of bias (Beaumont 2018; Charususin 2018; Dellweg 2017), increased the mean difference without exceeding the MCID (MD 8.90, 95% CI

−11.86 to 29.65; I^2 = 80%; 4 studies, 379 participants). However, it decreased when switching to the fixed-effect model (MD 0.73, 95% CI -4.80 to 6.26, I^2 = 61%).

12MWD

Three studies reported the 12MWD and showed a larger effect in the intervention group (MD 155.77 meters, 95% CI −84.53 to 396.08; I^2 = 79%; 80 participants; Analysis 1.6)

Wmax

Five studies reported Wmax and showed no difference between the groups (MD −1.01 watts, 95% CI −6.96 to 4.94; I^2 = 25%; 326 participants; Analysis 1.7).

Exercise time (seconds)

Four studies reported exercise time (seconds) and also showed a larger effect in the intervention group (MD 58.62 seconds, 95% CI −25.09 to 142.32; I^2 = 0%; 192 participants; Analysis 1.8). We did not include Berry 1996 in the meta-analysis because they did not specify the level of exercise at which they measured exercise time. However, it is unclear to what extent these changes are clinically relevant.

Health-related quality of life (HRQoL)

SGRQ

We pooled seven trials that explored the effect of the intervention on HRQoL using the SGRQ, which showed no difference in total scores (MD 0.13, 95% CI −0.93 to 1.20; I^2 = 0%; 908 participants; Analysis 1.9). This mean difference did not exceed the MCID threshold of −4 units (Welling 2015).

We downgraded the certainty of evidence by two levels due to very serious concerns with risk of bias.

Two studies that reported the three SGRQ domains showed no differences in symptoms (MD −2.33, 95% CI −6.28 to 1.62; Analysis 1.9), activity (MD 0.28, 95% CI −1.65 to 2.20) or impact (MD −1.63, 95% CI −5.38 to 2.11) scores.

In sensitivity analysis, effect estimates remained unchanged with a fixed-effect model. We could not explore the summary effect of low risk of bias studies because all the studies were at high risk of bias and some concerns.

CRQ

There were no differences in CRQ domain scores (Analysis 1.10): three RCTs reported 'Dyspnea' (MD −0.30, 95% CI −1.90 to 1.29) and 'Fatigue' (MD 0.28, 95% CI −0.76 to 1.31). Two RCTs reported 'Emotion' (MD −0.63, 95% CI −2.53 to 1.26) and 'Mastery' (MD −0.05, 95% CI −1.18 to 1.08). We used the generic inverse variance method to pool the results because Charususin 2018 showed a different adjusted mean difference compared to non-adjusted analysis. None of the differences exceeded the MCID threshold of +0.5 units (Alma 2018). One abstract (Sykes 2005), narratively reported an improved CRQ score in the intervention group.

CAT

Two studies that reported the CAT scale showed no difference between groups (MD 0.13, 95% CI −0.80 to 1.06; I^2 = 50%; 657 participants; Analysis 1.11) and the difference did not exceed the threshold of clinical significance, MCID of −1.6 units (American Thoracic Society). We considered the certainty of evidence to be very low due to very serious concerns with risk of bias and serious concerns with inconsistency.

Secondary outcomes

Inspiratory muscle strength: PImax (cmH_2O)

Aggregated data from 17 studies showed higher inspiratory muscle strength in the intervention group (MD 11.46, 95% CI 7.42 to 15.15; I^2 = 84%; 1329 participants; Analysis 1.12), but this did not exceed the MCID of 17.2 (Iwakura 2020). The statistical heterogeneity is due to the studies that reported change from baseline and had narrow confidence intervals.

We downgraded the certainty of evidence by one level due to serious concerns with risk of bias.

We performed a subgroup analysis according to the duration of intervention, which did not reveal a difference between subgroups (Chi^2 = 0.05, df = 2 (P = 0.98), I^2 = 0%; Analysis 1.13).

We carried out subgroup analysis between studies with participants with and without respiratory muscle weakness. The test for subgroup differences was not significant (Chi^2 = 1.72, df = 1 (P = 0.19), I^2 = 41.8%; Analysis 1.14).

Wang 2017 divided the participants of the intervention group according to the state of their respiratory muscles, and they reported a larger change in PImax with the normal respiratory muscle group. Sykes 2005 reported a higher PImax narratively in the intervention group.

Sensitivity analysis showed minimal impact of fixed-effect models on the synthesised results (MD 10.53, 95% CI 9.25 to 11.81, I^2 = 84%). Retaining studies at low risk of bias (Beaumont 2018; Charususin 2018; Dellweg 2017; Fanfa Bordin 2020; Schultz 2018; Tounsi 2021), also had minimal impact (MD 13.43, 95% CI 11.81 to 15.04; I^2 = 90%; 1008 participants).

Laboratory exercise test: VO_2peak

We combined five studies showing no additional effect of the intervention on VO_2peak (MD −0.01 L/min, 95% CI −0.05 to 0.03; I^2 = 0%; 313 participants; Analysis 1.15). Sykes 2005 reported no difference between the two groups, but without numerical data.

Respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)

Two studies reported P_{thmax}, and we pooled them in an SMD meta-analysis because they used different techniques to measure the outcome. We got an overall effect estimate (SMD 1.22 cmH_2O, 95% CI −0.18 to 2.66; I^2 = 80%; 52 participants; Analysis 1.16), which suggests a large effect according to Cohen's d effect size.

Respiratory muscle endurance time: T_{lim} (seconds)

We performed separate analyses according to the nature of the endurance test. We pooled three studies that measured the outcome through sustained ventilation according to %PImax (MD 84.62, 95% CI −50.77 to 220.02; 236 participants; Analysis 1.17), and two studies that measured it according to %MVV (MD 477.69, 95% CI 215.43 to 739.94; 51 participants; Analysis 1.18). For both methods of measurement, we found a larger effect in the intervention group.

Maximal voluntary ventilation (MVV)

We pooled in an SMD meta−analysis two studies that reported MVV in L/min (Berry 1996; Wang 2017), and one study in %Pred (Paneroni 2018). We got an overall effect estimate (SMD 0.40, 95% CI −0.02 to 0.83; I^2 = 4%; 93 participants; Analysis 1.19), which suggests a moderate effect according to Cohen's d effect size.

Respiratory function: forced expiratory volume at 1 second (FEV1)

We combined the studies according to whether they reported FEV1 in %Pred and in liters. We did not find a better effect of PR+IMT, showing an overall effect estimate (MD 0.77, 95% CI −1.72 to 3.26; I^2 = 0%; 6 studies, 173 participants; Analysis 1.20) and (MD 0.04, 95% CI −0.04 to 0.13; I^2 = 56%; 6 studies, 889 participants; Analysis 1.21) respectively.

Respiratory function: residual volume

One study reported this outcome (Charususin 2018) and did not show a difference between the two groups.

Adverse events

One abstract (Masanga 2011) reported some adverse effects that were considered "minor and self-limited": headache (six participants), jaw pain (six participants), neck pain (six participants), back pain (four participants), abdominal pain (two participants), cough (one participant), blood-streaked sputum (one participant), shoulder pain (one participant) and chest pain (one participant).

Comparison 2: inspiratory muscle training versus control/ sham

See: Summary of findings 2

Primary outcomes

Dyspnea

Borg scale

Six studies used the Borg scale to assess dyspnea at isotime, and we entered them into a meta-analysis. Breathlessness was lower with the intervention and the mean difference was close to the MCID of −1 unit (the lower limit of the 95% CI exceeded it), though results are imprecise (MD −0.94, 95% CI −1.36 to −0.51; I^2 = 0%; 6 studies, 144 participants; Analysis 2.1). Only one study was at low risk of bias.

We downgraded the certainty by three levels due to very serious concerns with risk of bias and serious concerns with imprecision.

BDI-TDI

Eight studies (nine arms) used BDI-TDI to measure dyspnea (Analysis 2.2). Three studies (four arms) reported the TDI 'Change in Functional impairment' (MD 0.88, 95% CI 0.51 to 1.25), TDI 'Change in Magnitude of task' (MD 0.73, 95% CI 0.35 to 1.12), and TDI 'Change in Magnitude of effort' (MD 0.86, 95% CI 0.42 to 1.30), showing no potential improvement in dyspnea, according to an MCID of +1 unit (Mahler 2005). Eight studies (nine arms) reported the TDI 'Focal score' and revealed a greater effect with IMT (MD 2.98, 95% CI 2.07 to 3.89; I^2 = 65%; 238 participants).

We created a subgroup analysis of the TDI 'Focal score' according to studies judged with or without respiratory muscle weakness. The test for subgroup differences was not significant (Chi^2 = 2.55, df = 1 (P = 0.11), I^2 = 60.8%; Analysis 2.3).

In sensitivity analysis, the overall effect estimates remained unchanged when switching to the fixed-effect model in the first three subgroups, while it increased to (MD 4.04, 95% CI 3.70 to 4.39, I^2 = 65%) with 'Focal score'. This effect mainly resulted from (Sanchez Riera 2001), which got the greatest weight.

Only one study was at low risk of bias (Langer 2018), and we considered the certainty of evidence to be very low due to very serious concerns with risk of bias and serious concerns with imprecision.

mMRC

Four studies reported the mMRC score, and the overall effect estimate revealed a possible improvement in dyspnea in the IMT group (MD −0.59, 95% CI −0.76 to −0.43; I^2 = 17%; 150 participants; Analysis 2.4), considering an MCID between −0.5 and −1 unit. We considered the certainty of evidence to be low due to serious concerns with risk of bias and imprecision.

Functional exercise capacity

6MWD

We combined 16 studies (17 arms) that reported the 6MWD, showing a better effect with the IMT compared to control/sham (MD 35.71, 95% CI 25.68 to 45.74; I^2 = 16%; 501 participants; Analysis 2.5).

We judged the certainty of evidence to be moderate due to serious concerns with risk of bias.

In the first subgroup analysis, we divided the studies according to the duration of the intervention. Only one study (Saher 2021), had a follow-up of fewer than four weeks. The test for subgroup differences was not significant (Chi^2 = 0.37, df = 2 (P = 0.83), I^2 = 0%; Analysis 2.6).

In the following subgroup analysis, we divided the studies according to the mean baseline PImax. The test for subgroup differences was not significant (Chi^2 = 0.17, df = 1 (P = 0.68), I^2 = 0%; Analysis 2.7). One trial (Xu 2018), performed a subgroup analysis within study data using the same cut-off.

In sensitivity analysis, keeping just the studies at low risk of bias (Cutrim 2019; Xu 2018), revealed a larger effect, standing at around twice our MCID (MD 49.13, 95% CI −27.62 to 125.88, I^2 = 83%). However, we should note that its confidence interval exceeded the line of no effect. The overall effect estimate remained nearly the same when switching to the fixed-effect model.

12MWD and Wmax

We did not find an additional effect of IMT when we pooled the studies that used the 12MWD and Wmax, revealing, respectively, an overall effect estimate (MD −33.31, 95% CI −158.10 to 91.48; I^2 = 59%; 3 studies, 101 participants = 101; Analysis 2.8) and (MD 0.66, 95% CI −6.44 to 7.76; I^2 = 42%; 7 studies, 206 participants; Analysis 2.9). However, for the 12MWD, we noticed large differences in baseline data between the two groups of Preusser 1994, which appeared significant when testing it with the RevMan calculator (P = 0.03). We removed that study in a sensitivity analysis, and we got a positive overall effect (MD 12.76, 95% CI −65.71 to 91.23, I^2 = 0%).

Exercise time

Five studies (six arms) reported exercise time, but we did not pool the studies because they used different measurement methods (Analysis 2.10). Globally, their results were consistent and showed a trend of a greater effect in the IMT group compared to the control/sham group.

SWT

Three studies used the SWT, and we included two trials in our primary analysis. We did not find an additional effect in the IMT group (MD −7.45 meters, 95% CI −92.74 to 77.83; Analysis 2.11).

Health-related quality of life (HRQoL)

SGRQ

Two studies (Berton 2015; Saka 2021), reported the items 'Symptoms' (MD −2.10, 95% CI −3.50 to −0.71), 'Activity' (MD −9.86, 95% CI −15.08 to −4.63) and 'Impact' (MD −6.06, 95% CI −13.76 to 1.65). Six studies reported the 'total score' of the SGRQ, showing a larger effect in the IMT group (MD −3.85, 95% CI −8.18 to 0.48; I^2 = 66%; 182 participants; Analysis 2.12). The lower limit of the 95% CI exceeded the MCID of −4 units. The statistical heterogeneity is due to the effect of Saka 2021. Only one study was at low risk of bias (Xu 2018), and it has a similar effect estimate to the overall. The overall effect estimate increased to MD −5.11 (95% CI −6.81 to −3.40, I^2 = 66%), when switching to the fixed-effect model.

We judged the certainty of the evidence as 'very low' due to very serious concerns with risk of bias and imprecision.

CRQ

Four studies (5 arms) reported the four items of the CRQ, while one trial (Larson 1999), reported only dyspnea and fatigue. We divided the items into subgroups. The RCTs showed consistent results across the items, and there was an improvement (considering an MCID of +0.5 unit) in 'Dyspnea' (MD 1.63, 95% CI 0.23 to 3.03; Analysis 2.13), 'Fatigue' (MD 1.32, 95% CI 0.08 to 2.55), 'Emotion' (MD 2.64, 95% CI 0.82 to 4.46), and 'Mastery' (MD 1.57, 95% CI 0.07 to 3.06). None of the included studies was at low risk of bias.

CAT

Two trials reported CAT, revealing an overall effect estimate (MD −2.97, 95% CI −3.85 to −2.10; participants = 86; I^2 = 0%; Analysis 2.14). We downgraded the certainty of evidence by one level due to serious concerns with imprecision.

SF-36 and CCQ

In the studies that used SF-36 (Chuang 2017; Nikoletou 2016), and CCQ (Leelarungrayub 2017), there was a better effect in the IMT group in some domains of the scales.

Secondary outcomes

Inspiratory muscle strength: PImax (cmH_2O)

PImax

32 RCTs (34 arms) measured PImax. The upper limit of the 95% CI of summary effect between IMT and control/sham exceeded the MCID of 17.2 cmH_2O (MD 14.57 cmH_2O, 95% CI 9.85 to 19.29; I^2 = 89%; 916 participants; Analysis 2.15).

We downgraded the certainty of evidence by two levels due to serious concerns with risk of bias and a strongly suspected publication bias.

We divided the studies according to the training duration (Analysis 2.16). The test for subgroup differences was not significant (Chi^2 = 0.67, df = 2 (P = 0.72), I^2 = 0%).

We carried out subgroup analysis between studies with participants with and without respiratory muscle weakness. The test for subgroup differences was not significant (Chi^2 = 0.34, df = 1 (P = 0.56), I^2 = 0%; Analysis 2.17).

We also conducted a subgroup analysis of the measurement method. The test for subgroup differences was not significant (Chi^2 = 0.93, df = 2 (P = 0.63), I^2 = 0%; Analysis 2.18) between studies that measured PImax at residual volume, at functional residual capacity, and the studies that did not report the level of measurement.

In sensitivity analysis, keeping just the studies at low risk of bias (Cutrim 2019; Langer 2018; Xu 2018), showed a similar result (MD 12.79 cmH_2O, 95% CI 3.63 to 21.95, I^2 = 55%). Similarly, the overall effect estimate of the random-effects model did not differ from the fixed-effect model.

Laboratory exercise test (VO_2peak)

We combined 11 studies (12 arms) in an SMD meta-analysis, since they were reported in different units (L/min, mL/min, and mL/kg/min). We got an overall effect estimate suggesting a low to moderate effect according to Cohen's rule of thumb (SMD 0.31, 95% CI 0.05 to 0.57; I^2 = 14%; 286 participants; Analysis 2.19).

Respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)

Eight RCTs used P_{thmax} in their respiratory endurance assessment, and they showed a larger overall effect in the IMT group (MD 9.71, 95% CI 4.93 to 14.50; I^2 = 53%; 179 participants; Analysis 2.20).

Respiratory muscle endurance time T_{lim} (seconds)

We pooled 10 studies (11 arms) that reported T_{lim}, and they showed a better improvement in the outcome in the IMT group (MD 270.57, 95% CI 182.44 to 358.71; I^2 = 63%; 260 participants; Analysis 2.21). One trial (Heijdra 1996) considered it as the time to reach P_{thmax} (not included in the analysis).

Maximal voluntary ventilation (MVV)

Two studies reported MVV. We pooled them in an SMD meta-analysis because Belman 1988 did not report the unit. We got a summary effect suggesting a large effect according to Cohen's d effect size (SMD 0.99, 95% CI 0.28 to 1.69; I^2 = 0%; 36 participants; Analysis 2.22).

Respiratory function: forced expiratory volume at 1 second

We ran two analyses according to **FEV1** unit without finding a significant difference between IMT and control/sham in either unit. Ten studies (11 arms) reported **FEV1** in %Pred showing a difference of (MD 2.62 %predicted, 95% CI 0.20 to 5.04 Analysis 2.23), while 12 studies (13 arms) reported it in liters (MD 0.04 L, 95% CI −0.06 to 0.14 Analysis 2.24).

Respiratory function: residual volume

Hill 2006 reported residual volume in %Pred and liters, showing a better improvement in the IMT group, while Ramirez Sarmiento 2002 reported it in liters and did not show a difference.

Adverse events

None of the included studies reported a side effect of the intervention.

DISCUSSION

This review has summarised the available evidence of the effect of inspiratory muscle training, used alone or in combination with pulmonary rehabilitation, in people with COPD. We combined the results of the studies in a logical way, so that no data were lost, taking into account the variety of scales, respiratory measurements and training protocols.

Summary of main results

We included 55 RCTs in this review (including trials with more than two arms). Twenty-two studies (1446 participants) investigated the effect of PR with IMT compared to PR, while 37 studies (1021 participants) focused on the effect of IMT compared to control/sham. Three trials (Abedi Yekta 2019; Larson 1999; Majewska-Pulsakowska 2016), explored both comparisons (four arms).

Comparison 1: pulmonary rehabilitation plus inspiratory muscle training versus pulmonary rehabilitation

In our first comparison (PR+IMT vs PR), we did not find a significant improvement in the intervention group in dyspnea measured with the Borg scale at isotime, referring to an MCID of −1 unit (moderate-certainty evidence). We also did not find a potential effect with the mMRC scale, based on an MCID between −0.5 to −1 unit (very low-certainty evidence.

Studies assessed functional exercise capacity with four measurements: 6MWD, 12MWD, Wmax, and exercise time. We did not find an additional effect of combining PR and IMT with the 6MWD, which we considered our main measurement for this outcome. The overall effect estimate did not reach the MCID of 26 meters (low-certainty evidence). In subgroup analysis, we divided the studies according to the training duration and mean baseline PImax. The test for subgroup differences was not significant. In sensitivity analysis, three studies at low risk of bias showed a relatively greater treatment effect.

The overall effect estimate of the 12MWD and exercise time showed a larger effect in the intervention group. However, it remains unclear to what extent this difference is clinically relevant because we did not find an MCID for this outcome. The studies that measured Wmax did not reveal a difference between the two groups.

Seven studies investigated the effect of the intervention on HRQoL through the SGRQ. The overall effect estimate showed a positive effect in two domains ('Symptoms' and 'Impact'), without exceeding the MCID of −4 units. There was no difference between the two groups with 'Impact' and 'Total score' (low-certainty evidence).

In the CRQ, we only found a clinically relevant difference (−0.5 units) in the 'Emotion' domain. The other items ('Dyspnea', 'Fatigue' and 'Mastery') did not show a difference, noting that only three studies reported this scale.

Two studies reported the CAT scale, and the overall effect estimate failed to reveal a benefit based on an MCID of about −1.6 units (very low-certainty evidence).

The combination of PR and IMT might have a greater effect on inspiratory muscle strength (PImax) than PR alone, but our treatment effect failed to reach the MCID (moderate-certainty evidence). In subgroup analysis, we did not find a difference between different training durations nor between studies with participants with or without respiratory muscle weakness.

The overall effect estimate of VO_2peak, MVV, FEV1 (%Pred and L), and residual volume did not reveal a difference between the two interventions. For respiratory muscle endurance tests (T_{lim} and P_{thmax}), we discovered a more significant effect in the PR plus IMT. Nonetheless, the clinical relevance of these estimations remained doubtful since we did not find an MCID.

Comparison 2: inspiratory muscle training versus control/sham

In our second comparison, IMT versus control/sham, taking account of the Borg MCID (−1 unit), we found a trend of an improvement in dyspnea in the IMT group (only the lower limit of the 95% CI exceeded the MCID) when the scale was measured at submaximal exercise capacity (very low-certainty evidence).

The studies that used BDI−TDI did not reveal a clinically meaningful change (MCID +1 unit) after IMT in the three items of the scale (Functional impairment, Magnitude of task, Magnitude of effort). On the other hand, we found a larger effect with 'Focal score' of the TDI (very low-certainty evidence). The difference between the items might be explained by the fact that more studies reported Focal score (N = 8) than the other items (N = 3). In subgroup analysis, we did not find a difference between studies with participants judged with and without respiratory muscle weakness.

The overall effect estimate of the mMRC showed a possible effect with IMT that exceeded the MCID of −0.5 units (low-certainty evidence).

Turning to functional exercise capacity, we combined 16 studies (17 arms) that used the 6MWD, showing a larger effect exceeding the MCID: 26 meters (moderate-certainty evidence). Following the same subgroup analysis of our first comparison, we did not find a difference between different training durations and between studies with participants judged with and without respiratory muscle weakness. In sensitivity analysis, studies at low risk of bias (N = 2) showed a greater treatment effect.

Studies also used other measurements to assess exercise capacity, and the overall estimation of the 12MWD and Wmax did not show an advantageous effect of IMT. We did not combine the studies that reported exercise time because the methods of measurement were inconsistent. Still, all the effect estimates were on the right-hand side of the line of no effect with different degrees of positive effect.

We pooled separately three scales (SGRQ, CRQ and CAT) that assessed the HRQoL in a meta-analysis. All the scales revealed a better improvement in life quality with IMT, but unlike CRQ and

CAT, only the lower limit of the 95% CI of SGRQ exceeded the MCID (−4 units; very low-certainty evidence). We noticed a larger effect estimate favouring the intervention in some items when other scales were used (CAT, SF-36, CCQ).

PImax was the main secondary outcome in our second comparison. There was a trend to a greater effect with IMT, considering an MCID of 17.2 cmH_2O (low-certainty evidence). We did not find a difference between medium-term and long-term training nor between studies with participants with or without respiratory muscle weakness. Measuring the outcome at residual volume or functional residual capacity showed similar results. We got similar results with studies at low risk of bias (N = 3).

We combined the studies that reported VO_2peak in an SMD meta-analysis. According to Cohen's rule of thumb, we considered the overall effect estimate between low to moderate.

The studies that reported respiratory muscle endurance tests (P_{thmax}, T_{lim}, MVV) showed a beneficial effect favouring IMT. However, we could not judge the clinical relevance of this effect since we did not find the MCID of these outcomes. The overall effect estimate of FEV1 (%Pred, L) did not reveal a potential improvement with IMT compared to control/sham.

Overall completeness and applicability of evidence

This review was conducted on patients with stable COPD, aged 44 years and over. It explored a wide range of participants and included all RCTs regardless of COPD stages and training protocols (duration, load, supervision, devices, follow-up, measurements). Most studies, except Ahmad 2013 excluded participants who were free from exacerbation for a couple of weeks preceding the trial and were not hospitalised. Therefore, the results of this review may not be applicable to IMT conducted just after an acute exacerbation. We also noticed a shift over the years from using resistive devices to threshold devices. We excluded RCTs that used resistive trainers without controlling the breathing pattern because participants could adapt a non-fatiguing respiratory pattern without exposing the respiratory muscles to the workload. Currently, with technological development, there has been increasing use of electronic devices that allow remote monitoring and accurate adjustment of the training load.

Studies that looked at the combined effect of PR plus IMT included people with mild to very severe COPD. One study (Dellweg 2017), performed the intervention on hypercapnic patients who remained dependent on non-invasive ventilation after prolonged weaning. Two studies (Beaumont 2015; Charususin 2018), specifically trained participants with reduced PImax, and two trials did subgroup analysis within study data according to the state of respiratory muscles (PImax ≤ or > 60 cmH_2O) (Beaumont 2018; Wang 2017). Participants in Magadle 2007 and Weiner 2000 received respectively three months and six weeks of PR before the start of IMT, while most of the other studies excluded this category of patients. These two studies had no impact on the overall effect size when we removed them in a sensitivity analysis. Apart from De Farias 2019, Mador 2005 and Paneroni 2018, which conducted endurance training, all the studies performed strength training with various loads and different training durations.

Furthermore, there was a wide range of PR protocols, starting from just breathing exercises and respiratory drainage to a mix of interventions (e.g. cycling, treadmill, muscle strengthening, therapeutic patient education). To the best of our knowledge, the current guidelines have not yet established a consensus for an optimal duration or components of a rehabilitation program. This might be explained by the multiple factors that could interfere with it, such as participants' motivation and financial and logistic resources.

In our second comparison, we were also exposed to a diversity of training protocols in the studies that compared IMT with control/sham. More than half of the included RCTs used a sham IMT, and only two (Bavarsad 2015; Dacha 2019), had some participants with mild COPD. One trial (Saher 2021), focused on patients receiving non-invasive ventilation as part of COPD management. Almost all the trials excluded participants who had exacerbations before starting the trial, and two RCTs worked on patients with limited functional performance (Covey 2001; ZhouL 2016). Two studies had a long intervention duration (Beckerman 2005; Kim 1993), equal to one year and six months respectively; two studies trained their participants with a load up to 100% of their PImax (Chuang 2017; Hill 2006); two trials conducted endurance IMT (Koppers 2006; Scherer 2000), and one trial performed both endurance and strength exercises (Petrovic 2012). The remaining studies had close characteristics (i.e. strength training, similar loads).

This review did not compare threshold IMT with normocapnic hyperpnea training (endurance IMT) nor compare training loads. We thought it would be best to work on these objectives in a separate review.

Overall, this review included all kinds of participants and interventions without preferences. However, our results might not be applicable for hospitalised patients following an exacerbation or patients with severe COPD who require long-term oxygen therapy.

Quality of the evidence

Using the GRADE approach, we assessed the certainty of the evidence of five outcomes: dyspnea (Borg, mMRC, BDI-TDI), functional exercise capacity (6MWD), HRQoL (SGRQ, CAT), and PImax. When the number of RCTs exceeded 10, we created a funnel plot to investigate publication bias.

For both comparisons, we considered the certainty of evidence to be from very low to moderate across all the outcomes (see Summary of findings 1; Summary of findings 2).

Comparison 1: pulmonary rehabilitation plus inspiratory muscle training versus pulmonary rehabilitation

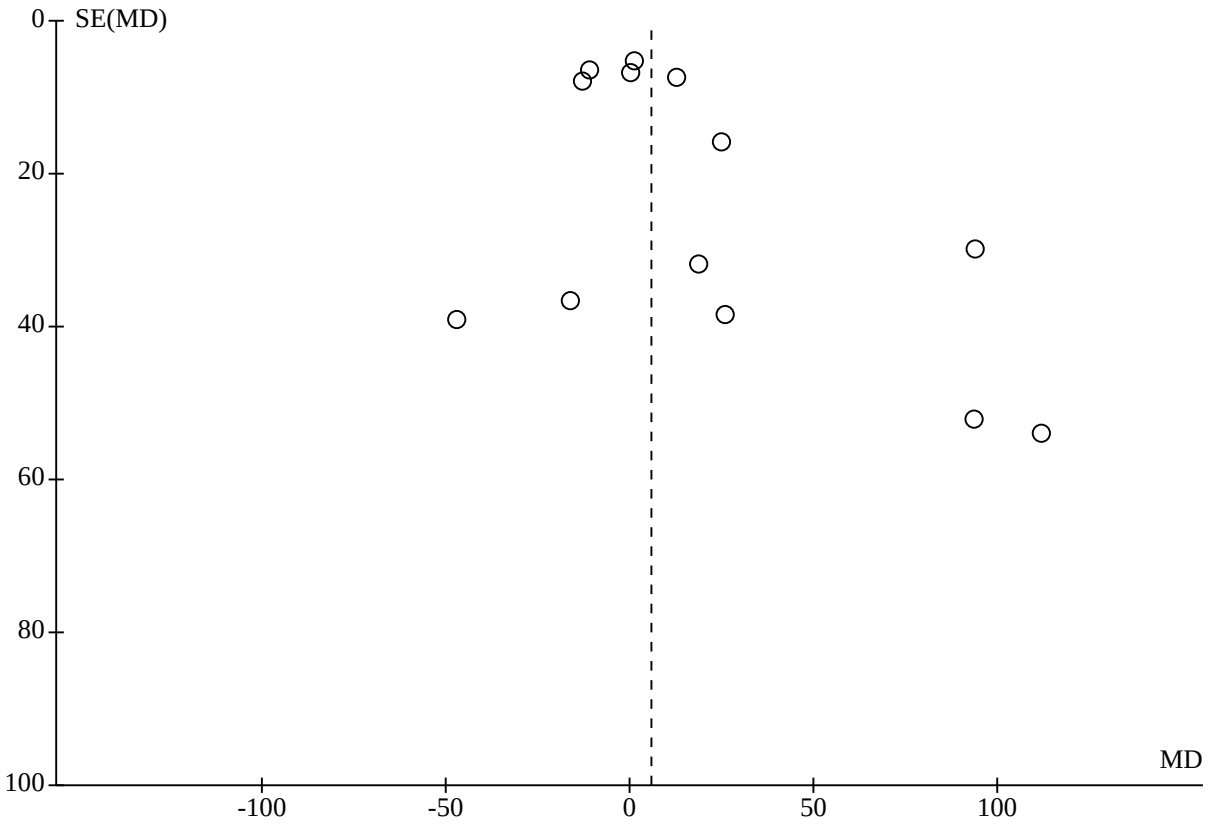
In our first comparison (PR+IMT versus PR), we downgraded the certainty of evidence by one level for the Borg scale measured at submaximal exercise capacity because of serious concerns about risk of bias related to blinding participants.

We downgraded the certainty of evidence of the mMRC to very low due to very serious concerns with risk of bias (all the trials are at high risk of bias) and serious concerns with imprecision (the sample size is less than 400, rule of thumb).

We considered the certainty of evidence of the 6MWD to be very low due to serious concerns with risk of bias (studies at low risk of bias had different effect estimate from the overall effect estimate) and very serious concerns with inconsistency, although

we explained part of the heterogeneity by the difference in training durations. Indeed, there was substantial statistical heterogeneity, and the effect estimates were wide on both sides of the line of no effect, making the benefit of the intervention doubtful. The funnel plot was symmetrical (Figure 2), so publication bias was improbable.

Figure 2. Funnel plot of comparison 7, PR+IMT vs PR, outcome: 7.3 functional exercise capacity: 6-minute walk distance (6MWD)

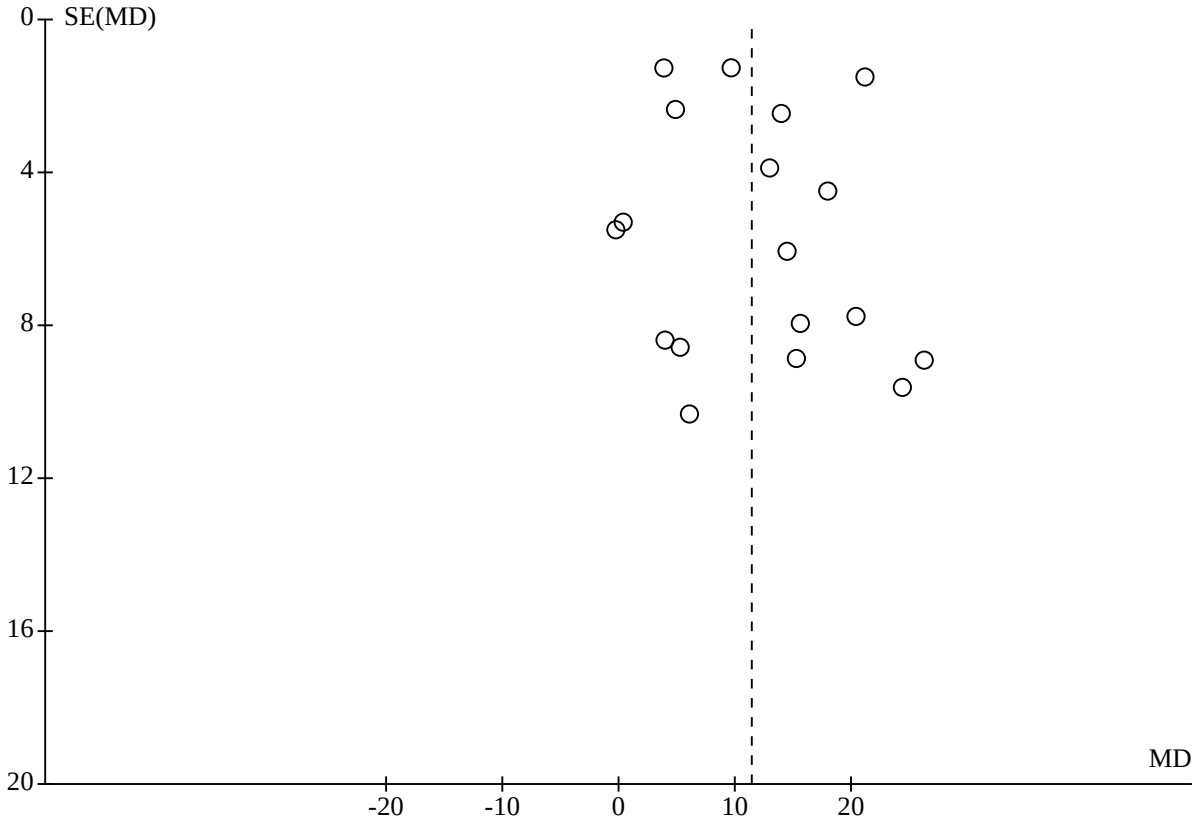


We judged the quality of evidence of the SGRQ (total score) as low because of very serious concerns with risk of bias. In fact, none of the studies was at low risk of bias; the main issue was the lack of blinding of participants (outcome measurement).

We considered the certainty of evidence of CAT to be very low due to very serious concerns with risk of bias (most of the evidence is from studies at high risk of bias and some concerns, lack of blinding) and serious concerns with inconsistency (considerable statistical heterogeneity, and confidence intervals do not overlap).

We downgraded the certainty of evidence of PImax by one level due to serious concerns with risk of bias (most of the evidence is from studies at high risk of bias and some concerns). We did not consider statistical heterogeneity because all the effect estimates were on one side showing a benefit). The funnel plot did not raise suspicions of publication bias (Figure 3). As a result, we considered the certainty of the evidence as moderate.

Figure 3. Funnel plot of comparison 7, PR+IMT vs PR, outcome: 7.12 respiratory muscle strength: PImax



Comparison 2: inspiratory muscle training versus control/ sham

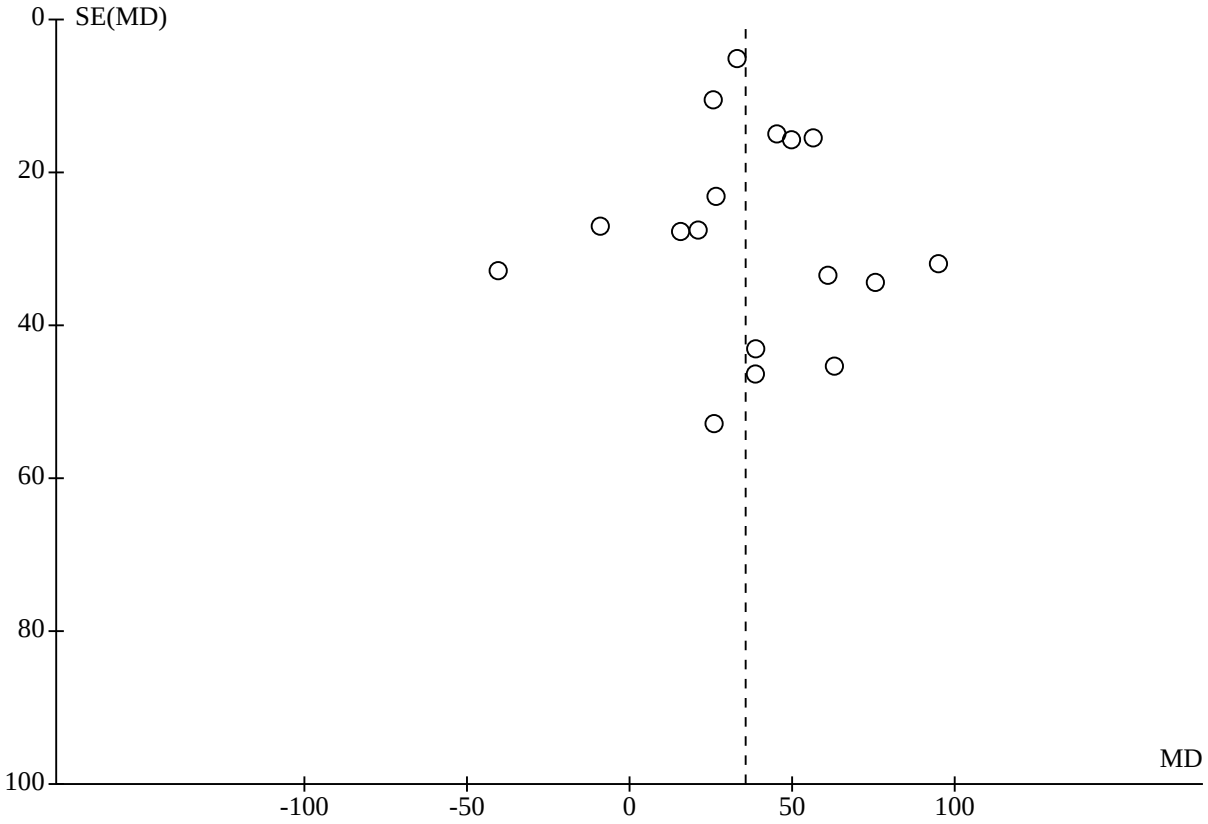
In our second comparison (IMT versus control/sham), we downgraded the certainty of evidence of Borg measured at submaximal exercise capacity to very low due to very serious concerns with risk of bias (most of the studies were at high risk or some concerns, with different effect estimates compared to low risk of bias studies, issues with blinding) and serious concerns with imprecision (small sample size less than 400 participants, rule of thumb).

For the same reasons explained above, we downgraded the certainty of evidence for dyspnea assessed with BDI-TDI by three levels.

We considered the certainty of evidence of mMRC to be low due to serious concerns with risk of bias (most of the evidence is from studies at high risk of bias and some concerns) and imprecision (sample size less than 400 participants, rule of thumb).

We judged the quality of evidence of the 6MWD as moderate due to serious concerns with risk of bias (most of the evidence is from studies at high risk of bias and with some concerns). We did not downgrade inconsistency, despite the substantial statistical heterogeneity, because the effect estimates were on one side of the line of no effect. So we were more confident about the direction of the effect. The funnel plot raised some concerns about publication bias (Figure 4), without downgrading the evidence.

Figure 4. Funnel plot of comparison 8, IMT vs control/sham, outcome: 8.8 functional exercise capacity: 6-minute walk distance (6MWD)

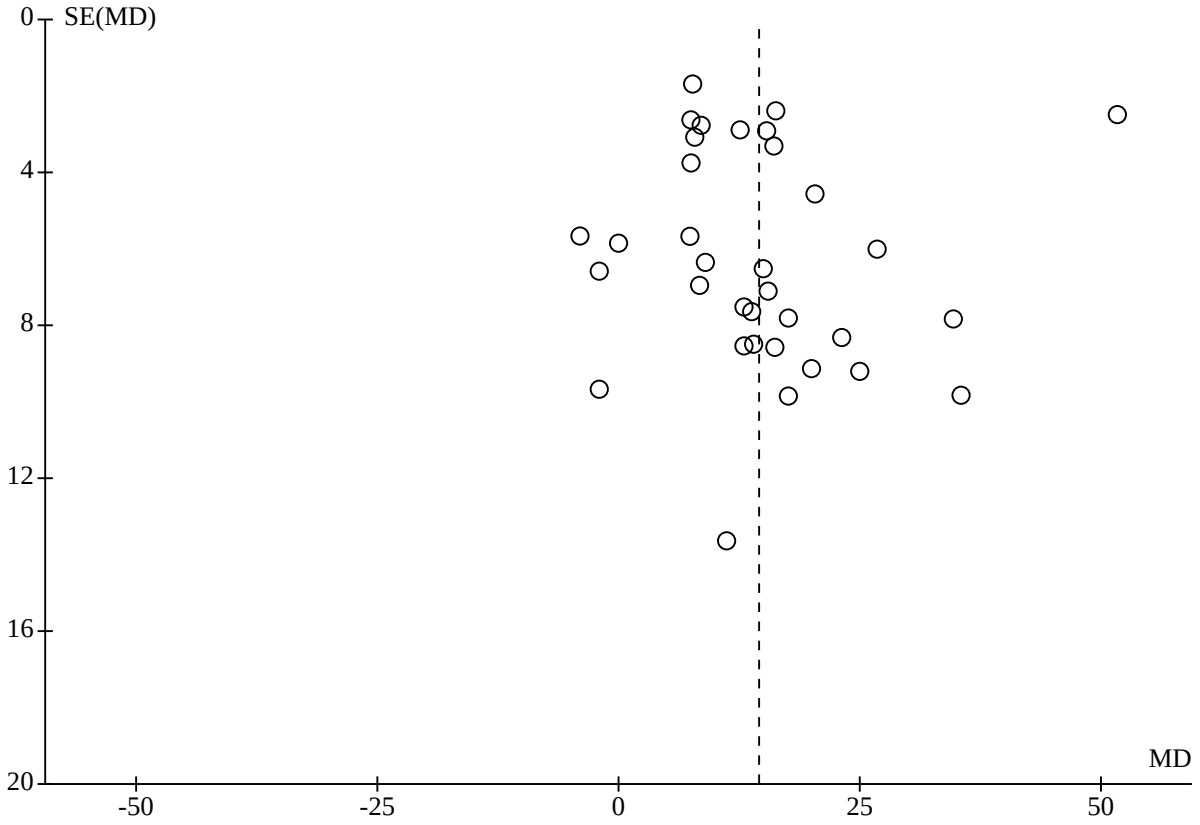


We downgraded the certainty of evidence of the SGRQ by three levels because of very serious concerns with risk of bias (studies with greater weight were at high risk of bias and some concerns, showing different effect estimates from studies at low risk of bias) and very serious concerns with imprecision (sample size less than 400 participants, rule of thumb; the 95% CI includes benefit and harm).

We considered the certainty of evidence of CAT to be moderate due to serious concerns with imprecision (sample size less than 400, rule of thumb).

We judged the certainty of evidence of PImax as low due to serious concerns with risk of bias (most of the evidence is from studies at high risk of bias and with some concerns) and a strongly suspected publication bias (Figure 5).

Figure 5.



Potential biases in the review process

The review is based on a published protocol (Ammous 2020). We discuss deviations from the protocol in the Differences between protocol and review section.

One of the main issues with the included studies in this review is the risk of bias, using RoB 2, which is outcome-dependent. Only six out of 22 studies were at low risk of bias for the first comparison, while only three out of 37 studies were at low risk for the second comparison. Across all the outcomes, the major problems were lack of detail about allocation concealment, some issues with missing data, participants being aware of their intervention (for the participant-reported outcome that involves judgments), and not publishing a protocol or listing the study in a trial register before launching the studies. Sometimes studies at high risk of bias tended to show a larger effect than the others, which reduced the confidence in our results.

One trial provided IMT for a short period of time (two weeks; Saher 2021), and participants received non-invasive ventilation throughout the trial.

From all our included studies, only one abstract (Masanga 2011), reported adverse events. Although it is unlikely that IMT may be associated with harm, we have some concerns due to the variety of side effects reported by Masanga 2011, and because the included studies did not discuss them. That is to say, one of the reasons for discontinuing the trial was the inability of participants to continue the intervention. But the studies did not discuss the reasons that made patients take that decision.

Moreover, when dividing the studies according to mean baseline PImax to classify participants with or without respiratory muscle weakness, we assumed that the proportion of participants not belonging to their assigned subgroup was balanced across the studies. In other words, getting individual data and conducting a subgroup analysis within study data was impossible. So, we assumed this variation was balanced between the studies, considering that PImax follows a normal distribution with fewer outliers.

Agreements and disagreements with other studies or reviews

Ten published reviews that explored the effect of IMT on COPD have been published over the years. The first one was published in the 90s (Smith 1992). This review included 17 trials in which the participants had chronic airflow limitation without specifying the types of the diseases. They summarised the effect estimate with SMD meta-analysis and interpreted it according to Cohen's d effect size. They found a small to moderate effect favouring IMT for MVV, PImax and laboratory exercise tests. However, this review included trials that run resistance training without controlling the breathing pattern.

Ten years later, another systematic review was published (Lötters 2002), including 15 RCTs. Unlike our review, this study pooled altogether in an SMD meta-analysis RCTs that looked at the effect

of IMT as a stand-alone intervention and when associated with PR. Then, they conducted a subgroup analysis to investigate the additional effect of PR. They found that IMT alone might improve dyspnea and respiratory muscle strength and endurance. When combined with PR, a beneficial effect was seen only in participants with respiratory muscle weakness.

The following review (16 studies) was conducted by Crowe 2005, followed by an update with 18 studies (O'Brien 2008), in which they compared IMT separately with different types of interventions (exercises, breathing techniques, education, PR). The authors concluded, based on a study-level analysis, that IMT might improve respiratory muscle strength. However, there was less confidence with dyspnea and HRQoL. In our review, we considered the participants who underwent therapeutic patient education or one type of breathing exercises as control, because the aim was not to compare IMT with another intervention but to create a psychological effect for patients not receiving IMT. We excluded the studies that focused on comparing IMT with breathing exercises. Similarly, the same authors worked on another systematic review (Geddes 2005), and then they updated it (Geddes 2008). These reviews compared IMT with no intervention, low versus high IMT, and two different modes of IMT, which is not the purpose of our review.

A narrative review (Shoemakher 2009), reported that IMT, in comparison with sham IMT or no intervention, might improve dyspnea, HRQoL and PImax. Following that, Gosselink 2011 showed similar results to Lötters 2002. The authors included 32 RCTs, and found a possible effect of IMT in improving dyspnea, functional exercise capacity, HRQoL, PImax and respiratory muscle endurance. In subgroup analysis, they reported a benefit of IMT when associated with PR only in participants with respiratory muscle weakness. They also found a larger effect of strength training compared to endurance training.

In a subsequent study, Beaumont 2018a included 37 trials in a meta-analysis showing an improvement in dyspnea, HRQoL, functional exercise capacity and PImax after threshold IMT. However, they did not find a difference when combining IMT with PR. The last meta-analysis (Figueiredo 2020), compared IMT alone or associated with other interventions with control, sham, or other interventions. The authors did not find an improvement in dyspnea, HRQoL, or a larger effect in participants with respiratory muscle weakness. They showed a trend of a larger effect with higher training loads.

Our systematic review is the first to have excluded trials that used resistive trainers without controlling the breathing pattern. We are also the first that have excluded the trials that did not measure Borg at isotime. Generally, our results were consistent with past systematic reviews regarding no effect when adding IMT to PR and a possible benefit with IMT as a stand-alone intervention. However, we could not conclude that there is a better effect in participants with respiratory muscle weakness. A possible explanation for this finding includes the fact that most studies worked on participants without respiratory muscle weakness.

AUTHORS' CONCLUSIONS

Implications for practice

When associated with pulmonary rehabilitation (PR), inspiratory muscle training (IMT) may not have an additional benefit on dyspnea, functional exercise capacity and health-related quality of life. There was an increase in inspiratory muscle strength and endurance, but this difference was not clinically meaningful.

IMT may improve dyspnea, functional exercise capacity (mainly the 6MWD) and health-related quality of life, compared to sham or no intervention. There was also an increase in inspiratory muscle strength and endurance, but judging the clinical significance of these outcomes was challenging due to a non-standardised minimal clinically important difference.

For both interventions, we could not conclude that there was a possible larger effect in participants with respiratory muscle weakness and with longer durations of training.

Implications for research

Overall, we did not detect any potential advantage of combining PR and IMT, which was consistent with past systematic reviews. However, it is still unclear if this intervention is more beneficial in participants with respiratory muscle weakness, and future research may focus more on this group of participants.

We think there is enough evidence for the effect of IMT alone since our results are consistent with past systematic reviews. However, all published trials had a small sample size. So we believe future trials should increase the number of participants, investigate the possible larger effect on participants with respiratory muscle weakness and compare different IMT protocols.

IMT may be a starter intervention for patients unable to undergo PR (e.g. severe COPD, logistical or financial issues). Still, this should be explored further in clinical trials.

For both comparisons, we highly suggest providing a sham IMT for the control group. Although a sham IMT might not influence the results of an observer-reported outcome such as the 6-minute walk distance, we strongly believe that participants who know they are undergoing an intervention may overestimate the effect measured with participant-reported outcomes that involve judgments. Furthermore, future research may consider training with higher inspiratory flow rate and training at high lung volume (closer to total lung capacity) to improve performance in hyperinflated COPD patients.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abedi Yekta 2019

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 17/15 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 51.33 (10.4) • Gender (M/F): 9/6 • BMI, mean (SD), kg/m^2: 27.6 (3.7) PR • N (randomized/analyzed): 17/14 • Loss to follow-up or excluded: 3 • Age, mean (SD) in years: 53.5 (10.37) • Gender (M/F): 8/6 • BMI, mean (SD), kg/m^2: 27.39 (5.11) IMT • N (randomized/analyzed): 17/16 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 51.88 (9.05) • Gender (M/F): 7/9 • BMI, mean (SD), kg/m^2: 27.05 (4.53) Control/sham • N (randomized/analyzed): 17/15 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 55.67 (11.08) • Gender (M/F): 7/8 • BMI, mean (SD), kg/m^2: 25.98 (4.1) Overall • N (randomized/analyzed): 68/60 • Loss to follow-up or excluded: 8 • Age, mean (SD) in years: 53.07 (10.11) • Range age (min, max): 32,70 • Gender (M/F): 31/29

Abedi Yekta 2019 *(Continued)*

	• COPD stage (GOLD): moderate to severe **Included criteria** • Stage 2 or 3 COPD according to the GOLD criteria; • Age range 30-70 years; • No previous known diseases, such as heart disease (e.g. congestive heart failure and coronary artery disease), renal disease (e.g. end-stage renal disease and chronic renal failure), or liver disease (e.g. hepatic cirrhosis and hepatic cancer); no history of known pulmonary diseases, such as lung cancer and pleural disease; no history of musculoskeletal diseases (e.g. myasthenia gravis) or restrictive deformities of the lungs; • Lack of severe limitations in the limbs inhibiting aerobic exercise; no pulmonary surgery in the past 12 months; • No recent fracture of the ribs in the past 6 months; • No history of psychotropic diseases; and no use of drugs, alcohol, or psychiatric drugs. **Excluded criteria** • Exacerbation of the disease during the study; • Need for long-term oxygen therapy for more than 15 h/d; • The occurrence of complications, such as pneumothorax or diseases exacerbating and disrupting the treatment.
Interventions	**Intervention characteristics** **PR:** consisted of aerobic exercise performed on a treadmill ergometer, at 40%-60% of the heart rate, 2 d/week, for 8 weeks and 40 min/session. **IMT:** conducted 2 d/week for 8 weeks, 15 min/session with Powerbreathe KH4. Each session lasted 15 min, all sessions were supervised, and the training load was set at 40%-60% of S-Index. **PR+IMT:** consisted of a combination of PR and IMT protocols. **Control:** no intervention received by this group.
Outcomes	HRQoL: SGRQ (Total)
Identification	**Sponsorship source:** Shahid Beheshti University of Medical Sciences **Country:** Iran **Setting:** Hospital Hussein Department of Physiotherapy **Author's name:** Saeed Rezaei **Institution:** Department of Sports Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran **Email:** saeedrezaee1394@yahoo.com **Clinical trial register:** https://www.irct.ir/trial/29724
Notes	A change of 4 units in SGRQ score was considered significant.

Bavarsad 2015

Study characteristics	
Methods	**Study design:** RCT

Bavarsad 2015 *(Continued)*

	Study grouping: parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 20/15 • Loss to follow-up or excluded: 5 • Age mean (SD) in years: 58.8 (6.82) • Gender (M/F): 13/2 • BMI mean (SD), kg/m^2: 24.88 (5.02) Control/Sham • N (randomized/analyzed): 20/15 • Loss to follow-up or excluded: 5 • Age mean (SD) in years: 54.2 (8.09) • Gender (M/F): 14/1 • BMI mean (SD), kg/m^2: 24.97 (4.72) Overall • N (randomized/analyzed): 40/30 • Loss to follow-up or excluded: 10 • Age range (min, max): 45, 65 • Gender (M/F): 27/3 • COPD stage (GOLD): mild to severe **Included criteria** • Patients with spirometric evidence of significant chronic airflow limitation(FEV1/FVC < 70%pred) with mild to very severe COPD diagnosis according to the GOLD criteria; • Age range 45-65 years; • No history of PR; • Established treatment plan 1 month prior to the study. **Excluded criteria** • BMI > 35; • Comorbid conditions such as diabetes, musculoskeletal disorders, cardiovascular diseases; and neurological diseases that can affect the results of 6MWD; • Having exacerbation for 1 month prior to the study; • A history of long-term oxygen therapy; • A history of spontaneous pneumothorax and rib fracture.
Interventions	**Intervention characteristics** **IMT** The training consisted of unsupervised sessions, 15 min/d, 6 d/week for 8 weeks. The device used was an incentive spirometer (Respivol), at a load equal to or more than the initial inspiratory volume. The researchers were informed of the training sessions through phone calls during the 8 weeks. A checklist, which was designed to be completed on weekdays, was prepared for the participants so that they could mark the relevant day after a training session **Control** No intervention was received by this group.
Outcomes	Dyspnea: Borg

Bavarsad 2015 *(Continued)*

	• Notes: dyspnea was assessed at the beginning and the end of the 6MWD Functional exercise capacity: 6MWD Respiratory function: FEV1 (%pred) Respiratory function: FEV1 (L)
Identification	**Sponsorship source:** The Deputy of Research Affairs at the Ahvaz Jundishapur University of Medical Sciences **Country:** Iran **Setting:** Specialized Pulmonary Clinic of Ahvaz **Author's name:** Esmaeil Eidani **Institution:** Pulmonary Unit, Department of Medicine, Ahvaz Jundishapur University of Medical Sciences **Email:** esmaileidani@gmail.com **Address:** Ahzav, Iran
Notes	

Beaumont 2015

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group **Subgroup analysis:** FEV1 > or ≤ 50% of the predicted value
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 16/16 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 62 (10) • Gender (M/F): 4/12 • BMI mean (SD), kg/m^2: 27.3 (4.2) PR • N (randomized/analyzed): 18/16 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 61 (8) • Gender (M/F): 7/11 • BMI mean (SD), kg/m^2: 26.8 (6.0) Overall • N (randomized/analyzed): 34/32 • Loss to follow-up or excluded: 0 • Gender (M/F): 11/23

Beaumont 2015 *(Continued)*

	• COPD stage (GOLD): moderate to very severe **Included criteria** COPD diagnosed according to American Thoracic Society/European Respiratory Society criteria; PImax > 60 cmH_2O at admission. **Excluded criteria** • Previous pneumonectomy or lobectomy in the past 6 months; • Impossibility to measure IC at the end of the 6MWD; • The incapacity to follow the standard rehabilitation program; • The absence of written informed consent. **Pretreatment:** FEV 1 was lower in the IMT group; the Borg scale was higher in the control group.
Interventions	**Intervention characteristics** **PR+IMT** • PR: conducted for 3 weeks, 5 d/week, and included aerobic exercise on a cycle ergometer and a treadmill (30 min/d each), strengthening of lower and upper limb muscle groups, therapeutic educational program, aerobic gymnastics in groups, smoking cessation program, and socio-psychological and dietary advice. • IMT: performed daily in 2 sessions of 15 min each, 5 times/week, for 3 weeks, supervised by a physiotherapist. The participants had to breathe slowly with an increased tidal volume. A threshold inspiratory muscle trainer (Threshold IMT1) was used at 40% of PImax. The intensity was not modified during the program. **PR** Participants in this group received only the standardised PR program.
Outcomes	Dyspnea: Borg Dyspnea: MDP • Unpleasantness • Sensory intensity • Muscle work/effort • Not enough air/smother/air hunger • Mental effort/concentrate • Tight/constricted • Breathing a lot (rapid, deep, and heavy) • Crush • Depression • Satisfaction • Anxiety • Frustration • Anger • Happiness • Fear Functional exercise capacity: 6MWD Respiratory muscle strength: PImax
Identification	**Sponsorship source:** EA3878 (G.E.T.B.O.), CIC INSERM 0502, University Hospital of Brest

Beaumont 2015 *(Continued)*

Country: France

Setting: Pulmonary Rehabilitation Unit, Morlaix Hospital Centre, European University of Occidental Brittany

Author's name: Marc Beaumont

Institution: Pulmonary Rehabilitation Unit, Morlaix HospitalCentre, European University of Occidental Brittany

Email: marc.beaumont@univ-brest.fr

Address: Morlaix29672, Cedex, France

Clinical trial register: NCT01545011

Notes	P-value of the change from baseline is from the adjusted analysis.

Beaumont 2018

Study characteristics

Methods	**Study design:** RCT **Study grouping:** parallel-group **Subgroup analysis:** PImax (> or ≤ 60 cmH_2O)
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 74/74 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 62.2 (8.0) • Gender (M/F): 44/30 • BMI, mean (SD), kg/m^2: 26.2 (5.9) PR • N (randomized/analyzed): 75/75 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 65.9 (8.9) • Gender (M/F): 50/25 • BMI, mean (SD), kg/m^2: 24.7 (5.9) Overall • N (randomized/analyzed): 149 • Loss to follow-up excluded: 2 • Gender (M/F): 94/55 • COPD stage (GOLD): severe to very severe **Included criteria** • Severe or very severe COPD diagnosed according to ATS/ERS criteria at admission(FEV1 < 50%pred **Excluded criteria**

Beaumont 2018 *(Continued)*

- Previous pneumonectomy or lobectomy in the past 6 months;
- Spontaneous risk of pneumothorax or rib fracture;
- Incapacity to follow a standard rehabilitation program (locomotor deficits, acute cardiac failure and acute exacerbation of COPD at the beginning of the program);
- The absence of written informed consent.

Pretreatment: 6 patients with lobectomy or pneumonectomy in the control group were included.

Interventions	**Intervention characteristics** **PR+IMT** • PR: conducted over 4 weeks, 5 d/week and included aerobic exercise on a cycle ergometer and a treadmill (each for 30 min/day), strengthening of lower and upper limb muscle groups, a therapeutic, educational program, aerobic gymnastics in groups, a smoking cessation program and socio-psychological and dietary advice. • IMT: consisted of 2 sessions of 15 min each, supervised by a physiotherapist, 5 times/week, over 4 weeks. The patients had to breathe slowly with an increased tidal volume; after 10 inspirations, they could have a break by breathing at rest for a short time. The cycle of 10 inspirations was repeated 15 times. The inspiratory muscle training was performed using a threshold inspiratory muscle trainer (PowerBreathe Medic; PowerBreathe, Southam, UK) at a resistance of 50% of PImax. The intensity was increased (+10%) after 10 days of training to reach 60% of the initial PImax. **PR:** participants in this group received only the standardised PR program.
Outcomes	Dyspnea: Borg Dyspnea: mMRC Dyspnea: MDP: • Unpleasantness • Sensory intensity • Muscle work/effort • Not enough air/smother/air hunger • Tight/constricted • Mental effort/ concentrate • Breathing a lot (rapid, deep, and heavy) • Depression • Anxiety • Frustration • Anger • Fear Functional exercise capacity: 6MWD HRQoL: SGRQ • Symptoms • Activity • Impact • Total Respiratory muscle strength: PImax
Identification	**Country:** France **Setting:** Rehabilitation programme unit of Centre Hospitalier des Pays de Morlaix **Author's name:** Marc Beaumont

Beaumont 2018 *(Continued)*

Institution: Pulmonary Rehabilitation Unit, Morlaix HospitalCentre, European University of Occidental Brittany

Email: marc.beaumont@univ-brest.fr

Address: 29672 Morlaix CEDEX, France

Clinical trial register: NCT02074813

Notes	Borg and MDP scales were conducted at the end of 6MWD. Subgroup analysis according to PImax (> or ≤ 60 cmH2O) was conducted. See supplementary table.

Beckerman 2005

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 21/17 • Loss to follow-up or excluded: 4 • Age, mean (SD), in years: 67.7 (16.49) • Gender (M/F): 17/4 Control/sham • N (randomized/analyzed): 21/14 • Loss to follow-up or excluded: 7 • Age, mean (SD), in years: 66.9 (15.12) • Gender (M/F): 15/6 Overall • N (randomized/analyzed): 42/31 • Loss to follow-up or excluded: 11 • Gender (M/F): 32/10 • COPD stage: severe to very severe **Included criteria** • Spirometric evidence of significant chronic airflow limitation (FEV1 < 50% of predicted, FEV1/FVC < 70% of predicted) with a diagnosis of COPD according to the criteria of the ATS were recruited from the community. • The patients were all new to an IMT program, and none were receiving additional regular exercise or dietary supplements. **Excluded criteria** • Patients with cardiac disease and poor compliance and needing supplemental oxygen
Interventions	**Intervention characteristics**

Beckerman 2005 *(Continued)*

	IMT: participants trained daily in 2 sessions of 15 min each, 6 times/week for 12 months. The training was performed using a threshold inspiratory muscle trainer (POWERbreathe; Gaiam Ltd; Southam, Warwickshire, UK). The participants started breathing at a resistance that required generation of 15% of Pimax for 1 week. The load was then increased incrementally, 5% to 10% each session, to reach 60% of Pimax at the end of the first month. IMT was then continued at 60% of the Pimax adjusted monthly to the new Pimax achieved. The training was conducted in a rehabilitation center for 1 month under the supervision of a respiratory therapist followed by home training, verified by a respiratory therapist daily by phone and once weekly by a personal visit, for the next 11 months. **Control/sham:** this group trained with the same protocol at a load equal to 7 cm H_2O.
Outcomes	Dyspnea: Borg Functional exercise capacity: 6MWD HRQoL: SGRQ Respiratory muscle strength: PImax
Identification	**Country:** Israel **Setting:** Home **Author's name:** Paltiel Weiner **Institution:** Department of Medicine A, Hillel Yaffe Medical Center **Email:** weiner@hillel-yaffe.health.gov.il **Address:** Hadera, Israel 38100
Notes	The study reported data as mean and SE, we computed SD for the baseline characteristics. The SE reported in the text of the trial is less than shown in the graph.

Belman 1988

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): not reported/8 • Age, mean (SD), in years: 64 (8.4) • Gender (M/F): 4/4 Control/sham • N (randomized/analyzed): not reported/9 • Age, mean (SD), in years: 64 (9.0) • Gender (M/F): 6/3 Overall • N (randomized/analyzed): 20/17 • Loss to follow-up or excluded: 3

Belman 1988 *(Continued)*

- Gender (M/F): 10/7
- COPD stage: moderate to severe

Included criteria

- Presence of COPD as defined by the ATS, and improvement in FEV1 < 20% after inhaled isoproterenol

Excluded criteria

- Evidence of coronary artery disease, cardiac arrhythmias, congestive heart failure, and orthopedic problems such as shoulder girdle and spinal abnormalities, which would interfere with the performance of the breathing manoeuvres

Interventions	**Intervention characteristics** **IMT:** the training protocol consisted of unsupervised sessions, 2 sessions/d, 7/week for 6 weeks. Each session lasted 15 min, using a Pflex device (the breathing pattern was controlled), and the training load was as tolerated. **Control/sham:** the control group received similar training at a load of around 7.5-10 cmH_2O.
Outcomes	Respiratory muscle strength: PImax (FRC) Respiratory muscle endurance: • MVV • P_{thmax} Respiratory function: FEV1 (L)
Identification	**Country:** USA **Setting:** hospital **Author's name:** Michael J Belman **Institution:** Division of Pulmonary Medicine, Cedars-Sinai Medical Center, and The University of California **Address:** Los Angeles, California 90048
Notes	

Berry 1996

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 8/7 • Loss to follow-up or excluded: 1 • Age, mean (SD), in years: 67.0 (3.39) • Gender (M/F): 4/4

Berry 1996 *(Continued)*

PR

- N (randomized/analyzed): 9/9
- Loss to follow-up or excluded: 0
- Age, mean (SD), in years: 70.8 (4.8)
- Gender (M/F): 6/3

Overall

- N (randomized/analyzed): 17/16
- Loss to follow-up or excluded: 1
- Gender (M/F): 10/7
- COPD stage (GOLD): moderate to severe

Included criteria

- FEV1/FVC < 0.65;
- Dyspnea on exertion experienced during activities of daily living;
- A history of cigarette or tobacco smoke exposure > 20 pack-years;
- The ability to self ambulate;
- Age > 60 years;
- Willingness to undergo testing and intervention procedures;
- COPD under appropriate medical management.

Excluded criteria

- Significant cardiac disease;
- Orthopedic or neurologic impairment, serious renal, liver, or gastrointestinal disorders; current psychiatric illness or substance dependence; uncontrolled diabetes or hypertension;
- Current or previous (within 6 months) enrollment in a rehabilitation or exercise program;
- SaoO2 < 90% during exercise at a heart rate > 50% of age-predicted maximum.

Interventions

Intervention characteristics

PR+IMT

- PR: the rehabilitation program involved walking, upper extremity strength training, and progressive IMT. Walking intensity was set at 50%-75% of the participant's heart rate reserve. This prescription was based on the heart rate response from the participant's initial graded exercise test. The duration of walking was increased progressively throughout the intervention to a maximum of 20 min. Participants were taught to monitor their heart rate during walking by palpating their radial artery and to adjust their exercise intensity as needed. Heart rates were taken midway through and at the end of the walking sessions. Upper extremity weight-training consisted of 5 different exercises. Participants performed 2 sets of 12 repetitions for each exercise with the weight being progressively increased as their strength increased. All walking and strength training was performed at the exercise center.
- IMT: was performed twice daily for a 15-min period, 7 d/week, for 12 weeks, using threshold IMT device (Healthscan Products, Cedar Grove, NJ). The initial pressure setting was set at 15% of the participant's PImax for 2 weeks. During Weeks 3 and 4, the threshold pressure was increased to 30% of the participant's PImax. During weeks 5 and 6, the threshold pressure was increased to 60% of the participant's PImax. During Weeks 7 through 12, the threshold pressure was set at 80% of the participants PImax.

PR + sham IMT: this group underwent PR as described above, and IMT at 15% of PImax for the duration of the 12-week study period.

Outcomes

Dyspnea: Borg

Functional exercise capacity:

- exercise time (treadmill)
- 12MWD

Berry 1996 *(Continued)*

	Respiratory muscle strength: PImax Laboratory exercise test: VO2peak (mL/kg/min) Respiratory muscle endurance: MVV Respiratory function: • FEV1 (%pred) • FEV1 (L)
Identification	**Sponsorship source:** **Country:** USA **Setting:** Wake Forest University **Author's name:** MichaelJ.Berry **Institution:** Department of Health and Sport Science **Address:** P.O. Box 7234, Wake ForestUniversity, Winston-Salem, NC 27109
Notes	All values are adjusted means ± SEM. Values were adjusted using pre-intervention scores as the covariate.

Berton 2015

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): /7 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 65.3 • Gender (M/F): 3 • BMI, mean (SD), kg/m^2: 25.8 Control/sham • N (randomized/analyzed): /6 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 66.3 (9.2) • Gender (M/F): 1/5 • BMI, mean (SD), kg/m^2: 24.5 (5.0) Overall • N (randomized/analyzed): 24/13 • Loss to follow-up or excluded: 9 • Age, mean (SD) in years: 66.8 (9.1) • Gender (M/F): 4/9 • COPD stage: moderate to very severe

Berton 2015 *(Continued)*

	Included criteria • Patients with spirometric evidence of significant chronic airflow limitation (FEV1 < 70%pred, FEV1/FVC < 0.7) according to the criteria of Global Strategy for Diagnosis, Management, and Prevention of COPD; • Patients with a long history of smoking (> 20 pack-years) were invited to participate from the tertiary clinic care center. • Participants were receiving continuously formoterol/budesonide (12/400 µg) twice a day (dry powder inhaler), short-acting bronchodilators as rescue medications, and had not participated in PR in the previous 24 months. **Excluded criteria** • Exacerbation of COPD in the previous 3 months or during the study; • Cardiac disease (acute coronary syndrome in the previous 3 months or cardiac ejection fraction < 50%); • long term oxygen therapy or arterial oxygen saturation < 90% at rest, • Neuromuscular disease, peripheral arterial disease, cancer; • Physically unable to move.
Interventions	**Intervention characteristics** **IMT:** the training was unsupervised, 30 min/d, 7 d/week, for 8 weeks. The device used was Power-breathe(Southam, UK) set at 30% of PImax. **Control/sham:** this group underwent similar training at no load.
Outcomes	Dyspnea: Borg Functional exercise capacity: exercise time HRQoL: SGRQ • Symptoms • Activity • Impact • Total Inspiratory muscle strength (PImax)
Identification	**Country:** Brazil **Author's name:** Danilo C. Berton **Institution:** Graduation Program in Pulmonology, Federal University of Rio Grande do Sul (UFRGS), Brazil **Email:** dberton@hcpa.edu.br **Address:** Rua Ramiro Barcelos, 2350, Room 2050. Postal Code: 90035-003, Porto Alegre, RS, Brazil **Clinical trial register:** NCT 01945398
Notes	Participants were instructed to maintain diaphragmatic breathing, with a breathing rate of 15-20 breaths/min.

Bustamante 2007

Study characteristics	

Bustamante 2007 *(Continued)*

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 12/12 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 62 (13.7) • BMI, mean (SD), kg/m^2: 26.03 (3.46) Control/sham • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 61.5 (8.6) • BMI, mean (SD), kg/m^2: 26.9 (4.41) Overall • N (randomized/analyzed): 22/22 • Loss to follow-up excluded: 0 • COPD stage (GOLD): moderate to severe **Included criteria** • Patients with a clinically stable COPD for a month before selection. **Excluded criteria** • Hypoxemia (PaO_2 < 60 mmHg), asthma, coronary heart disease, metabolic diseases, orthopedic diseases, history of recent thoracic or abdominal surgery, treatment with corticosteroid, hormones and chemotherapy.
Interventions	**Intervention characteristics** **IMT:** the training was unsupervised, conducted twice a day, 15 min/session, 7 d/week, for 6 weeks. Threshold IMT device was used at the maximum tolerated load. **Control/sham:** this group underwent a similar training at a load equal to 7cmH_20.
Outcomes	HRQoL: CRQ • Dyspnea • Fatigue • Emotion • Mastery Respiratory muscle strength: PImax Respiratory muscle endurance time: T_{lim} (Threshold device) **Notes**: sustained time with a threshold of 66% of PImax
Identification	**Country:** Spain **Author's name:** Víctor Bustamante Madariaga **Institution:** Servicio de Neumología. Hospital de Basurto. Osakidetza. Vizcaya. España

Bustamante 2007 *(Continued)*

Email: VICTOR.BUSTAMANTEMADARIAGA@hbas.osakidetza.net

Notes	

Charususin 2018

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 110/89 • Loss to follow-up or excluded: 26 • Age, mean (SD) in years: 66 (8) • Gender (M/F): 52/58 • BMI, mean (SD), kg/m^2 : 25 (6) PR • N (randomized/analyzed): 109/85 • Loss to follow-up or excluded: 29 • Age, mean (SD) in years: 65 (7) • Gender (M/F): 43/66 • BMI, mean (SD), kg/m^2 : 24 (6) Overall • N (randomized/analyzed): 219/174 • Loss to follow-up or excluded: 55 • Gender (M/F): 95/124 • COPD stage (GOLD): moderate to very severe **Included criteria** • Clinically stable COPD patients with reduced maximal inspiratory mouth pressure (PImax < 60 cm H2O or < 50% of the predicted normal value) participated in the study between February 2012 and October 2016. **Excluded criteria** • Diagnosed psychiatric or cognitive disorders • Progressive neurological or neuromuscular disorders • Severe orthopaedic problems having a major impact on daily activities • Previous inclusion in a rehabilitation program (< 1 year) **Pretreatment:** "One of the centres offering a 36 session program (32% of total inclusions) consistently exceeded between-group differences in the centre offering 20 sessions (36% of total inclusions). In the other centres offering 36 sessions (combined 32% of total inclusions), between-group differences in these outcomes were consistently smaller than in the centre offering a lower training volume (see online supplementary table E4)"
Interventions	**Intervention characteristics**

Charususin 2018 *(Continued)*

PR+IMT

- PR: consisted of cycling, treadmill walking, stair climbing, arm ergometry and resistance training of arm as well as leg muscles training volume, and ranged from 20 sessions (Germany) to 36 sessions (other centers). Training frequency ranged from 3-5 sessions/week. Duration of training sessions was around 60 min. Participants performed endurance training or interval training at moderate to high intensities. During PR, training intensities were progressively increased according to a Borg CR-10 scale ratings of 4–6 on dyspnea sensation.
- IMT: performed daily using the PowerBreathe KHP2 device (POWERbreatheKHP2, HaB International, Southam, UK) according to previously described methods: 2-3 sessions/d, 7 min each, 7 d/week, for 12 weeks. Training intensity in the intervention group was set initially at a load of approximately 50% of participants' maximal inspiratory mouth pressure (PImax). This initial load was then continuously and gradually increased to the highest tolerable intensity during each of the supervised sessions.

PR +sham IMT: this group underwent the same training as described above with IMT load at 10% of PImax. The load was not modified throughout the intervention period.

Outcomes

Dyspnea: Borg

- post-6MWD
- Incremental cycle ergometer test
- Constant cycle ergometer test

Functional exercise capacity:

- 6MWD
- Wmax
- Exercise time

HRQoL: CRQ

- Dyspnea
- Fatigue
- Emotion
- Mastery
- Total

Respiratory muscle strength: PImax

Laboratory exercise test: VO2peak

Respiratory muscle endurance: MVV

Respiratory muscle endurance time: T_{lim}

Respiratory function:

- FEV1 (L)
- RV

Identification

Sponsorship source: DL and HD are postdoctoral fellows of Research Foundation Flanders. HaB International (Southam, UK) and McRoberts (The Hague, The Netherlands) provided equipment for testing and training in this study on loan. This study was further supported by local funds throughout the participating centers. The following specific funding sources were reported: University Hospital Leuven, Belgium (FWO grant GOA4516N en KU Leuven grant C22/15/035); Ghent University Hospital, Belgium (UZ Gent grant FS/LGZ/994); Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec, Canada (Ordre professionnel de la physiothérapie du Québec).

Country: Belgium, The Netherlands, Germany, Canada

Setting: multicenter

Charususin 2018 *(Continued)*

	Author's name: Daniel Langer **Institution:** Department of Rehabilitation Sciences, KU Leuven **Email:** daniel. langer@ kuleuven. be **Address:** Leuven 3001, Belgium **Clinical trial register:** NCT01397396
Notes	Adjusted difference (95% CI) at post-training with its P value were reported.

Chuang 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 30/27 • Loss to follow-up or excluded: 3 • Age, mean (SD), in years: 66.22 (12.76) • Gender (M/F): 17/10 Control/sham • N (randomized/analyzed): 30/28 • Loss to follow-up or excluded: 2 • Age, mean (SD), in years: 66.04 (10.99) • Gender (M/F): 19/9 Overall • N (randomized/analyzed): 60/55 • Loss to follow-up or excluded: 5 • Gender (M/F): 36/19 • COPD stage (GOLD): moderate to very severe **Included criteria** • Outpatients with a stable condition • Showed airflow limitation on pulmonary function test, that is FEV1 < 80% and FEV1/FVC < 70% • Participants were conscious and able to express themselves orally, were self-walkers and co-operated with the intervention. **Excluded criteria** • Cardiovascular diseases • Severe unstable diseases, such as pulmonary heart disease or cancer • Ongoing oxygen treatment • Muscle power rating < 5 • ADL scale score < 80

Chuang 2017 *(Continued)*

	• Severe mental illness
Interventions	**Intervention characteristics** **IMT:** the training was conducted 5 d/week, for 8 weeks. Each session lasted for 21–30 min. It consisted of a cycle of 2 min inspiratory training with a pressure threshold loading device and 1 min of rest, and then repeated 7 cycles. The training load ranged from 15 cmH_20 to 40 cmH_2O. Each participant was followed up once a day by phone from Monday–Friday, and visits were made by research assistants every 2 weeks to increase the pressure threshold loading progressively after assessing the participant's condition. **Control:** no intervention was received by this group.
Outcomes	Dyspnea: BDI Functional exercise capacity: 6MWD HRQoL: SF-36 Questionnaire • Physiological functions • Mental functions Respiratory muscle strength: PImax
Identification	**Country:** Taiwan **Author's name:** Hsiao-Yun Chang **Institution:** Department of Nursing, Fooyin University, Kaohsiung City **Email:** chang369@gmail.com **Address:** Taiwan
Notes	

Covey 2001

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	IMT • N (randomized/analyzed): 19/12 • Loss to follow-up or excluded: 10 • Age mean (SD) in years: 65 (6) • BMI, mean (SD), kg/m^2: 26 (4.8) Control/sham • N (randomized/analyzed): 18/15 • Loss to follow-up or excluded: 3 • Age mean (SD) in years: 67 (10) • BMI, mean (SD), kg/m^2: 28.8 (6) Overall

Covey 2001 *(Continued)*

- N (randomized/analyzed): 37/27
- Loss to follow-up or excluded: 10
- Gender (M/F): 18/9
- COPD stage: severe to very severe

Included criteria

- Severe to very severe airflow obstruction (FEV1 < 50%pred)
- Age: 45-75
- Severely limited functional performance

Excluded criteria

- History of asthma or > 25% increase in FEV1 after bronchodilator
- History of a major exacerbation within the past 2 months
- Current oral corticosteroid use (> 10 mg prednisone per day)
- Other health problems that would inhibit their ability to participate

Interventions	**Intervention characteristics** **IMT:** participants performed IMT at home 5 d/week, 30 min/d for 16 weeks (for a total of 80 training sessions) using Threshold IMT device. Starting training loads were 30% of PImax as tolerated. Participants were visited weekly at home by a nurse who supervised training, evaluated training loads, and progressively increased the training load as tolerated with a goal of achieving 60% of PImax. Home visits generally lasted approximately 30 min. An interval training protocol was used with participants performing 6 work sets of 5 mins' duration separated by rest intervals lasting 1-3 min. **Control/sham:** participants were visited by a nurse every 2 weeks for 16 weeks for a structured program of health education. Each home-based session lasted approximately 1-1.5 h and covered such topics as nutrition, relaxation techniques, pursed lip breathing, respiratory medications, respiratory infection, energy conservation techniques, oxygen therapy, and smoking cessation.
Outcomes	Dyspnea: Borg HRQoL: CRQ Respiratory muscle strength (PImax) Respiratory muscle endurance pressure: Pthmax
Identification	**Sponsorship:** This study was supported by a grant from the National Institutes of Nursing Research, grant number NRO1428; and was conducted at the University of Illinois at Chicago, College of Nursing, Chicago, Ill and Hines VA Hospital, Section of Critical Care and Pulmonary Medicine, Hines, Ill. **Country:** USA **Setting:** home-based **Author's name:** Margaret K. Covey **Institution:** University of Illinois at Chicago, College of Nursing **Email:** mkcovey@uic.edu **Address:** 845 South Damen Avenue, Chicago, IL 60612
Notes	

Cutrim 2019

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 11/11 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 66 (8.5) • Gender (M/F): 8/3 • BMI, mean (SD), kg/m^2 : 25 (4) Control/sham • N (randomized/analyzed): 11/11 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 70 (8.0) • Gender (M/F): 9/2 • BMI, mean (SD), kg/m^2 : 25 (4) Overall • N (randomized/analyzed): 22/22 • Gender (M/F): 17/5 **Included criteria** • Patients with COPD without heart failure or pulmonary hypertension • With inspiratory muscle weakness (PImax < 70% of predicted) and with stable pharmacological treatment, i.e. no drug change at least 1 month before the start of IMT **Excluded criteria** • Functional limiting factors that would interfere with the performance of IMT and/or the exercise capacity test, such as acute myocardial infarction 3 months before inclusion in the study, unstable angina or unstable ventricular arrhythmia or in the last 3 months prior to initiation, acute respiratory disease, rheumatic diseases, degenerative diseases, neurological sequelae, cognitive deficit etc
Interventions	**Intervention characteristics** **IMT:** the session of IMT consisted of 30 min (in a clinical setting) 3 times/week, using the Threshold Inspiratory Muscle Training device (POWERbreathe Medic+Plus, NCS, Barueri, SP, Brazil). The inspiratory load was set at 30% of PImax, for 12 weeks. During exercise, participants were instructed to maintain diaphragmatic breathing at a rate of 15–20 breaths/min. **Control/sham:** no intervention received by this group (except diaphragmatic breathing).
Outcomes	Functional exercise capacity: 6MWD Respiratory muscle strength: PImax
Identification	**Sponsorship source:** Fundação de Amparo à Pesquisa do Estado do Maranhão (FAPEMA); Hospital Universitário Presidente Dutra; Cristiano Mostarda received grants from CNPq (Universal 442374/2014-3) and FAPEMA (Bolsa Produtividade and Universal 00358/15). **Country:** Brazil

Cutrim 2019 *(Continued)*

	Setting: Hospital Universitário Presidente Dutra
	Author's name: Cristiano Teixeira Mostardaa
	Institution: Universidade Federal do Maranhão, São Luís, Brazil
	Email: cristiano.mostarda@gmail.com
	Address: Av. dos Portugueses, 1966, Cidade Universitária Dom Delgado, São Luís, MA, Brazil
	Clinical trial register: RBR-4mz6w9
Notes	Participants were instructed to maintain diaphragmatic breathing at a rate of 15–20 breaths/min. Adjusted analysis for age, weight and baseline were reported.

Dacha 2019

Study characteristics	
Methods	**Study design:** RCT
	Study grouping: parallel-group
Participants	**Baseline characteristics**
	IMT
	• N (randomized/analyzed): not reported/6 • N (analyzed): 6 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 65 (4) • Gender (M/F): 3/3 • BMI, mean (SD), kg/m^2 : 29 (8) • COPD stage (GOLD): mild to very severe
	Control/sham
	• N (randomized/analyzed): not reported/4 • N (analyzed): 4 • Loss to follow-up excluded: 0 • Age, mean (SD), in years: 68 (9) • Gender (M/F): 1/3 • BMI, mean (SD), kg/m^2: 22 (2) • COPD stage (GOLD): moderate to very severe
	Overall
	• N (randomized/analyzed): 24/10 • N (analyzed): 10 • Loss to follow-up excluded: 0 • Gender (M/F): 4/6 • COPD stage (GOLD): mild to very severe
	Included criteria
	• Clinical Diagnosis of COPD • Inspiratory muscle weakness (PImax < 70%pred or < 60 cmH2O)

Dacha 2019 *(Continued)*

- BDI < 7
- Peripheral muscle fatigue present after CPET

Excluded criteria

- Major cardiovascular limiting exercise capacity more than pulmonary function impairment
- Severe orthopedic with a major impact on ADL
- Psychiatric or cognitive disorders
- Progressive neurological or neuromuscular disorders
- Long term O2 therapy
- Previous inclusion in a rehabilitation program (< 1 year)

Interventions	**Intervention characteristics** **IMT:** the training was conducted twice a day, 7 d/week, for 8 weeks. All the sessions were supervised, 5 min each, using Powerbreathe device set at a 50% of PImax. **Control/sham:** participants in this group received a similar protocol with a training load at 10% of PI-max.
Outcomes	Dyspnea: Borg Respiratory muscle strength: PImax Laboratory exercise test: VO2peak
Identification	**Sponsorship source:** KU Leuven **Country:** Belgium **Author's name:** Sauwaluk Dacha **Institution:** Faculty of Kinesiology and Rehabilitation Sciences, Department of Rehabilitation Sciences, Research Group for Rehabilitation in Internal Disorders **Email:** sauwaluk.dacha@kuleuven.be **Address:** KU Leuven, Leuven, Belgium **Clinical trial register:** NCT03240640
Notes	This study is still ongoing.

De Farias 2019

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	Overall - N (randomized/analyzed): 33/31 - Loss to follow-up or excluded: 2 - Age, mean (SD) in years: 66.2 (4.9) - BMI: 28 (4.3)

De Farias 2019 *(Continued)*

Inclusion criteria

- Individuals with a clinical diagnosis of COPD according to GOLD
- Being treated at the Ambulatory Pulmonology department of University Hospital Onofre Lopes (HUOL)/Empresa Brasileira de Serviços Hospitalares (EBSERH)
- Aged 40-80 years
- Living in the city of Natal, RN/Brazil
- Not using oxygen therapy or presenting disease exacerbation in the last 3 months
- Not practising regular physical activity in the last 6 months

Exclusion criteria

- Musculoskeletal comorbidities that impair gait
- SpO_2 < 90% during 6MWD
- Hypertensive without control medication as well as those presenting with a hypertensive peak (> 140/90 mmHg) for > 3 consecutive days
- An intellectual understanding impairment that interferes with the evaluation tests
- Those who stop the therapeutic program, miss activity for > 1 week, or miss reevaluation

Interventions	**Intervention characteristics** **PR+ sham IMT** • PR: performed 3 times/week for 10 weeks. All individuals were instructed to perform the rehabilitation program 5 days/week — 3 days with supervision and 2 without supervision — for at least 1 h/d. The program consisted of health education, treadmill aerobic training with 70% of max incremental shuttle walk test speed and peripheral muscle strength training. • Sham IMT: performed with Powerbreathe device at no load for 3 cycles of 12 repetitions. **PR+ threshold IMT** • PR: the same protocol as described above • Threshold IMT: participants trained using POWERbreathe KH1 (POWERbreathe International Ltd.) at 35% of MIP), increasing 5% every week until reaching 80% of MIP at the 10th week, which was maintained until the end of the protocol. The MIP was assessed weekly to adjust the training load percentage. Participants performed 3 cycles of 12 repetitions. **PR + isocapnic hyperpnea** • PR: the same protocol as described above. • Isocapnic hyperpnea: participants received training with a duration of up to 20 min, 1 min of training and 1 min of rest, where they were encouraged with instructions such as “breathe faster.” The training respiratory rate chosen was calculated as 35-fold FEV1, so that ventilation corresponded to 50%–60% of MVV. The device used was STMedical device (SpiroTiger, Chamonix Mont Blanc, France).
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD Respiratory muscle strength: PImax
Identification	**Sponsorship source:** no funding **Country:** Brazil **Author's name:** Guilherme Augusto de Freitas **Institution:** PneumoCardioVascular Lab/HUOL, Empresa Brasileira de Serviços Hospitalares - EBSERH), Universidade Federal do Rio Grande do Norte (UFRN), **Email:** fregonezi.guilherme@gmail.com

De Farias 2019 *(Continued)*

	Address: Natal, Rio Grande do Norte, Brazil
Notes	

Dekhuijzen 1991

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 58/8 • Gender (M/F): 14/6 PR • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 60/7 • Gender (M/F): 16/4 Overall • N (randomized/analyzed): 40/40 • Loss to follow-up or excluded: 0 • Gender (M/F): 30/10 • COPD stage (GOLD): moderate to severe **Included criteria:** patients with functional limitations due to COPD **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **PR+IMT** • PR: consisted of exercise training, i.e. cycling, walking, and training of back, shoulder, and abdominal muscles. The intensity of the exercise training was determined by the symptoms of the patients. Moreover, the heart rate during these exercises did not exceed 80% of the maximal heart rate reached during the maximal bicycle ergometer test. Other parts of the PR program were callisthenics, conventional physiotherapy (breathing retraining, relaxation exercises), and education about pulmonary disease and the purpose and use of the medications. The training was conducted 2 h every day, 5 d/week, for 10 weeks. • IMT: was conducted along with PR, 15 min twice a day, supervised by the physiotherapist, using incentive spirometer at 70% of PImax. **PR:** this group received only the PR described above.
Outcomes	HRQoL: ADL Functional exercise capacity:

Dekhuijzen 1991 *(Continued)*

- 12MWD
- Wmax (incremental cycle ergometer test)

Respiratory muscle strength: PImax

Laboratory exercise test: VO2peak

Respiratory muscle endurance time: T_{lim}

Identification	**Country:** The Netherlands **Setting:** Medical Centre Dekkerswald (outpatient clinic) **Author's name:** P. N. Richard Dekhuijzen **Institution:** the University of Nijmegen, Department of Pulmonary Diseases, Medical Centre Dekkerswald **Address:** Groesheek, the Netherlands
Notes	We used convertunits.com to convert from Kpa to cmH2O.

Dellweg 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 15/15 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 66 (8) • Gender (M/F): 7/8 • BMI, mean (SD), kg/m^2: 24.5 (6.4) PR • N (randomized/analyzed): 14/14 • Loss to follow-up or excluded: 0 • Age, mean (SD), in years: 66 (7.5) • Gender (M/F): 9/5 • BMI, mean (SD), kg/m^2: 23.9 (4) Overall • N (randomized/analyzed): 29/29 • Loss to follow-up or excluded: 0 • Gender (M/F): 16/13 • COPD stage (GOLD): severe to very severe **Included criteria** • Patients with persistent hypercapnic respiratory failure who required non-invasive ventilation after prolonged weaning according to the criteria of Boles et al (Boles 2007)

Dellweg 2017 *(Continued)*

- Main diagnosis of COPD
- Participants had to be admitted to our in-patient post-weaning rehabilitation unit, had to be ambulatory, co-operative, and physically able to participate in twice-daily physiotherapeutic sessions
- Patients had to have confirmed COPD stage 3 or 4 by a lung function test (FeV1 < 50%, Fev1/FVC < 70%)
- Had to be free of exacerbation

Excluded criteria

- Renal impairment (serum creatinine levels < 2 mg/dL)
- Severe cardiac impairment (ejection fraction < 40%)

Interventions	**Intervention characteristics** **PR+IMT:** • PR: consisted of twice daily, hour-long physiotherapy group sessions in the rehabilitation gym. Physiotherapy sessions included training with arm and leg ergometers, as well as weight training. Additionally, every patient participated in daily ergotherapy group sessions lasting 1 h each to improve fine motor skills. • IMT: consisted of supervised sessions, once daily during weekdays, for 4 weeks. Participants underwent strength training at 80% of PImax and endurance training at 60% of PImax using Respifit S Trainer (Biegler, Mauerbach, Austria) **PR+ (sham IMT):** participants in this group received a similar protocol as described above with IMT training load fixed at 5 cm H_2O, and using Threshold IMT (Philips-Respironics, Pittsburgh, PA, USA).
Outcomes	Functional exercise capacity: 6MWD Respiratory muscle strength: PImax (RV) Respiratory function: FEV1
Identification	**Sponsorship source:** no funding **Country:** Germany **Author's name:** Dominic Dellweg **Institution:** Department for Pulmonology, Intensive Care and Rehabilitation **Email:** d.dellweg@fkkg.de **Address:** 1, 57392 Schmallenberg, Germany **Clinical trial register:** NCT00291460
Notes	

Fanfa Bordin 2020

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT

Fanfa Bordin 2020 *(Continued)*

- N (randomized or analyzed): 10/10
- Loss to follow-up or excluded: 0
- Age, mean (SD) in years: 63.2 (5.7)
- Gender (M/F): 5/5
- BMI, mean (SD), kg/m^2 : 25.3 (5.1)

PR

- N (randomized/analyzed): 12/10
- Loss to follow-up or excluded: 2
- Age, mean (SD) in years: 66.2 (9.2)
- Gender (M/F): 4/6
- BMI, mean (SD), kg/m^2 : 25.4 (5.8)

Overall

- N (randomized/analyzed): 22/20
- Loss to follow-up or excluded: 2
- Gender (M/F): 9/11
- COPD stage (GOLD): moderate to very severe

Included criteria

- COPD patients at the stages 2-4, according to the GOLD classification
- Participating in a lung rehabilitation program for at least 2 months
- Clinically stable
- Signed the informed consent

Excluded criteria

- Individuals with asthma, and/or cardiovascular disease and individuals with cognitive and/or behavioral impairments

Interventions	**Intervention characteristics** **PR+IMT** • PR: the lung rehabilitation program included 30 min of cycling exercise on a vertical cycle ergometer for lower limbs (Movement, BM 2700, Brazil) set at 60% of the maximal heart rate determined using the Karvonen method modified for the reserve heart rate (Meyer 2013). Participants also performed strengthening exercises for the upper and lower limbs' major muscles, with the intensity of 50%-80% of the 1 repetition maximum test (1RM). • IMT: involved supervised sessions, 3 times/week for 20 min over 4 weeks, which was increased to 25 min on weeks 5 and 6, and to 30 min on weeks 7 and 8. Participants used Threshold IMT set at 50% of PImax. **PR:** this group received only the PR described above.
Outcomes	Respiratory muscle strength: PImax
Identification	**Country:** Brazil **Setting:** Santa Cruz do Sul Hospital, Brazil **Author's name:** Diogo Fanfa Bordin **Institution:** Universidade de Santa Cruz do Sul (Unisc) – Santa Cruz do Sul (RS), Brazil **Email:** diogo.fanfa@hotmail.com

Fanfa Bordin 2020 *(Continued)*

Clinical trial register: NCT02014155

Notes

Harver 1989

Study characteristics

Methods

Study design: RCT

Study grouping: parallel-group

Participants

Baseline characteristics

IMT

- N (randomized/analyzed): not reported/10
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 61.1 (9.5)
- Gender (M/F): 8/2

Control/sham

- N (randomized/analyzed): not reported/9
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 64.8 (8.4)
- Gender (M/F): 8/1

Overall

- N (randomized/analyzed): 23/19
- Loss to follow-up or excluded: 4
- Gender (M/F): 16/3
- COPD stage (GOLD): moderate to severe

Included criteria

- Participants for the study were recruited from the clinical practice of pulmonary physicians at the institution
- Participants were stable both clinically and functionally, and medications were not changed during the study.

Excluded criteria: not reported

Interventions

Intervention characteristics

IMT: participants trained twice a day, 15 min each session, 7 d/week, for 8 weeks. The training device was Pflex (with a controlled breathing pattern), and the training load ranged from 5 cmH_2O to 35 cmH_2O (≈30% PImax FRC)

Control/sham: this group received a similar IMT protocol with a training load set at 5cmH_2O

Outcomes

Dyspnea: BDI-TDI:

- Functional impairment
- Magnitude of task
- Magnitude of effort

Harver 1989 *(Continued)*

- Focal score

Respiratory muscle strength: PImax

- RV
- FRC

Respiratory function: FEV1

- L

Respiratory muscle endurance: MVV

Identification	**Sponsorship source:** The American Lung Association of New Hampshire and by grants HL07449 and HL29068 from the National Heart, Lung, and Blood Institute **Country:** USA **Setting:** Outpatient pulmonary clinic and pulmonary function laboratory **Author's name:** Andrew Harver **Institution:** Department of Psychology, SUNY Stony Brook **Address:** Stony Brook, NY 11794
Notes	

Heijdra 1996

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 62.4 (8.8) • Gender (M/F): 7/3 • BMI, mean (SD), kg/m^2: 23.7 (3.3) Control/sham • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 61.8 (7.3) • Gender (M/F): 8/2 • BMI, mean (SD), kg/m^2: 23 (3.2) Overall • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 • Gender (M/F): 15/5

Heijdra 1996 *(Continued)*

	• COPD stage (GOLD): moderate to very severe **Included criteria** • Mean nocturnal arterial oxygen saturation was < 92% • All participants were in a stable condition at the time of study as defined by a fluctuation in FEV1 of < 10% in the preceding 6 months **Excluded criteria** • Patients with other pulmonary diseases, chest wall deformations, a previous thoracotomy, diabetes mellitus, neuromuscular diseases, obstructive sleep apnea syndrome, or an overlap syndrome
Interventions	**Intervention characteristics** **IMT:** participants trained at home, daily, 2 sessions of 15 min/day for 10 weeks. They used incentive flowmeter (INSPIRx; Resprecare Medical Inc., the Hague, the Netherlands) set at 60% of PImax **Control/sham:** participants received a similar training protocol and the resistance was set at 10% of PI-max
Outcomes	Inspiratory muscle strength (PImax) Respiratory muscle endurance time (T_{lim})
Identification	**Sponsorship source:** Dutch Asthma Foundation (No. 90-27) **Country:** The Netherlands **Author's name:** Yvonne F. Heijdra, Department of Pulmonary Diseases **Institution:** University of Nijmegen, Medical Centre Dekkerswald **Address:** P.O. Box 9001, 6560 GB Groesbeek, the Netherlands
Notes	

Hill 2006

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 18/16 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 69.4 (7.2) • Gender (M/F): 11/5 • BMI, mean (SD), kg/m^2: 24.9 (4.3) Control/sham • N (randomized/analyzed): 17/17 • Loss to follow-up or excluded: 0

Hill 2006 *(Continued)*

- Age, mean (SD) in years: 66.6 (9.8)
- Gender (M/F): 11/6
- BMI, mean (SD), kg/m^2: 24.1 (3.7)

Overall

- N (randomized/analyzed): 35/33
- Loss to follow-up or excluded: 2
- Gender (M/F): 22/11
- COPD stage (GOLD): severe to very severe

Included criteria

- Participants who had a diagnosis of COPD
- Smoking history of 10 pack-years
- FEV1 ranging 15%–70% of predicted normal

Excluded criteria

- Comorbid conditions likely to reduce exercise capacity (e.g. symptomatic ischemic heart disease, BMI > 35 kg.m^2)
- Previous lung surgery
- The use of long-term oxygen therapy
- Weaning doses of oral corticosteroids

Interventions	**Intervention characteristics** **IMT:** participants attended supervised training sessions 3 times/week for 8 weeks. Each session lasted 21 min and comprised 7 cycles of 2 min of breathing on an inspiratory threshold loading device (Threshold IMT; Respironics, Cedar Grove, NJ, USA) followed by 1 minute of rest. The training load was set at a range of around 45%-101% of PImax **Control/sham:** this group received a similar IMT protocol with a training load set at 10% of PImax
Outcomes	Dyspnea: Borg • Post 6MWD • Wmax Functional exercise capacity: • 6MWD • Wmax HRQoL: CRQ • Dyspnea • Fatigue • Emotion • Control • Total Respiratory muscle strength (PImax) Respiratory muscle endurance: Respiratory muscle endurance pressure (P_{thmax}) Laboratory exercise test: VO2peak (mL/kg/min) Respiratory function: FEV1 • %pred

Hill 2006 *(Continued)*

- L

Respiratory function: RV

- %pred
- L

Identification	**Sponsorship source:** The National Health and Medica Research Council (Canberra, Australia) grant number 212016 **Country:** Australia **Author's name:** P.R. Eastwood **Institution:** Dept of Pulmonary Physiology, Sir Charles Gairdner Hospital **Email:** peter.eastwood@health.wa.gov.au **Address:** Hospital Avenue Nedlands Western Australia, Australia 6009
Notes	

Hill 2007

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 18/16 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 69.4 (7.2) • Gender (M/F): 11/5 • BMI, mean (SD), kg/m^2: 24.9 (4.3) Control/sham • N (randomized/analyzed): 17/17 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 66.6 (9.8) • Gender (M/F): 11/6 • BMI, mean (SD), kg/m^2: 24.1 (3.7) Overall • N (randomized/analyzed): 35/33 • Loss to follow-up or excluded: 2 • Gender (M/F): 22/11 • COPD stage (GOLD): severe to very severe **Included criteria** • Participants who had a diagnosis of COPD • Smoking history of 10 pack-years

Hill 2007 *(Continued)*

	• FEV1 ranging 15%–70% of predicted normal **Excluded criteria** • Comorbid conditions likely to reduce exercise capacity (e.g. symptomatic ischemic heart disease, BMI > 35 kg.m^2) • Previous lung surgery • The use of long-term oxygen therapy • Weaning doses of oral corticosteroids
Interventions	**Intervention characteristics** **IMT:** participants attended supervised training sessions 3 times/week for 8 weeks. Each session lasted 21 min and comprised 7 cycles of 2 min of breathing on an inspiratory threshold loading device (Threshold IMT; Respironics, Cedar Grove, NJ, USA) followed by 1 minute of rest. The training load was set at a range of around 45%-101% of PImax **Control/sham:** this group received a similar IMT protocol with a training load set at 10% of PImax
Outcomes	Respiratory muscle endurance time: T_{lim} Respiratory muscle endurance pressure (P_{thmax}) • Note: the same as Hill 2006
Identification	**Sponsorship source:** The National Health and Medica Research Council (Canberra, Australia) grant number 212016 **Country:** Australia **Author's name:** P.R. Eastwood **Institution:** Dept of Pulmonary Physiology, Sir Charles Gairdner Hospital **Email:** peter.eastwood@health.wa.gov.au **Address:** Hospital Avenue Nedlands Western Australia, Australia 6009
Notes	

Hsiao 2003

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT (Threshold device) • N (randomized/analyzed): not reported/10 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 68.2 (6.5) • Gender (M/F): 10/0 IMT (Incentive spirometer)

Hsiao 2003 *(Continued)*

- N (randomized/analyzed): not reported/10
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 70.4 (5.3)
- Gender (M/F): 8/2

Control/sham

- N (randomized/analyzed): not reported/10
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 71.1 (3.9)
- Gender (M/F): 8/2

Overall

- N (randomized/analyzed): 42/30
- Loss to follow-up or excluded: 12
- Gender (M/F): 26/4
- COPD stage (GOLD): moderate to severe

Included criteria

- Patient with moderate to severe COPD
- FEV1 < 2L and FEV1/FVC < 60%

Excluded criteria

- Restrictive lung disease
- History of cardiovascular disease or musculoskeletal conditions that could interfere with the training or the testing maneuvers

Interventions	**Intervention characteristics** **IMT:** participants trained twice a day, 15 min/session, 5days/week for 8 weeks. The sessions were unsupervised. Participants were divided into two groups using either Threshold IMT or Respirex, which were set at 50% of PImax **Control/sham:** this group did not receive any intervention
Outcomes	Functional exercise capacity: 6MWD Respiratory muscle strength: PImax (RV) Respiratory muscle endurance time: T_{lim} (Threshold device) • Notes: measured while breathing against 70% of PImax
Identification	**Country:** Taiwan **Setting:** Pulmonary clinic of 1 university hospital **Author's name:** Ying Tai Wu **Institution:** School and graduate institute of physical therapy, college of medicine, National Taiwan University Hospital **Address:** 7 Chung Shan South Road, Taipei 100, Taiwan
Notes	

Kim 1993

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): not reported/41 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 66 (7) • BMI, mean (SD), kg/m^2: 25 (4) Control/sham • N (randomized/analyzed): not reported/26 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 63 (8) • BMI, mean (SD), kg/m^2: 25 (4) Overall • N (randomized/analyzed): 129/67 • Loss to follow-up or excluded: 62 • Gender (M/F): 51/16 • BMI, mean (SD), kg/m^2: • COPD stage (GOLD): severe to very severe **Included criteria** • No history of asthma or restrictive lung disease • Free of respiratory tract infection for at least 2 months prior to enrollment and free of other chronic health problems that would interfere with their ability to participate in the study **Excluded criteria** • > 10 mg of prednisone daily
Interventions	**Intervention characteristics** **IMT:** participants trained 7 days/week, 30 min/session, for 6 months. Training sessions were unsupervised, and the device used was a Threshold IMT device set at 30% of PImax **Control/sham:** this group received IMT at no load
Outcomes	Functional exercise capacity: 12MWD Respiratory muscle endurance time: T_{lim} • Notes: measured while breathing at 66% of PImax. Respiratory muscle strength: PImax (RV)
Identification	**Sponsorship source:** supported by a grant from the National Center for Nursing Research, grant number NRO1428 **Country:** USA **Author's name:** Mija Kim

Kim 1993 *(Continued)*

	Institution: College of Nursing, University of Illinois at Chicago
Notes	

Koppers 2006

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group **Subgroup analysis:** PImax < 75%pred
Participants	IMT • N (randomized/analyzed): 19/18 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 54.4 (7.7) • Gender (M/F): 8/10 • BMI, mean (SD), kg/m^2: 26.7 (5.0) Control/sham • N (randomized/analyzed): 20/18 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 57.0 (8.5) • Gender (M/F): 9/9 • BMI, mean (SD), kg/m^2: 27.5 (3.3) Overall • N (randomized/analyzed): 39/36 • Loss to follow-up or excluded: 3 • Range age (min, max): 38,73 • Gender (M/F): 17/19 • COPD stage (GOLD): moderate to severe **Included criteria** • Chronic airflow obstruction, defined as an FEV1/FVC ratio 70%, FEV1of 30%-80%pred, after bronchodilation • Stable clinical condition for at least 6 weeks **Excluded criteria** • Hypoxemia at rest or during exercise • Cardiac orthopaedic disease • BMI > 30 kg/m^2
Interventions	**Intervention characteristics** **IMT:** respiratory muscle endurance training was performed by means of tube breathing. A tube (internal diameter, 3 cm) connected to a mouthpiece was added to the respiratory system to rebreathe exhaled carbon dioxide (normocapnic hyperpnea). The maximum ventilatory capacity that can be sustained for 15 min is approximately 60% of MVV. Therefore, the aimed level of ventilation during training

Koppers 2006 *(Continued)*

	was set at 60% of MVV, which was calculated from 35 times FEV1 (60% MVV = 0.6 * 35 * FEV1). The dead space was adjusted to 60% of the participant's IVC plus the resting tidal volume. Participants trained twice daily, for 15 min, 7 d/week for 5 weeks. **Control/sham:** participant breathed 6-7 times/min through an incentive flowmeter (Inspirx; Respre-care Medical; the Hague, the Netherlands). Airflow resistance was set at 5% of PImax.
Outcomes	Dyspnea: Borg • Notes: Borg was measured at isocapnic time during constant-load exercise training on a cycle ergome-ter Functional exercise capacity: • 6MWD • Wmax • Exercise time (Constant cycle ergometer test) HRQoL: CRQ (Total) Respiratory muscle strength: PImax (RV) Laboratory exercise test: VO2peak (mL/kg/min) Respiratory muscle endurance: Respiratory muscle endurance pressure (P_{thmax}) Respiratory function: FEV1 (L)
Identification	**Sponsorship source:** **Country:** The Netherlands **Setting:** Department of Pulmonology Dekkerswald, University Medical Center Nijmegen **Author's name:** Ralph J. H. Koppers **Institution:** MedicalCenter Leeuwarden, Leeuwarden; and Department of Pulmonology (Drs. Vos, Boot, and Folgering), Dekkerswald, University Medical Center Nijmegen **Email:** R.J.H.Koppers@ZNB.nl **Address:** Nijmegen, the Netherlands
Notes	

Langer 2018

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 73 (4)

Langer 2018 *(Continued)*

- Gender (M/F): 4/6
- BMI, mean (SD), kg/m^2: 24.1 (4.6)

Control/sham

- N (randomized/analyzed): 10/10
- Loss to follow-up or excluded: 0
- Age, mean (SD) in years: 67 (8)
- Gender (M/F): 3/7
- BMI, mean (SD), kg/m^2: 25.1 (6.7)

Overall

- N (randomized/analyzed): 20/20
- Loss to follow-up or excluded: 0
- Age, mean (SD) in years: 70 (7)
- Gender (M/F): 7/13
- BMI, mean (SD), kg/m^2: 24.6 (5.6)
- COPD stage (GOLD): moderate to very severe

Included criteria

- Participants were clinically stable COPD patients with reduced inspiratory muscle strength (Pimax < 70 cmH2O measured at plethysmographic FRC)
- Persistent activity-related dyspnea (BDI < 9) despite optimal medical therapy

Excluded criteria

- Inability to perform physiological testing
- Active cardiovascular comorbidity (i.e.severe heart failure with reduced left ventricular ejection fraction, cardiomyopathy, recent acute myocardial infarction, cardiac arrhythmias, or stroke), or other conditions that could impact dyspnea or exercise capacity

Interventions	**Intervention characteristics** **IMT:** the training was performed with a home-based protocol using an electronic device: Powerbreathe KH2 (HAB International, Southam, UK). Participants trained 2-3 daily sessions of 30 breaths (4-5 min/session) performed 7 days/week for 8 weeks. The training load started at around 40% of PImax and it was increased weekly until the highest tolerable intensity **Control/sham:** this group performed IMT at a load of < 10% of PImax
Outcomes	Dyspnea: Borg • isotime cycle ergometer test) • peak exercise cycle ergometer test) • Notes: Borg measured at isotime: cycle ergometer test Dyspnea: BDI-TDI: Total Dyspnea: mMRC Functional exercise capacity: Exercise time (constant cycle ergometer test) Respiratory muscle strength: PImax • RV • FRC Respiratory muscle endurance time (T_{lim})

Langer 2018 *(Continued)*

	• Notes: measured through breathing against 50%-60% of PImax Laboratory exercise test: VO2peak (Constant cycle ergometer test) (L/min) Respiratory function: FEV1 (L)
Identification	**Sponsorship source:** this work was supported by the Ontario Thoracic Society, Spear/StartEndowment Fund, Queen's University. D. Langer received a postdoctoral fellowship and travel grant from the Research Foundation Flanders; thePowerBreathe devices used in the study were provided by HaB International **Country:** Canada **Setting:** Queen's University Health Sciences and Affiliated Teaching Hospitals **Author's name:** D. E. O'Donnell **Institution:** Respiratory Investigation Unit, Queen's University and Kingston Health Sciences Centre **Email:** odonnell@queensu.ca **Address:** 102 Stuart St., Kingston, ON, Canada, K7L 2V6 **Clinical trial register:** NCT01900873
Notes	webplotdigitizer used to extract IMT training load intensity. Adjusted analysis were provided.

Larson 1988

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): not reported/10 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 60 (6) Control/sham • N (randomized/analyzed): not reported/12 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 68 (3) Overall • N (randomized/analyzed): 45/22 • Loss to follow-up or excluded: 23 • Gender (M/F): 20/2 • COPD stage (GOLD): severe to very severe **Included criteria** • FEV1 < 65%pred

Larson 1988 *(Continued)*

- Stable condition
- Patients with a recent history of exacerbation were allowed to enter the study only after they reported that their ability to function and day-to-day symptoms had returned to baseline
- All patients were enrolled > 2 months after recovery from an exacerbation except 1 who enrolled 1 month after recovery from an exacerbation because he insisted that his breathing would not improve any further
- Patients were advised against participation if they indicated that the 12MWD was too strenuous.

Excluded criteria

- Evidence of restrictive lung disease based on lung volumes
- A history of asthma, and if they had a history of cardiovascular disease or musculoskeletal conditions that could interfere with either the training or testing maneuvers
- Taking psychotropic drugs or abusing alcohol
- Participants were dropped from the study if they: experienced an exacerbation, required a change in their pharmacologic regimen, or reported < 80% compliance with the training protocol.

Interventions	**Intervention characteristics** **IMT:** participants trained 7 d/week for 8 weeks using the Threshold IMT device at 30% of PImax. They initiated the training for 15 min/d during the first week and gradually increased the duration to 30 min/day for the remaining 7 weeks. **Control/sham:** this group received the same IMT protocol with the training load set at 15% of PImax
Outcomes	Respiratory muscle strength: PImax (RV) Functional exercise capacity: 12MWD Respiratory muscle endurance time: T_{lim} • Note: measured through breathing against 66% of PImax
Identification	**Sponsorship source:** supported in part by Grant No. HL-31558 from the National Institutes of Health and by a grant from Sigma Theta Tau, Psi Chapter **Country:** USA **Author's name:** Janet L. Larson **Institution:** College of Nursing, University of Illinois at Chicago **Address:** 845 S.Damen Avenue, Chicago,IL 60612
Notes	

Larson 1999

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): not reported/14

Larson 1999 *(Continued)*

- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 68 (6)
- BMI, mean (SD), kg/m^2: 27 (4)

PR

- N (randomized/analyzed): not reported/14
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 66 (6)
- BMI, mean (SD), kg/m^2: 26 (4)

IMT

- N (randomized/analyzed): not reported/13
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 66 (5)
- BMI, mean (SD), kg/m^2: 28 (4)

Control/sham

- N (randomized/analyzed): /12
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 62 (7)
- BMI, mean (SD), kg/m^2: 26 (5)

Overall

- N (randomized/analyzed): 130/53
- Loss to follow-up or excluded: 83
- COPD stage (GOLD): moderate to severe

Included criteria

- Patients between 45 and 75 years of age;
- Moderate to severe airflow obstruction (FEV1 < 65%pred and FEV1/FVC < 70%)
- Complaints of dyspnea on exertion
- Clinically stable condition
- No participation in a pulmonary rehabilitation program in the last year

Excluded criteria

- A history of asthma
- Experienced a major exacerbation in the 2 months before enrollment
- Took > 10 mg of prednisone/d
- Required home oxygen therapy or experienced oxyhemoglobin desaturation < 85% with exercise, and/or had other health problems that would interfere with exercise

Interventions	**Intervention characteristics** **PR:** participants performed cycle ergometer training at home on a calibrated stationary cycle ergometer (BodyGuard 990; BodyGuard, Sandnes, Norway), 20 min/d, 5 d/week for 2 months. An interval training protocol was used with participants performing 4 work sets, 5 min in duration, separated by rest intervals (2–4 min) of unloaded cycling. The training was initiated at 50% of the peak work rate, taken from the best baseline graded exercise test, and evaluated weekly with progressive increases as tolerated. Patients were instructed to pedal at a rate of 60 revolutions/minute (rpm), and they were encouraged to push themselves to the limits of their dyspnea, without exceeding a heart rate equal to 85% of the predicted maximal heart rate. **IMT:** the participants trained with Threshold IMT (HealthScan, Cedar Grove, NJ), 30 min/d, 5 d/week for 2 months. the training was initiated at 30% of PImax with progressive increases up to 60% of PImax

Larson 1999 *(Continued)*

	PR+IMT: participants received both PR and IMT as described above. **Control/sham:** this group participated in a structured program of health education
Outcomes	Dyspnea: Borg • P_{thmax} • Wmax • Submaximal exercise at 50% of Wmax HRQoL: CRQ • Dyspnea • Fatigue Respiratory muscle strength: PImax (RV) Respiratory muscle endurance: respiratory muscle endurance pressure (Pthmax) Functional exercise capacity: Wmax Laboratory exercise test: VO2peak (L/min)
Identification	**Sponsorship source:** funded by a research grant from the National Institute of Nursing Research, National Institutes of Health, RO1-NR01428 **Country:** USA **Author's name:** Janet L. Larson **Institution:** University of Illinois at Chicago **Email:** LLarson@uic.ed **Address:** 845 S. Damen, Chicago, IL60612
Notes	

Leelarungrayub 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 12/10 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 63.25 (1.49) • Gender (M/F): 4/6 • BMI, mean (SD), kg/m^2: 20.6 (1.9) Control/sham • N (randomized/analyzed): 12/10 • Loss to follow-up or excluded: 2

Leelarungrayub 2017 *(Continued)*

- Age, mean (SD) in years: 68.75 (2.39)
- Gender (M/F): 6/4
- BMI, mean (SD), kg/m^2: 22.1 (2.4)

Overall

- N (randomized/analyzed): 24/20
- Loss to follow-up or excluded: 2
- Gender (M/F): 10/10
- COPD stage (GOLD): moderate

Included criteria

- All the participants were ex-smokers
- They had a stable clinical condition during the experiments

Excluded criteria

- Uncontrolled hypertension, unstable cardiac disease, recurrent symptoms of pneumothorax, thoracic or chest pain including neuromuscular disorders, liver diseases or endocrine abnormalities
- Participants taking supplements or any nutrients such as vitamins or N-acetylcysteine compounds during this study

Interventions	**Intervention characteristics** **IMT:** participants trained with Portex (Smith Medical ASD), 20-30 min/session, 7 d/week for 6 weeks. They started breathing through a 6 mm hole once daily for the first 2 weeks, before changing to 4 mm and 2 mm holes in the 2nd and 4th week, respectively. 30 slowly repeated inspirations passed through the device, with a 3-min interval of rest in each of 4 training sessions. **Control:** this group did not receive any intervention
Outcomes	Functional exercise capacity: 6MWD HRQoL: CCQ • Symptom score • Mental score • Function score • Total score Respiratory muscle strength: PImax (RV) Respiratory function: FEV1 • L • %pred
Identification	**Sponsorship source:** **Country:** Thailand **Setting:** Sansai hospital, Sansai, Chiang Mai Province, Thailand **Author's name:** Jirakrit leelarungrayub **Institution:** Department of Physical Therapy, Faculty of associated Medical sciences, Chiang Mai University **Email:** donrawee.leela@cmu.ac.th **Address:** Intawaroroj road, Sripoom, Chiang Mai 50200, Thailand

Leelarungrayub 2017 *(Continued)*

Notes	We calculated the SD manually from the SE (SD = SE*√N). This study also used a prototype that was excluded from our analysis because it hasn't been validated yet. We contacted the Portex manufacturer to ask for further information about the device.

Lisboa 1997

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 61 (6.32) • Age (SD): 6.32 • Gender (M/F): 6/4 Control/Sham • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 64 (6.32) • Age (SD): 6.32 • Gender (M/F): 7/3 Overall • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 • Gender (M/F): 13/7 • COPD stage (GOLD): severe **Included criteria** • A stable period of their disease • Dyspnea during ADL • FEV1/FVC < 60% • The absence of cardiac or any other disease that could interfere with exercise performance **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **IMT:** participants trained at home using a Threshold IMT device (HealthScan Products Inc., NJ, USA), for 30 min/d, 6 d/week for 10 weeks at 30% of PImax **Control/sham:** this group received a similar IMT protocol and trained at 10% of PImax
Outcomes	Dyspnea: BDI-TDI (Total) Dyspnea: Borg • Notes: It was evaluated under basal conditions

Lisboa 1997 *(Continued)*

	Functional exercise capacity: 6MWD Respiratory muscle strength: PImax (FRC) Respiratory function: FEV1 (L) Functional exercise capacity: Wmax • Notes: we considered 1W = 6.11 kpm/min Laboratory exercise test: VO2peak (mL/min)
Identification	**Country:** Chile **Author's name:** C. Lisboa **Institution:** Dept of respiratory disease, Catholic University of Chile **Address:** Santiago, Chile
Notes	The authors mentioned COPD in the discussion section.

Mador 2005

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 19/15 • Loss to follow-up or excluded: 4 • Age mean (SD) in years: 69.7 (7.7) • BMI, mean (SD), kg/m^2: 28.3 (8.9) PR • N (randomized/analyzed): 19/14 • Loss to follow-up or excluded: 5 • Age mean (SD) in years: 70.9 (7.4) • BMI, mean (SD), kg/m^2: 26.9 (3.3) Overall • N (randomized/analyzed): 38/29 • Loss to follow-up or excluded: 9 • COPD stage: moderate to very severe **Included criteria** • Confirmed diagnosis of COPD
Interventions	**Intervention characteristics** **PR+IMT**

Mador 2005 *(Continued)*

	• PR: participants trained on a cycle ergometer, initially at 50% of Wmax and keeping Borg score ≤ 5 during exercise. They also trained on a treadmill at a speed ranging from 1.1-2.0 miles per hour (1.7-3.2 km/h) at 0% elevation based on the participant's functional capacity (i.e. on 6MWD results). When the participants could exercise for 20 min without intolerable dyspnea or leg fatigue, the speed and/or elevation was increased. • IMT: participants trained 15-20 min/d, 3 d/week for 8 weeks, and breathed from a rebreathing bag while obtaining fresh air through a side port. $\dot{V}E$ and $PetCO_2$ were continuously recorded using a metabolic cart (Medgraphics; St. Paul, MN), and oxygen saturation was measured by pulse oximetry. Rebreathing bags of 1.5-2.0 L, depending on the participant's vital capacity, were used, and the size of the bag was additionally adjusted with a clamp until stable normocapnia as estimated by the $PetCO_2$ was obtained during preliminary trials. **PR:** this group received only the PR program described above
Outcomes	Functional exercise capacity: • 6MWD • Exercise time • Wmax HRQoL: CRQ Respiratory muscle strength: PImax Respiratory muscle endurance time: T_{lim}
Identification	**Country:** USA **Author's name:** M. Jeffery Mador **Institution:** Division of Pulmonary, Critical Care, and Sleep Medicine, Section 111S **Email:** mador@acsu.buffalo.edu **Address:** State University of New York at Buffalo, Veterans Administration Medical Center, 3495 Bailey Ave, Buffalo, NY 14215
Notes	

Magadle 2007

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 16/14 • Loss to follow-up or excluded: 2 • Age (mean): 65.2 (13.6) PR • N (randomized/analyzed): 15/13 • Loss to follow-up or excluded: 2

Magadle 2007 *(Continued)*

- Age (mean): 66.1 (12.39)

Overall

- N (randomized/analyzed): 31/29
- Loss to follow-up or excluded: 2
- COPD stage (GOLD): moderate to severe

Included criteria

- Patients with spirometric evidence of significant chronic airflow limitation (FEV1 < 50%pred, FEV1/FVC < 70%pred) and were diagnosed as having COPD according to ATC criteria

Excluded criteria

- Patients with cardiac disease, poor compliance, or requirement of supplemental oxygen

Interventions	**Intervention characteristics** **PR+IMT** • PR: this program included lower extremity endurance exercise (walking or cycling), upper extremity exercise and strength training with free weights. This phase included 36 sessions of 90 min duration (3 times/week for 12 weeks). In the 2nd phase, participants trained 1 h 3 times/week for 6 months. • IMT: started in the 2nd phase of the trial, and consisted of training 30 min/session, 3 times/week for 6 months. They used the Threshold IMT device at a training load ranged from 15%- 60% of PImax. **PR (+sham IMT):** this group received a similar training protocol and participants performed IMT at no load.
Outcomes	Functional exercise capacity: 6MWD HRQoL: SGRQ (Total) Respiratory muscle strength: PImax (RV) Respiratory function: FEV1 (%pred)
Identification	**Country:** Israel **Setting:** community-based rehabilitation center **Author's name:** Paltiel Weiner **Institution:** Department of Medicine A, Hillel Yaffe Medical Center **Email:** weiner@hillel-yaffe.health.gov.il **Address:** Hadera 38100, Israel
Notes	Participants were enrolled in a 1st phase that consisted of 36 sessions of PR for 3 months (90 min/session).

Majewska-Pulsakowska 2016

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group

Majewska-Pulsakowska 2016 *(Continued)*

Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 13/13 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 61.5 (6.1) • Gender (M/F): 10/3 • BMI, mean (SD), kg/m^2: 28.8 (6.2) PR • N (randomized/analyzed): 9/9 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 62.3 (5.2) • Gender (M/F): 6/3 • BMI, mean (SD), kg/m^2: 28.2 (6.2) IMT • N (randomized/analyzed): 8/8 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 63.4 (9.8) • Gender (M/F): 2/6 • BMI, mean (SD), kg/m^2: 26.1 (5.9) Control/sham • N (randomized/analyzed): 13/13 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 65.5 (7.0) • Gender (M/F): 7/6 • BMI, mean (SD), kg/m^2: 27.8 (4.9) Overall • N (randomized/analyzed): 43/43 • Loss to follow-up or excluded: 0 • Gender (M/F): 25/18 • COPD stage (GOLD): moderate to severe **Included criteria** • COPD treated for at least 1 year, stage 2 and 3 according to GOLD (2014) • 50–70 years old • A stable clinical condition with no exacerbations over the period of 4 weeks before the study **Excluded criteria** • Participation in PR in the year preceding the study • Diagnosed bronchial asthma • Long-term home oxygen therapy • Clinically significant diseases of the cardiovascular system • Any uncontrolled chronic disease; muscle and nervous disorders reducing the patient's mobility • Mental disorders preventing contact and co-operation with the patient
Interventions	**Intervention characteristics**

Majewska-Pulsakowska 2016 *(Continued)*

	PR: consisted of training on a cycle ergometer, 3 times/week for 8 weeks in an ambulatory setting under the supervision of a cardiologist. Each training session began (warm-up) and finished (relaxation) with a pedalling load of 10 W for 3 min. The duration of a training session was initially 23 min, and then it was gradually increased up to 45 min. **IMT:** consisted of home-based training using Threshold IMT device (Respironics; Philips Healthcare, DA Best, The Netherlands), twice a day (5-15 min), 5 d/week for 8 weeks. The training load ranged from 30%-60% of PImax **PR+IMT:** this group received both interventions described above. **Control/sham:** this group did not receive any intervention.
Outcomes	HRQoL: SGRQ Respiratory function: FEV1 • L • %pred
Identification	**Country:** Poland **Author's name:** K. Wytrychowski **Institution:** Department of Internal Diseases, Geriatry andAllergology, Wroclaw Medical University **Email:** Polande-mail:anhw@op.plK **Address:** 66 Sklodowskiej-Curie St., 50-369 Wroclaw, Poland
Notes	

Masanga 2011

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): not reported/11 PR • N (randomized/analyzed): not reported/9 Overall • N (randomized/analyzed): not reported/21 **Included criteria:** stable patients with moderate to severe COPD **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **PR+IMT:**

Masanga 2011 *(Continued)*

	• PR: consisted of Occupational therapy, Education, Dietary instruction. • IMT: at a training load that ranged from 10 cmH_2O to 40-90 cmH_2O. **PR:** Participants received only the PR program described above.
Outcomes	This abstract reported only adverse events: headache (6), jaw pain (6), neck pain (6), back pain (4), abdominal pain (2), cough (1), blood-streaked sputum (1), shoulder pain (1) and chest pain (1)
Identification	**Country:** Philippines **Author's name:** L. Masanga
Notes	

Nikoletou 2016

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 34/21 • Loss to follow-up or excluded: 13 • Age, mean (SD) in years: 70.1 (8.4) • Gender (M/F): 14/9 • BMI, mean (SD), kg/m^2: 24.9 (5.2) Control/sham • N (randomized/analyzed): 34/18 • Loss to follow-up or excluded: 16 • Age, mean (SD) in years: 71.1 (9.6) • Gender (M/F): 11/8 • BMI, mean (SD), kg/m^2: 26.5 (8.1) Overall • N (randomized/analyzed): 68/39 • Loss to follow-up excluded: 29 • Gender (M/F): 25/17 • COPD stage (GOLD): moderate to very severe **Included criteria** • No exacerbation of COPD • Not changed their medication for at least 4 weeks prior to the initial assessment **Excluded criteria** • Patients with an a1-antitrypsin deficiency • Co-existing heart disease, hypertension, or long-term use of oral corticosteroids

Nikoletou 2016 *(Continued)*

- Patients with significant thoracic musculoskeletal abnormalities, such as kyphosis or scoliosis
- Patients unsuitable for magnetic stimulation, for example, those with cardiac pacemakers

Interventions	**Intervention characteristics** **IMT:** 2 sessions/d, 6 d/week for 7 weeks, home-based, using the Powerbreathe inspiratory muscle trainer (HaB International, Southam, Warwickshire, UK). Participants started training at 30% of their baseline PImax and increased the intensity once a week as tolerated. The average weekly increase in the intensity of training was 5% and the mean (SD) intensity at the end of the program was 62% (SD: 11.7) of the baseline PImax **Control/sham:** participants received a similar IMT program and trained at 15% of PImax
Outcomes	Functional exercise capacity: incremental SWT Dyspnea: Borg • Notes: Borg post-incremental SWT HRQoL: CRQ • Dyspnea • Fatigue • Emotion • Mastery HRQoL: SF-36 Questionnaire • Physical functioning • Physical problems • Emotional problems • Social functioning • Mental health • Energy/ Vitality • Pain • General health perception • Change in health Respiratory muscle strength: PImax (FRC) Respiratory muscle endurance time: T_{lim}
Identification	**Country:** UK **Setting:** respiratory outpatient clinics at King's College Hospital, GP practices and British Lung Foundation Breathe Easy groups **Author's name:** Dimitra Nikoletou **Institution:** School of Rehabilitation Sciences, Faculty of Health, Social care and Education, Kingston University and St George's University of London **Email:** D.Nikoletou@sgul.kingston.ac.uk **Address:** Grosvenor Wing, Cranmer Terrace, London SW17 0RE, UK
Notes	

Paneroni 2018

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 15/12 • Loss to follow-up or excluded: 3 • Age, mean (SD) in years: 67.8 (9.8) • Gender (M/F): 10/2 • BMI, mean (SD), kg/m^2: 26.9 (5.3) PR • N (randomized/analyzed): 11/10 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 65.8 (25.0) • Gender (M/F): 8/2 • BMI, mean (SD), kg/m^2: 25.0 (5.1) Overall • N (randomized/analyzed): 26/26 • Loss to follow-up or excluded: 4 • Gender (M/F): 18/4 • COPD stage (GOLD): mild to very severe **Included criteria** • MVV of < 90% of predicted • The ability to perform the 6MWD • The absence of chronic respiratory failure (arterial oxygen (PaO2) and carbon dioxide (PaCO2) tensions at rest > 60 and < 45 mmHg, respectively) **Excluded criteria** • Refusal to participate • Cognitive impairment as assessed by a Mini-Mental State Examination score of < 25 points • Hemodynamic instability, and severe clinical events (e.g. COPD exacerbations or heart failure treated with infusions of vasopressors and/or inotropes) in the month before enrollment
Interventions	**Intervention characteristics** **PR+IMT:** • PR: incremental exercise training according to Maltais et al (Maltais 1997) until performing 30 min of continuous cycling at 50%–70% of the maximal load calculated based on the initial 6MWD plus 30-min sessions of abdominal, upper, and lower limb muscle activities, lifting progressively increasing weights (300–500 g), shoulder and full arm circling, and other exercises according to Clark et al (Clark 1996) • IMT: participants received twice a day, 5 d/week for 2 weeks, 20 15-min sessions of normocapnic hyperpnea training using SpiroTiger device (Idiag; Fehraltorf, Switzerland). The initial target of minute ventilation (VE) was 66% of participants' MVV. Once the participant was able to perform 15-min training sessions without interruptions, the target VE was increased to 75% of MVV, by increasing only the respiratory rate. Thereafter, training involved further 10% increments of MVV, when the participant could perform without interruption three 15-min sessions at the set level

Paneroni 2018 *(Continued)*

	PR (+sham IMT): participants in this group received a similar training PR program, and they performed IMT using Threshold IMT device at no resistance
Outcomes	Functional exercise capacity: 6MWD Respiratory muscle strength: PImax Respiratory muscle endurance time: T_{lim} (normocapnic hyperpnea) • **Notes**: it is the sustained VE at 66% of their MVV. If there was no exhaustion in 15 min, the test was repeated the following day at 75% of MVV Respiratory muscle endurance time: T_{lim} (Threshold device) • **Notes**: the pressure was set at 30% of the patients' baseline PImax Respiratory muscle endurance: MVV
Identification	**Country:** Italy **Setting:** Respiratory Rehabilitation Divisions of the Lumezzane and Pavia Institutes of the Istituti Clinici Scientifici Maugeri, Italy **Author's name:** Mara Paneroni **Institution:** Istituti Clinici Scientifici Maugeri, IRCCS **Address:** Salvatore Maugeri 2, 27100 Pavia, Italy **Clinical trial register:** NCT01556139
Notes	

Petrovic 2012

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 58.7 (5.2) • Gender (M/F): 6/4 • BMI, mean (SD), kg/m^2: 24.3 (4.0) Control/sham • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 60.3 (5.3) • Gender (M/F): 5/5 • BMI, mean (SD), kg/m^2: 24.2 (3.4)

Petrovic 2012 *(Continued)*

	Overall • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 • Gender (M/F): 11/9 • COPD stage (GOLD): moderate to severe **Included criteria** • Required participants to be < 70 years old • Moderate to severe non-reversible airflow obstruction **Excluded criteria** • Exacerbation of COPD within the previous 6 weeks • Neoplastic disease or the presence of a disease that could contribute to dyspnea, or exercise limitation (cardiovascular, neuromuscular, or other respiratory diseases) • No patients had received treatment with systemic cortisone over the last 6 months
Interventions	**Intervention characteristics** **IMT:** performed once/d, 7 d/week, for 8 weeks using Respifit Sdevice (Mauerbach, Australia). The training consisted of strength training at 80% of PImax (≃12 min each session) and endurance training at 60% of PImax (≃ 13.5 min each session) **Control/sham:** this group did not receive any intervention
Outcomes	Dyspnea: Borg • Constant cycle ergometer test • Incremental cycle ergometer test • Notes: the sensation of dyspnea was assessed every 2 min during exercise Respiratory muscle strength: PImax Respiratory muscle endurance time: T_{lim} • Notes: measured through breathing against 60% PImax Laboratory exercise test: VO2peak (mL/min) • Constant cycle ergometer test • Incremental cycle ergometer test
Identification	**Country:** Austria **Setting:** outpatient clinic **Author's name:** Milos Petrovic **Institution:** Pulmonary Department and Karl Landsteiner Institute for Clinical and Experimental Pulmology **Email:** milos.petrovic@wienkav.at **Address:** Hietzing Hospital, Wolkensbergenstrasse 1, 1130 Vienna, Austria **Clinical trial register:** NCT00469313
Notes	

Preusser 1994

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): /12 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 68/10 • Gender (M/F): 6/6 Control/sham • N (randomized/analyzed): /8 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 62/17 • Gender (M/F): 1/7 Overall • N (randomized/analyzed): 22/20 • Loss to follow-up or excluded: 2 • Gender (M/F): 7/13 • COPD stage (GOLD): severe to very severe **Included criteria** • The presence of COPD as defined by the ATS • Willingness to participate in a 3-month inspiratory muscle training protocol **Excluded criteria** • Uncontrolled cardiac disease, diabetes, hypertension, musculoskeletal, and neuromuscular diseases
Interventions	**Intervention characteristics** **IMT:** consisted of supervised sessions, 3 days/week for 12 weeks, using Threshold IMT device at 52% of PImax. The training duration ranged from 5 min in week 1 to 18 min in week 12 **Control/sham:** this group received a similar IMT protocol and trained at 22% of PImax
Outcomes	Functional exercise capacity: 12MWD Respiratory muscle strength: PImax (FRC) Respiratory muscle endurance: Respiratory muscle endurance pressure (P_{thmax}) • Notes: "After quietly breathing through an unloaded system for 2 min, the threshold load began at -4 cm H2O pressure and increased by -2 cm after every fifth breath (every 15 s) until the subject either signalled to stop the test or was unable to match respiratory rate, duty cycle and flow rate during three of the five breaths for that pressure load. The maximal threshold load successfully completed during the ramp test was recorded"
Identification	**Sponsorship source:** supported by grant F31 NR06378, National Center for Nursing Research; a grant from the American Nurses Foundation; and the Epsilon Chapter of Sigma Theta Tau

Preusser 1994 *(Continued)*

Country: USA

Author's name: Barbara A. Preusser

Institution: College of Nursing, The Ohio State University, and the Department of Pulmonary Medicine, The Ohio State University Hospitals, Columbus

Address: University of Utah College of Nursing, 25 South Medical Drive, Salt Lake City 84112

Notes

Ramirez Sarmiento 2002

Study characteristics

Methods

Study design: RCT

Study grouping: parallel-group

Participants

Baseline characteristics

IMT

- N (randomized/analyzed): not reported/7
- Loss to follow-up or excluded: not reported
- Age, mean (SD) in years: 65
- BMI, mean (SD), kg/m^2: 29

Control/sham

- N (randomized/analyzed): not reported/7
- Loss to follow-up or excluded: 2
- Age, mean (SD) in years: 66 (6)
- BMI, mean (SD), kg/m^2: 26 (4)

Overall

- N (randomized/analyzed): 16/14
- Loss to follow-up or excluded: 2
- BMI, mean (SD), kg/m^2:
- COPD stage (GOLD): severe to very severe

Included criteria

- Patients with COPD

Excluded criteria

- Hypoxemia (PaO2 < 60 mmHg breathing room air)
- Asthma; coronary disease; undernourishment (BMI < 20 kgm^2)
- Chronic metabolic disease
- Orthopedic disease
- Previous abdominal or thoracic surgery
- Treatment with steroids, hormones or cancer chemotherapy

Interventions

Intervention characteristics

Ramirez Sarmiento 2002 *(Continued)*

	IMT: participants trained 30 min/day, 5 d/week for 5 weeks. The sessions were supervised and using Threshold IMT device set at 50% of PImax **Control/sham:** participants received a similar IMT protocol and trained at no load
Outcomes	Functional exercise capacity: • 6MWD • Wmax Respiratory muscle strength: PImax Respiratory muscle endurance: Respiratory muscle endurance pressure (P_{thmax}) • Notes: breathing against incremental loads (8 cmH2O) every 2 min until maximal sustainable threshold pressure was reached Respiratory muscle endurance time: T_{lim} • Notes: breathing against a constant a submaximal constant load (equivalent to 80% of maximal threshold pressure) Laboratory exercise test: VO2peak (mL/kg/min) • Notes: measured during incremental cycle test Respiratory function: FEV1 (%pred) Respiratory function: RV (%pred)
Identification	**Sponsorship source:** supported, in part, by grants BIOMED (BMH-4-CT98-3406), FIS, SEPAR, and SIBEL **Country:** Spain **Author's name:** Mauricio Orozco-Levi **Institution:** Servei Grup de Recera de Pneumologica, Hospital del MarIMIM **Email:** morozco@imim.es **Address:** Passeig Maritim 25, E-080003, Barcelona (Catalonia), Spain
Notes	

Saher 2021

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 23/17 • Loss to follow-up or excluded: 6 • Age, mean (SD) in years: 62.8 (6.72) • Gender (M/F): 9/5

Saher 2021 *(Continued)*

	• BMI, mean (SD), kg/m^2 : 22.7 (4.25) Control • N (randomized/analyzed): 23/17 • Loss to follow-up excluded: 6 • Age, mean (SD) in years: 61.8 (11.93) • Gender (M/F): 12/8 • BMI, mean (SD), kg/m^2 : 23.7 (5.51) Overall • N (randomized/analyzed): 46/34 • Loss to follow-up or excluded: 12 • Gender (M/F): 21/13 • COPD stage (GOLD): moderate to very severe **Included criteria** • Hypercapnic moderate to severe COPD patients • Patients were required to have hypercapnic respiratory failure ($PaCO_2$ > 46 mmHg), already receiving non-invasive ventilation for at least 8 h/d, and with a decreased inspiratory muscle strength (PImax < 60 cm H_2O) **Excluded criteria** • Patients with any other severe respiratory disease apart from COPD, or with any other severe non-pulmonary disease limiting prognosis (e.g. metastatic cancer, active tuberculosis, congestive heart failure, liver cirrhosis)
Interventions	**Intervention characteristics** **IMT:** participants performed IMT 15 min/session, 2 session/day, for 10 days. They used an IMT threshold device (Powerbreath, Gaiam Ltd., Southam, UK). The training load started at 30% of PImax, and it was increased by 5%-10% daily until 60% **Control:** this group did not receive any training Note: both groups received non-invasive ventilation (NIV) as part of COPD management.
Outcomes	Functional exercise capacity: 6MWD Inspiratory muscle strength (PImax)
Identification	**Country:** India **Setting:** Metro Center for Respiratory Disease, Metro Hospital **Author's name:** T. Saher **Institution:** Center for Physiotherapy and Rehabilitation Sciences **Email:** jmoiz@jmi.ac.in **Address:** Jamia Millia Islamia, New Delhi, 110025, India
Notes	

Saka 2021

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 23/20 • Loss to follow-up or excluded: 3 • Age, mean (SD) in years: 62.30 (7.43) • Gender (M/F): 19/1 • BMI, mean (SD), kg/m^2 : 26.04 (4.41) Sham IMT • N (randomized/analyzed): 22/20 • Loss to follow-up excluded: 2 • Age, mean (SD) in years: 62.10 (7.76) • Gender (M/F): 18/2 • BMI, mean (SD), kg/m^2 : 27.11 (4.88) Overall • N (randomized/analyzed): 45/40 • Loss to follow-up or excluded: 5 • Gender (M/F): 37/3 • COPD stage (GOLD): moderate to severe **Included criteria** • FEV1:FVC ratio < 70% in PFT • Age: ≥ 18 years old • Being able to read written and understand spoken language **Excluded criteria** • A history of COPD exacerbation in the last 6 weeks • The presence of comorbidities affecting ambulation/activity (e.g. severe cardiac or neurological disorders, cancer, musculoskeletal problems) and cognitive disorders (Mini-Mental State Examination < 24)
Interventions	**Intervention characteristics** **IMT:** the training was performed 15 min twice a day, 5 d/week, for 8 weeks. Home-based training with 1 session supervised by a physiotherapist. Participants used Threshold IMT device (Threshold IMT® Philips Respironics, UK) at a load of 30% of PImax. **Sham IMT:** participants received the same protocol with a training load set at 15% of PImax.
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD HRQoL: SGRQ • Symptoms • Activity

Saka 2021 *(Continued)*

- Impacts
- Total

HRQoL: CAT

Inspiratory muscle strength (PImax)

Respiratory function: FEV1

- L
- %pred

Identification	**Sponsorship:** Scientific Research Projects Unit of Bezmialem Vakıf University, project number 9.2017/31 **Country:** Turkey **Setting:** Bezmialem Vakif University Division of Physiotherapy and Rehabilitation, Cardiopulmonary Physiotherapy and Rehabilitation Department. **Author's name:** Seda Saka **Institution:** Cardiopulmonary Physiotherapy Rehabilitation Department, Institute of Health Sciences, Bezmialem Vakif University, Istanbul, Turkey **Email:** fztsedasaka@gmail.com **Address:** Division of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Bezmialem Vakif University, Silahtaraga St. No:189, Alibeykoy, 34060, Istanbul, Turkey **Clinical trial register:** NCT03517839
Notes	

Sanchez Riera 2001

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 67 (4) • Gender (M/F): 9/1 Control/Sham • N (randomized/analyzed): 10/10 • Loss to follow-up/excluded: 0 • Age, mean (SD) in years: 67.6 (5) • Gender (M/F): 9/1 Overall

Sanchez Riera 2001 *(Continued)*

- N (randomized/analyzed): 20/20
- Loss to follow-up or excluded: 0
- Gender (M/F): 18/2
- COPD stage (GOLD): moderate to severe

Included criteria

- The presence of COPD as defined by the ATS
- Patients were in stable condition

Excluded criteria

- Clinical evidence of cardiovascular, musculoskeletal, or neuromuscular disease or of any other disease that might interfere with exercise

Interventions	**Intervention characteristics** **IMT:** participants trained at home 30 min/d, 6 d/week for 6 months using incentive flowmeter device (INSPIRx; Intertech Resources Inc; Ft. Myers, FL) set at 30% of PImax. The breathing pattern was controlled during the exercise. **Control/sham:** participants received a similar IMT protocol and trained at no load.
Outcomes	Dyspnea: Borg (Constant cycle ergometer test) Functional exercise capacity: SWT • Notes: "Patients were required to walk 10 m back and forth. The walking speed was paced by an audio signal from a cassette that emitted beeps at regular intervals. The speed was increased each minute by 0.17 m/s until the next level was attained. The end of the test was determined by patients when they were too breathless to maintain the required speed, or by operators, if patients failed to complete a shuttle in the time allowed" Functional exercise capacity: Wmax • Notes: "performed on a cycle ergometer. After 1 min of unloaded pedalling, the work rate was increased 10 W/min at a time. The test was stopped when patients were unable to continue because of dyspnea or leg fatigue" Respiratory muscle strength: PImax (FRC) Laboratory exercise test: VO2peak (L/min) Respiratory muscle endurance: Respiratory muscle endurance pressure (P_{thmax})
Identification	**Sponsorship source:** Supported by “Junta de Andalucia” grant No. 94//535–119 **Country:** Spain **Setting:** home-based training **Author's name:** Hildegard Sanchez Riera **Institution:** Pneumology Service, Virgen Del Rocio University Hospital **Email:** ablucil@mx2.redestb.es **Address:** “La Motilla,” C/Rayo 4, 41700 Dos Hermanas, Sevilla, Spain
Notes	CRQ was not included because study did not fully report control group data

Scherer 2000

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): not reported/15 • Loss to follow-up or excluded: not reported • Age, mean (SD) in years: 66.9 (9.2) • Gender (M/F): 9/6 • BMI, mean (SD), kg/m^2: 23.8 (3) Control/sham • N (randomized/analyzed): 15 • Loss to follow-up or excluded: not reported • Age, mean (SD): 71.0 (4.6) • Gender (M/F): 10/5 • BMI, mean (SD), kg/m^2: 25.9 (3.48) Overall • N (randomized/analyzed): 34/30 • Loss to follow-up or excluded: 4 • Range age (min, max): 46,80 • Gender (M/F): 19/11 • COPD stage (GOLD): moderate to severe **Included criteria** • Chronic airflow obstruction (FEV1 < 70%pred, FEV1/FVC < 70%pred, < 15% improvement in FEV1 after bronchodilatation with 200 mg of albuterol inhaled from a pressurized metered-dose inhaler with a spacer) • Aged 20-80 years • A stable clinical condition for at least 1 month • The patients' physical activity had to be limited by pulmonary dyspnea only **Excluded criteria** • Patients with dyspnea at rest • Cardiac disease, poor compliance, drug or alcohol abuse, pregnancy or lactation, a requirement for supplemental oxygen, CO2 retention, or use of any mechanical ventilatory support
Interventions	**Intervention characteristics** **IMT:** respiratory muscle endurance training was conducted twice daily, 5 d/week for 8 weeks. The device was developed and consisted of tubing (I.D. 5 19 mm) connecting a rebreathing bag with a mouthpiece at a 90° angle. The breathing frequency was 60% of MVV. **Control/sham:** participants trained following the same pattern of the description above, at no load using incentive spirometer (COACH 2 Volumetric Incentive Spirometer; DHD Healthcare, Canastota, NY). The respiratory rate was 6-8 breaths/min, and the target inspiration was set at 70% of each participant's ventilatory capacity.

Scherer 2000 *(Continued)*

Outcomes	Dyspnea: BDI-TDI (Total) Functional exercise capacity: • 6MWD • Exercise time (treadmill) Respiratory muscle strength: PImax (RV) Laboratory exercise test: VO2peak (mL/kg/min) Respiratory muscle endurance time: T_{lim} • Notes: respiratory muscle endurance was measured as sustained ventilation at 66% of each participant's highest MVV. The time during which participants were able to sustain this target ventilation was recorded. If a participant surpassed 15 min of breathing at this level, the test was repeated on the following day at 75% of MVV. Respiratory function: FEV1 (%pred)
Identification	**Sponsorship source:** supported by grants from Astra Pharmaceutica, Dietikon, and Merck Sharpe and Dohme-Chibret, and Rhône-Poulenc Rorer **Country:** Switzerland **Setting:** outpatient clinic of the Pulmonary Division of the Triemli Hospital **Author's name:** Thomas A. Scherer **Institution:** LungenZentrum Hirslanden **Email:** thsche@swissonline.ch **Address:** Witellikerstrasse 36, 8008 Zurich, Switzerland
Notes	

Schultz 2018

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 307/300 • Loss to follow-up or excluded: 26 • Age, mean (SD) in years: 57.7 (8.2) • Gender (M/F): 188/112 • BMI, mean (SD), kg/m^2: 26.6 (6.4) PR • N (randomized): 304/302 • Loss to follow-up or excluded: 24 • Age, mean (SD) in years: 57.9 (6.6)

Schultz 2018 *(Continued)*

- Gender (M/F): 201/101
- BMI, mean (SD), kg/m^2: 26.9 (6.6)

Overall

- N (randomized): 611/602
- Loss to follow-up or excluded: 50
- Gender (M/F): 389/213
- COPD stage (GOLD): moderate to severe

Included criteria

- Medical history of COPD
- FEV1/FVC < 70% and FEV1 %pred < 80% post-bronchodilation

Excluded criteria

- Lack of language or cognitive abilities to fill out questionnaires
- Hypercapnic respiratory failure (arterial carbon dioxide tension > 50 mmHg at rest)
- Indication for intermittent noninvasive ventilation
- Contraindications for inspiratory muscle training (e.g. a history of recent lung surgery, recent pulmonary embolism; a history of recurrent spontaneous pneumothorax)
- Severe comorbidities that confer significantly greater morbidity than COPD (e.g. active cancer without successfully completed curative tumor therapy)

Interventions	**Intervention characteristics**
	
	PR+IMT:
	
	• PR: consists of 2 components
	  ◦ Obligatory components: (mostly 30- to 60-min sessions) including physical training (endurance training: 4 or 5 sessions per week; strength training: three sessions/week; whole-body vibration muscle training: 7 sessions/week), patient education (≥ 7 sessions) and respiratory physiotherapy in groups (2-4 sessions/week).
	  ◦ Optional components: smoking cessation (8 sessions), mucolytic physiotherapy, saline inhalation, psychological interventions, social counselling, nutritional counselling and occupational therapy
	• IMT: conducted 21 min/d, 7 d/week for 3 weeks, using Threshold IMT device (POWERbreathe Medic; POWERbreathe International, Southam, UK). The initial training load was at least 30% of PImax and was progressively increased to at least 60%, and about half of the sessions were supervised
	
	PR (+ sham IMT): this group received a similar training protocol as described above and the IMT was conducted at no load.

Outcomes	Dyspnea: BDI-TDI (Total) Functional exercise capacity: 6MWD HRQoL • SGRQ (Total) • CAT • CCQ: (Total score) Respiratory muscle strength: PImax Respiratory function: FEV1 (L)
Identification	**Sponsorship source:** this study was supported by Deutsche Rentenversicherung Bayern Süd. Funding information for this article has been deposited with the Crossref Funder Registry **Country:** Germany

Schultz 2018 *(Continued)*

	Setting: Bad Reichenhall Clinic
	Author's name: Konrad Schultz
	Institution: Center for Rehabilitation, Pulmonology and Orthopedics, Klinik Bad Reichenhall
	Email: konrad.schultz@klinik-bad-reichenhall.de
	Address: Salzburger Strasse 8–11, 83435 Bad Reichenhall, Germany
	Clinical trial register: DRKS00004609
Notes	Adjusted mean differences with 95% CI were reported

Sykes 2005

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 PR • N (randomized/analyzed): 20/20 • Loss to follow-up or excluded: 0 Overall • N (randomized/analyzed): 40/40 • Loss to follow-up or excluded: 0 • Range age (min, max): 60,84 • Gender (M/F): 34/6 **Included criteria:** not reported **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **PR+IMT:** participants received exercise training and IMT with Threshold IMT at a load ranged from 30%-60% of PImax **PR:** this group received only exercise training
Outcomes	
Identification	**Country:** China **Setting:** Tai Po Hospital **Author's name:** Sykes

Sykes 2005 *(Continued)*

Notes	The systematic review (Gosselink 2011) reported data from this trial.

Tounsi 2021

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 17/16 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 62 (5) • Gender (M/F): 17/0 • BMI, mean (SD), kg/m^2: 23.13 (4.37) PR • N (randomized): 18/16 • Loss to follow-up or excluded: 2 • Age, mean (SD) in years: 63 (4) • Gender (M/F): 18/0 • BMI, mean (SD), kg/m^2: 23.41 (5.19) Overall • N (randomized): 35/32 • Loss to follow-up or excluded: 3 • Gender (M/F): 35/0 • COPD stage (GOLD): moderate to very severe **Included criteria** • patients with forced expiratory volume in 1 s (FEV1) <80% predicted and FEV1 /forced vital capacity (FVC) <70% • Age between 45–75 years • Clinically stable **Exclusion criteria** • Cardiovascular problem • Psychiatric or cognitive disorders • Progressive neuromuscular diseases • Severe orthopedic problems with a significant impact on daily activities • Prior inclusion in a rehabilitation program (<1 year)
Interventions	**Intervention characteristics** **PR+IMT:** • PR: an 8-week program with three sessions per week. the training program consists of aerobic supervised exercise training. The training consisted of 30 min of supervised treadmill exercise per session.

Tounsi 2021 *(Continued)*

	Each session ended with upper and lower limb stretching. Each participant received an individualized program based on 60% to 80% of the average speed achieved during the six-minute walk test. • IMT: The training was performed once a day, 7 days per week for 8 weeks, using a handle device (PowerBreathe1 Medic, IMT Technologies Ltd, Birmingham, UK). The training consists in making two sets of 30 breaths (4–5 min/set) with 5–10 min of rest between each set. The Respiratory resistive load was set at 50% of the initial PImax and then increased by 10% of the initial PImax every two weeks of training. Part of the IMT was performed and well instructed in the pulmonary rehabilitation center (3 days/ week) for 8 weeks; the other part was home-based training. **PR:** this group received a similar training protocol as described above without IMT.
Outcomes	Functional exercise capaticy: 6MWD Respiratory muscle strength: PImax
Identification	**Sponsorship source:** the authors received no funding for this work **Country:** Tunisia **Setting:** Farhat Hached Hospital of Sousse **Author's name:** Bilel Tounsi **Institution:** 1/ Laboratory of Exercise Physiology and Rehabilitation (APERE, UR-EA 3300), Sport Sciences Department, Picardie Jules Verne University, Amiens, France, 2/ Research Laboratory of Exercise Physiology and Pathophysiology: From Integral to Molecular Biology, Medicine and Health (LR19ES09), Faculty of Medicine of Sousse, University of Sousse, Sousse, Tunisia **Email:** bilel.tounsi@u-picardie.fr **Address:** Department of sports sciences, Picardie Jules Verne University, Amiens, France **Clinical trial register:** NCT04084405
Notes	

Tout 2013

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 61 (9.32) PR • N (randomized/analyzed): 10/10 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 58.1 (8.72) Overall

Tout 2013 *(Continued)*

- N (randomized/analyzed): 20/20
- Loss to follow-up or excluded: 0
- Age, mean (SD) in years: 60.38 (8.02)
- Gender (M/F): 19/21
- BMI, mean (SD), kg/m^2: 28.3 (3.11)
- COPD stage (GOLD): mild to moderate

Included criteria

- Co-operating COPD patients
- Diagnosed clinically and through spirometric measurement (grades 1 and 2 in the Gold classification); presenting with 50% < FEV1 < 80% of predicted or theoretical value in the spirometric test
- Presenting with an improvement < 15% of the FEV1 following use of bronchodilators
- From 45-75 years of age
- Of either sex

Excluded criteria

- Heart failure or associated cardiac pathology
- Previous pulmonary or cardiac surgery
- Patient depending on oxygen therapy or undergoing cortisone treatment
- Associated neuromuscular pathologies

Interventions	**Intervention characteristics** **PR+IMT:** • PR: 16 rehabilitation sessions that consisted of bronchial decluttering meant to clear the airways; diaphragmatic rehabilitation (solicitation of the physiological diaphragmatic contraction) aimed at improved stamina; reinforcing of the lower limb muscles so as to limit functional deconditioning; psychological support and therapeutic education • IMT: 20-30 min/session, twice/week for 8 weeks, using Threshold IMT at a training load ranged from 30%-60% of PImax **PR:** this group received only the PR protocol described above.
Outcomes	Functional exercise capacity: 6MWD HRQoL: SGRQ • Symptoms • Activity • Impact • Total Respiratory function: FEV1 (L)
Identification	**Country:** Lebanon **Author's name:** Rola Tout **Institution:** Institut de Physiothérapie, université Saint-Joseph **Email:** rolatout@yahoo.com **Address:** URAF, rue de Damas, Beyrouth, Lebanon
Notes	

Wang 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group **Subgroup analysis:** PImax less or more than 60 cmH2O
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 28/28 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 70.8 (4.5) • BMI, mean (SD), kg/m^2: 21.31 (2.76) PR • N (randomized/analyzed): 27/27 • Loss to follow-up/ excluded: 0 • Age, mean (SD) in years: 70.6 (6.3) • BMI, mean (SD), kg/m^2: 22.40 (2.85) Overall • N (randomized/analyzed): 55/55 • Loss to follow-up or excluded: 0 • COPD stage (GOLD): moderate to severe **Included criteria** • Age > 40 years • Diagnosis of stable COPD based on the GOLD guidelines; • No participation in any PR program in the previous 2 months • The participants had to be able to understand the investigator's instructions and complete the tests required in the study **Excluded criteria** • Acute or chronic airway diseases other than COPD, cardiovascular disorders (such as acute coronary syndrome), metabolic conditions (such as diabetes or hyperthyroidism), or other health problems that would interfere with exercise performance or the testing procedures
Interventions	**Intervention characteristics** **PR+IMT:** • PR: consisted of 30 min of cycle ergometer training 3 times/week for 8 weeks. The exercise intensity threshold in lower limbs was calculated as 70% VO_2max during cardiopulmonary exercise training • IMT: conducted 3 times/week for 8 weeks using a Threshold IMT device (model HS730, Philips, Amsterdam, the Netherlands), around 14 min/session at 30% of PImax **PR:** this group received only the PR protocol described above
Outcomes	Dyspnea: Borg • 6MWD

Wang 2017 *(Continued)*

- Incremental cycle ergometer test
- Notes: Borg was measured during peak cycle endurance test

Dyspnea: mMRC

Functional exercise capacity:

- 6MWD
- Wmax: measured through an incremental load of 5 w/min or 10 w/min

HRQoL: CAT

HRQoL: SGRQ (Total)

Respiratory muscle strength: PImax

Respiratory muscle endurance: MVV

Laboratory exercise test: VO2peak

- mL/min
- mL/kg/min

Respiratory function: FEV1

- %pred
- L

Identification	**Sponsorship source:** this work was supported by Guangzhou Municipal Science and Technology Project (201507020033), Medical Scientific Research Foundation of Guangdong Province (A2016399), Open Project of State Key Laboratory of Respiratory Disease (SKLRD2016OP019), and Clinical Research training program of Southern Medical University (LC2016PY032). **Country:** China **Setting:** Zhujiang Hospital affiliated to Southern Medical University **Author's name:** Xin Chen **Institution:** Department of Respiratory Medicine, Zhujiang Hosptial, Southern Medical University **Email:** chen_xin1020@163.com **Address:** 253 Gongye Road, Guangzhou 510282, China **Clinical trial register:** NCT02285400
Notes	Adjusted P values were reported. Authors reported a subgroup analysis for intervention group participants with or without respiratory muscle weakness.

Weiner 1992

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics**

Weiner 1992 *(Continued)*

PR+IMT

- N (randomized/analyzed): 12/12
- Loss to follow-up or excluded: 0
- Age, mean (SD in years): 67.2 (9)

PR

- N (randomized/analyzed): 12/12
- Loss to follow-up or excluded: 0
- Age, mean (SD in years): 64.4 (10.3)

Overall

- N (randomized/analyzed): 24/24
- Loss to follow-up or excluded: 0
- COPD stage (GOLD): severe to very severe

Included criteria

- Patients with spirometric evidence of chronic airflow limitation that was not corrected by bronchodilator therapy

Excluded criteria: not reported

Interventions	**Intervention characteristics**
	
	PR+IMT:
	
	• PR: consisted of
	  ○ 20 min of cycling on cycle ergometer. Participants started cycling with low load that was then gradually increased, about 5% each session, to reach 50% of the initial Wmax.
	  ○ 10 min of rowing
	  ○ 15 min of muscle exercises to strengthen upper and lower extremities and abdominal muscles
	• IMT: 15 min/session, 3 times/week for 6 months using the Threshold IMT device. Participants breathed at 15% of their PImax for 1 week. The resistance was then increased by 5% to reach 60% of PImax at the end of the first month and 80% at the end of the second month.
	
	PR+ (sham IMT): this group received the same training protocol as described above, and IMT was conducted at no load.

Outcomes	Functional exercise capacity: • 12MWD • Exercise time (constant cycle ergometer test) • Notes: endurance work time at 2/3 of Wmax Respiratory muscle strength: PImax (RV) Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax}) • Notes: participantss inspired through a 2-way HansRudolph valve whose inspiratory port was connected to a chamber and plunger to which weights could be added externally. Inspiratory elastic work was then increased by the progressive addition of 25-100 g weights at 2-min intervals. The pressure achieved with the heaviest load (tolerated for at least 60 s) was defined as the peak pressure (P_{thmax}) Respiratory function: FEV1 (%pred)
Identification	**Country:** Israel **Author's name:** Paltiel Weiner

Weiner 1992 *(Continued)*

	Institution: Department of Medicine, Hillel-Yaffe Medical Center, and the Institute for Respiratory Disease **Address:** Hadera, Israel
Notes	

Weiner 2000

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 12/11 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 62.5 (8.31) PR • N (randomized/analyzed): 5/4 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 61.0 (5.4) Overall • N (randomized/analyzed): 17/15 • Loss to follow-up or excluded: 2 • COPD stage (GOLD): severe **Included criteria** • Spirometric evidence of chronic airflow limitation • Diagnosis of moderate-to-severe COPD according to the criteria of the ATS **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **PR+IMT:** the training program is the same as described in (Weiner 1992). Participants trained 3 times/week and each session consisted of 1 h of supervised training. When only exercise training was performed, participants trained the whole hour, and when IMT was added, exercise training was cut to 30 min. **PR+ SHAM:** participants in this group received the same rehabilitation protocol and IMT was conducted at no load
Outcomes	Respiratory muscle strength: PImax (RV)
Identification	**Country:** Israel **Author's name:** Paltiel Weiner **Institution:** Department of Medicine A, Hillel-Yaffe Medical Center

Weiner 2000 *(Continued)*

	Address: Hadera, Israel
Notes	

Weiner 2003

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 8/8 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 63.1 (8.7) • Gender (M/F): 6/2 Control/sham • N (randomized/analyzed): 8/8 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 61.8 (9) • Gender (M/F): 7/1 Overall • N (randomized/analyzed): 16/16 • Loss to follow-up or excluded: 0 • Gender (M/F): 13/3 • COPD stage (GOLD): severe **Included criteria** • Spirometric evidence of significant chronic airflow limitation (i.e. FEV1 of < 50% of predicted and FEV1/FVC ratio of 70% of predicted) in whom COPD had been diagnosed, according to the criteria of the ATS **Excluded criteria** • Patients with cardiac disease • Poor compliance • A requirement for supplemental oxygen therapy • CO2 retention
Interventions	**Intervention characteristics** **IMT:** participants trained daily, 1 h/d, 6 times/week for 3 months using Threshold IMT device. They started breathing at a resistance equal to 15% of their PImax or PEmax for 1 week. The resistance then was increased incrementally 5% to 10% each session, to reach 60% of their PImax or PEmax at the end of the first month of training. **Control/sham:** participants trained at 7 cmH_2O throughout the trial
Outcomes	Dyspnea: BDI-TDI:

Weiner 2003 *(Continued)*

- Functional impairment
- Magnitude of task
- Magnitude of effort
- Focal score

Functional exercise capacity: 6MWD

Respiratory muscle strength: PImax (RV)

Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax})

Identification	**Country:** Israel **Author's name:** Paltiel Weiner **Institution:** Department of Medicine A, Hillel Yaffe Medical Center **Email:** weiner@hillel-yaffe.health.gov.il **Address:** Hadera, Israel 38100
Notes	Because only the IMT group data were reported in the results, and there were differences between the graphs and what was reported numerically, we included both groups' data from the graphs to guarantee consistency.

Weiner 2006

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 14/14 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 63.0 (7.66) • Gender (M/F): 8/6 • BMI, mean (SD), kg/m^2: 28.0 (5.72) Control/sham • N (randomized/analyzed): 14/14 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 62.7 (7.58) • Gender (M/F): 8/6 • BMI, mean (SD), kg/m^2: 28.0 (5.68) Overall • N (randomized/analyzed): 28/28 • Loss to follow-up or excluded: 0 • Gender (M/F): 16/12 • COPD stage (GOLD): severe

Weiner 2006 *(Continued)*

	Included criteria • Spirometric evidence of severe chronic air flow limitation (FEV 1 < 50% of predicted) and FEV 1/FVC < 70% of predicted **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **IMT:** participants trained daily, 1 h/d, 6 d/week for 8 weeks using Powerbreathe (Southam, UK). They started breathing at a resistance equal to 15% of their PImax for 1 week. The resistance was then increased incrementally (5%–10% each session), to reach 60% of their PImax at the end of the 1st month. IMT was then continued at 60% of their PImax adjusted weekly to the new PImax achieved **Control/sham:** participants trained with a resistance of 7 cmH_20 following the same protocol described above
Outcomes	Respiratory muscle strength: PImax (RV)
Identification	**Country:** Israel **Author's name:** Paltiel Weiner **Institution:** Department of Medicine A, Hillel Yaffe Medical Center **Email:** weiner@hillel-yaffe.health.gov.il **Address:** Hadera 38100 Israel
Notes	

Wu 2017

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT (Threshold device) • N (randomized/analyzed): 19/19 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 59.74 (6.14) • BMI, mean (SD), kg/m^2: 18.40 (2.19) IMT (resistive device) • N (randomized/analyzed): 21/21 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 62.24 (7.36) • BMI, mean (SD), kg/m^2: 19.25 (2.17) Control/sham • N (randomized/analyzed): 20/29 • Loss to follow-up or excluded: 0

Wu 2017 *(Continued)*

- Age, mean (SD) in years: 60.30 (6.55)
- BMI, mean (SD), kg/m^2: 18.54 (2.58)

Overall

- N (randomized/analyzed): 60/60
- Loss to follow-up or excluded: 0
- COPD stage (GOLD): moderate to severe

Included criteria

- Moderate, severe and very severe COPD (post-bronchodilator FEV1/FVC < 70% and FEV1 < 50% of predicted (GOLD B, C and D, respectively)
- Inspiratory muscle weakness (PImax < 60 cm H2O)
- Bronchial dilation test (BDT) negative
- No history of PR

Excluded criteria

- Time from most recent exacerbation > 2 months
- With no medication changes in 1 month prior to enrollment
- Obesity (BMI > 30 m^2/kg)
- Severe orthopedic problems having a major impact on ADL
- Previous inclusion in a rehabilitation program (< 1 year)
- Concomitant heart failure and pulmonary vascular diseases
- Diagnosed psychiatric or cognitive disorder
- Progressive neurological or neuromuscular disorder

Interventions	**Intervention characteristics** **IMT:** participants trained twice a day, 15 min/session for 8 weeks using either Threshold IMT (Respironics Inc; Pittsburgh, PA, USA) or Pflex (Respironics Inc, Pittsburgh, PA, USA) devices set at 60% of PImax **Control/sham:** no intervention received by this group
Outcomes	Dyspnea: BDI-TDI • Functional impairement • Magnitude of task • Magnitude of effort • Focal score Functional exercise capacity: • Wmax (Incremental cycle ergometer test: measured by increasing the work rate by 10 w/min after one minute of unloaded pedalling) • Exercise time (Incremental cycle ergometer test) HRQoL: CRQ • Dyspnea • Fatigue • Emotion • Mastery • Total Respiratory muscle strength: PImax (RV) Laboratory exercise test: VO2peak (L/min) (Incremental cycle ergometer test)

Wu 2017 *(Continued)*

	Respiratory function: FEV1 • L • %pred
Identification	**Sponsorship source:** the study was supported by the Science and Technology Project of Guangdong Province (2017A020211018) and the Guangzhou Healthcare collaborative innovation major project (201604040012) and State's Key Project of Research and Development Plan(2017YFSF11078). **Country:** China **Setting:** Guangzhou Institute of Respiratory Disease **Author's name:** Rongchang Chen **Institution:** Guangzhou Institute of Respiratory Disease, State Key Laboratory of Respiratory Disease **Email:** chenrc_vip@163.com **Address:** Guangzhou, China **Clinical trial register:** NCT03101774
Notes	

Xu 2018

Study characteristics	
Methods	**Study design:** RCT **Study grouping:** parallel-group **Subgroup analysis:** PImax: < or > 60 cmH2O
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 23/23 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 67.49 (6.17) • BMI, mean (SD), kg/m^2: 22.09 (3.37) Control/sham • N (randomized/analyzed): 23/23 • Loss to follow-up or excluded: 0 • Age, mean (SD) in years: 69.43 (6.44) • BMI, mean (SD), kg/m^2: 20.86 (4.41) Overall • N (randomized/analyzed): 46/46 • Loss to follow-up or excluded: 0 • COPD stage (GOLD): moderate to severe **Included criteria** • Patients with clinically stable COPD

Xu 2018 *(Continued)*

	• Naive to PR and willing to participate **Excluded criteria** • Cognitive disorders • Organ failure • Malignant tumors • Metabolic diseases
Interventions	**Intervention characteristics** **IMT:** participants trained daily, at home, 48 min/d for 8 weeks using Threshold IMT (Respironics, USA). The training load ranged from 30%-45% of PImax **Control/sham:** participants received the same protocol and trained at no load.
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD HRQoL: • SGRQ (Total) • CAT Respiratory muscle strength: PImax Respiratory function: FEV1 • L • %pred
Identification	**Sponsorship source:** this work was funded unconditionally by Clinical Research training program of Southern Medical University (LC2016PY032), National Key R&D Program of China (2017YFC1310601), The Guangzhou Healthcare Collaborative Innovation Major Project (201604020012), Guangzhou Innovation and Entrepreneurship Education Project of Universities (201709T26), Special Fundsfor the Cultivation of Guangdong College Students' Scientific and Technological Innovation (PDJHB0101). The sponsors have no any role in design, conduct, data interpretation of the study, and preparation, review or approval of this manuscript **Country:** China **Setting:** Zhujiang Hospital of Southern Medical University **Author's name:** Xin Chen **Institution:** Department of Respiratory Medicine, Zhujiang Hosptial, Southern Medical University **Email:** chen_xin1020@163.com **Address:** 253 Gongye Road, Guangzhou 510282, China **Clinical trial register:** NCT02326181
Notes	

ZhouL 2016

Study characteristics

ZhouL 2016 *(Continued)*

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 22/22 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 66.4 (5.5) • Gender (M/F): 17/5 • BMI, mean (SD), kg/m^2: 22.5 (2.1) Control/sham • N (randomized/analyzed): 22/22 • Loss to follow-up or excluded: 1 • Age, mean (SD) in years: 66.8 (6.2) • Gender (M/F): 16/6 • BMI, mean (SD), kg/m^2: 21.8 (2.2) Overall • N (randomized/analyzed): 44/44 • Loss to follow-up or excluded: 2 • Gender (M/F): 33/11 • BMI, mean (SD), kg/m^2 • COPD stage (GOLD): severe to very severe **Included criteria** • Age: 40-80 years • Severe or extremely severe COPD in lung functions • Combined with chronic respiratory failure (under normal inhalation, blood gas analysis PCO2 ≥ 50 mmHg after 1 h of rest • No acute occurrence of exacerbating episode in the past 4 weeks **Excluded criteria** • People who smoke > 10 cigarettes/d • Patients with unstable cardiac hemodynamics, such as acute left heart failure, unstable angina • Combined with other respiratory diseases, such as typical bronchiectasis, typical pulmonary fibrosis, sleep apnea, lung tumors, sequelae of tuberculosis (damage to the lung) • Those suffering from neuromuscular diseases or sequelae of severe cerebrovascular accidents
Interventions	**Intervention characteristics** **IMT:** participants trained twice a day, without supervision, 30 min/d, 6 d/week for 8 weeks using Threshold IMT device set at 60% of PImax. This group also received non-invasive positive pressure ventilation **Control:** this group received long-term oxygen therapy
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD Respiratory muscle strength: PImax

ZhouL 2016 *(Continued)*

Identification	**Sponsorship source:** National Natural Science Foundation of China (81361128004); Public welfare research and Capacity building special fund project (2014A020215033); Guangzhou Medical University Scientific Research Fund (2014c22) **Country:** China **Setting:** Guangzhou Institute of Respiratory diseases **Comments:** **Author's name:** Chen Rongchang **Institution:** Frist Affiliated Hospital of Guangzhou Medical University **Email:** member@wc.rf.org **Address:** Guangzhou 510120, China **Clinical trial register:** 0192675
Notes	

6MWD: six-minute walk distance; **12MWD:** 12-minute walk distance; **ADL:** activities of daily living; **ATS:** American Thoracic Society; **BDI:** Baseline Dyspnea Index; **BMI:** body mass index; **CAT:** Chronic Obstructive Pulmonary Disease Assessment Test; **CCQ:** Clinical COPD Questionnaire; **CI:** confidence interval; **COPD:** chronic obstructive pulmonary disease; **CPET:** cardiopulmonary exercise testing; **CRQ:** Chronic Respiratory Disease Questionnaire; **ERS:** European Respiratory Society; **FEV1:** forced expiratory volume at 1 second; **FRC:** functional residual capacity; **FVC:** forced vital capacity; **GOLD:** Global Initiative for Chronic Obstructive Lung Disease; **HRQoL:** health-related quality of life; **IMT:** inspiratory muscle training; **ISWT:** incremental shuttle walk test; **IVC:** inspiratory vital capacity; **MDP:** Multidimensional Dyspnea Profile; **MIP:** maximal inspiratory pressure; **mMRC:** Modified Medical Research Council; **MVV:** maximal voluntary ventilation; **PEmax:** maximal expiratory pressure; **PFT:** pulmonary function test; **PImax:** maximal inspiratory pressure; **PR:** pulmonary rehabilitation; **P_{thmax}:** respiratory muscle endurance pressure; **RCT:** randomized controlled trial; **RV:** residual volume; **SD:** standard deviation; **SE:** standard error; **SEM:** standard error of the mean; **SGRQ:** St George's Respiratory Questionnaire; **SpO_2:** Peripheral oxygen saturation; **SWT:** shuttle walk test; **TDI:** Transition Dyspnea Index; **VO_2max:** maximal oxygen consumption; **Wmax:** maximum exercise workload

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmad 2013	Ineligible intervention
Aldrich 1985	Ineligible study design
Anand 2013	Ineligible intervention
Baines 2005	Ineligible comparator
Basso Vanelli 2016	Ineligible comparator
Battaglia 2009	Ineligible intervention
Belman 1994	Ineligible comparator
Bgin 1991	Ineligible study design
Bissett 2016	Ineligible patient population

Study	Reason for exclusion
Bjerre Jepsen 1981	Ineligible intervention
Cader 2010	Ineligible patient population
Chen 1985	Ineligible intervention
Daynes 2018	Ineligible study design
de Andrade 2005	Ineligible study design
de Lucas Ramos 1998	Ineligible study design
Di Mambro 2007	Ineligible study design
DRKS00005637	Ineligible comparator
DRKS00006021	Cancelled Clinical trial
Elbouhy 2014	Ineligible patient population
Elmorsi 2016	Ineligible study design
Enright 2005	Ineligible comparator
Garcia 2008	Ineligible study design
Goldstein 1989	Ineligible intervention
Gregg 1989	Ineligible study design
Guyatt 1992	Ineligible intervention
Hart 2000	Ineligible patient population
Heydari 2015	Ineligible comparator
Hopp 1996	Ineligible study design
Ibakordor 2013	Ineligible comparator
Ionescu 2005	Non-RCT
Izumizaki 2008	Ineligible study design
Johnson 1996	Ineligible study design
Kivastik 2015	Ineligible study design
Koch 2020	Ineligible study design
Kolesnikova 2016	Ineligible intervention
Levine 1986	Ineligible comparator
Liao 2015	Ineligible intervention

Study	Reason for exclusion
Lin 2012	Ineligible intervention
Lisboa 1994	Ineligible patient population
Lisboa 1995a	Ineligible study design
Lisboa 1995b	Ineligible patient population
Lisboa 1998	Ineligible study design
Madariaga 2007	Ineligible comparison
Madsen 1985	Ineligible comparator
Martin 2006	Ineligible intervention
McKeon 1986	Ineligible patient population
Meshcheriakova 2006	Ineligible intervention
Minoguchi 2002	Ineligible study design
NCT01218295	Ineligible study design
NCT01556139	Ineligible patient population
NCT01747694	Ineligible intervention
NCT01945398	Ineligible study design
NCT01956565	Ineligible study design
NCT02186340	Ineligible study design
NCT02278523	Ineligible comparator
NCT02579200	Ineligible patient population
NCT02914093	Ineligible comparator
NCT02935166	Ineligible study design
NCT03186092	Ineligible patient population
NCT03500042	Ineligible outcomes
NCT03739879	Ineligible study design
NCT03844711	Ineligible comparator
NCT03880630	Ineligible study design
NCT04084405	Ineligible comparator
NCT04117399	Ineligible outcomes

Study	Reason for exclusion
NCT04460261	Ineligible study design
Neves 2014a	Ineligible intervention
Neves 2014b	Ineligible study design
Nield 2007	Ineligible intervention
Noseda 1987	Ineligible comparator
O'Connor 2019	Ineligible study design
Okura 2019	Ineligible study design
Okura 2020	Ineligible study design
PACTR201703002095224	Ineligible comparator
Padula 2001	Ineligible patient population
Perez 2010	Ineligible intervention
Pescaru 2016	Ineligible study design
Quintero 1999	Ineligible study design
Richardson 1989	Ineligible study design
Rocha 2015	Ineligible intervention
Sassoon 1992	Ineligible intervention
Serón 2005	Ineligible patient population
Shahin 2008	Ineligible study design
Shioya 2007	Ineligible intervention
Similowski 1994	Ineligible study design
Sivashanmugam 2019	Ineligible comparator
Soicher 1998	Ineligible study design
Sonne 1982	Ineligible study design
Sudo 1997	Ineligible intervention
Sugiyama 2010	Ineligible study design
Sun 2003	Ineligible intervention
TCTR20191009004	Ineligible intervention
UMIN000030937	Ineligible intervention

Study	Reason for exclusion
Van't Hul 2006	Ineligible intervention
Villafranca 1998	Ineligible study design
Wada 2016	Ineligible intervention
Wu 2006	Ineligible intervention
Xi 2015	Ineligible intervention
Yamaguti 2012	Ineligible intervention
Yan 1996	Ineligible intervention
Yang 2005	Ineligible intervention
Zhang 2008	Ineligible study design

Characteristics of studies awaiting classification *[ordered by study ID]*

Barter 1987

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Bustamante 1997

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Cassidy 2009

Methods	**Study design:** RCT **Study grouping:** parallel-group

Cassidy 2009 *(Continued)*

Participants	**Baseline characteristics** IMT • N (randomized/analyzed): 14/14 • Loss to follow-up or excluded: 0 • Gender (M/F): 7/7 Control/sham • N (randomized/analyzed): 14/14 • Loss to follow-up or excluded: 0 • Gender (M/F): 5/9 Overall • N (randomized/analyzed): 28/28 • Loss to follow-up or excluded: 0 • Gender (M/F): 12/16 • COPD stage: moderate to severe **Included criteria:** patients with COPD, following an acute exacerbation **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **IMT:** participants underwent 8 weeks of unsupervised IMT using a Threshold IMT device **Control/sham:** participants received sham IMT
Outcomes	Respiratory muscle strength: PImax Functional exercise capacity: 6MWD HRQoL: CRQ
Notes	**Country:** Ireland **Setting:** home-based training **Author's name:** C.Cassidy **Institution:** Respiratory Assessment Unit, CREST Directorate **Address:** St. James's Hospital, Dublin 8, Ireland

Cejudo 1998

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Chen 2017

Methods	**Study design:** RCT **Study grouping:** parallel-group **Clinical trial register:** NCT02200549
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 24/not reported PR • N (randomized/analyzed): 25/not reported Overall • N (randomized/analyzed): 49 not reported **Included criteria:** not reported **Excluded criteria:** not reported
Interventions	**Intervention characteristics** **PR+IMT:** • PR: 8 weeks of cycle ergometer trainning. • IMT: 8 weeks of IMT **PR:** training with a cycle ergometer for 8 weeks
Outcomes	Dyspnea Functional exercise capacity HRQoL: CRQ Respiratory muscle strength
Notes	**Country:** China **Author's name:** X.Chen **Institution:** Zhujiang Hospital- Southern Medical University, Department of Respiratory Medicine **Address:** Guangzhou, China

Croitoru 2013

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT

Croitoru 2013 *(Continued)*

- N (randomized/analyzed): 14/14
- Loss to follow-up or excluded: 0
- Age mean (SD) in years: 63.4 (8)

PR

- N (randomized/analyzed): 14/14
- Loss to follow-up or excluded: 0
- Age mean (SD) in years: 60.3 (11)

Overall

- N (randomized/analyzed): 28/28
- Loss to follow-up or excluded: 0
- COPD stage: moderate to severe

Included criteria: not reported

Excluded criteria: not reported

Interventions	**Intervention characteristics** **PR+IMT:** • PR: outpatient, 8 weeks, lower and upper limbs training, education, and psychological support • IMT: daily, at home, with Threshold device, 30 min/d **PR:** participants received the same PR protocol described above.
Outcomes	Functional exercise capacity: 6MWD HRQoL: SGRQ Respiratory muscle strength: PImax
Notes	

Del Castillo Otero 1998

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Di Marzo 2000

Methods	Unfound
Participants	Unfound

Di Marzo 2000 *(Continued)*

Interventions	Unfound
Outcomes	Unfound
Notes	

Di Marzo 2002

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Downes Vogel 2002

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Eastwood 2005

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Gething 2001

Methods	Unfound
Participants	Unfound

Gething 2001 *(Continued)*

Interventions	Unfound
Outcomes	Unfound
Notes	

Göhl 2006

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

IRCT201104266299N1

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** Overall • N (randomized/analyzed): 30 **Included criteria** • Patients with mild to very severe COPD • Having an established treatment plan • BMI < 35 • Absence of other diseases such as neurological disorders, musculoskeletal system, peripheral vascular disease, and independence to the long-term oxygen therapy **Exclusion criteria** • Changes in the treatment plan during the study.
Interventions	**Intervention characteristics** **IMT:** participants trained at home daily for 21 min, 6 d/week for 8 weeks **Control/sham:** no intervention
Outcomes	Dyspnea HRQoL: SGRQ
Notes	

IRCT20180205038633N1

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 15/unknown PR • N (randomized/analyzed): 15/unknown IMT • N (randomized/analyzed): 16/unknown Control/sham: • N (randomized/analyzed): 15/unknown Overall • N (randomized/analyzed): 61/unknown • COPD stage: moderate to severe **Inclusion/exclusion criteria** • Willing to participate in the study • Grade 2 or 3 COPD based on GOLD criteria • Age 40-70 years; • Lack of other pulmonary diseases • Lack of severe limb limbs • Lack of pulmonary surgery in the last 12 months • Recent fracture failure at the level of ribs (6 months) • No history of psychotropic disease and related drugs and alcohol and psychotropic substances
Interventions	**Intervention characteristics** **IMT:** the intensity of training was 40%-60% (S-Index 40%-60%), 2 d/week, and 5 sessions of dermal muscle training with repeat 50 (5 Repeat 10) for about 15 min/session. **PR:** aerobic exercise method: with a treadmill and foot pedometer, 2 times a week, with 40%-60% heart rate reserve for 40 min/session **PR+IMT:** in each session, breathing exercises were performed first and then aerobic exercises were performed on the lower extremities **Control:** this group did not take any special intervention other than the usual treatments (control group)
Outcomes	Dyspnea: mMRC Respiratory muscle strength: PImax Functional exercise capacity: 6MWD Respiratory function: FEV1
Notes	

ISRCTN19258620

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • 80 non-hypercapnic patients with moderate (FEV < 40%) recruited from consultant hospital and community chest clinics • All patients will be receiving optimum medical management and will have been stable for at least 4 weeks prior to their initial assessment **Exclusion criteria** • Hypercapnia (PaCO2 > 45 mmHg) • Any patient who is unsuitable for magnetic stimulation (pacemakers, artificial heart valves, metal prosthesis)
Interventions	**IMT:** using Powerbreathe device
Outcomes	Dyspnea: Borg Functional exercise capacity: SWT Respiratory muscle strength: PImax Respiratory muscle endurance pressure: P_{thmax} Respiratory muscle endurance time: T_{lim}
Notes	

Jones 1985

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** Overall • N (randomized/analyzed): 21 **Inclusion criteria:** FEV1 < 1.2 L
Interventions	**Intervention characteristics** **IMT:** training with resistive device for 10 weeks **Control/sham:** placebo training group
Outcomes	Functional exercise capacity: Wmax Functional exercise capacity: 12MWD

Jones 1985 *(Continued)*

Notes	

Koppers 2004

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Liu 1989

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Manuel Vargas 1995

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** Overall • N (randomized/analyzed): 23
Interventions	**Intervention characteristics** **IMT:** participants trained with a Threshold device at 30% of PImax **Control/sham:** no training was provided
Outcomes	Functional exercise capacity
Notes	

Mendoza 2007

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	Unfound

Meshcherykova 2018

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** IMT • N (randomized/analyzed): not reported/17 • Age mean (SD) in years: 62.5 (7.5) Control/sham • N (randomized/analyzed): not reported/11 • Age mean (SD) in years: 63.5 (9.8) Overall • N (randomized/analyzed): not reported/ 28 • COPD stage: severe **Included criteria:** patients with severe COPD
Interventions	**Intervention characteristics** **IMT:** participants received IMT for 3 months **Control/sham:** training with no load
Outcomes	Dyspnea: BDI-TDI Functional exercise capacity: 6MWD Respiratory function: FEV1 Respiratory function: RV
Notes	

NCT01056081

Methods	**Study design:** RCT **Study grouping:** parallel-group

NCT01056081 *(Continued)*

Participants	**Baseline characteristics** Overall: • N (randomized/analyzed): 19/unknown **Inclusion criteria** • Patients with a clinical and spirometric diagnosis of moderate to severe COPD according to GOLD • In a stable condition (without exacerbations or infections for at least a month) • Had to be former smokers (> 6 months without smoking) • Patients referred by a physician to the pulmonary rehabilitation program **Exclusion criteria** • Patients with a known history of asthma, or severe and/or unstable heart disease or any other pathological condition that could impair their physical activities
Interventions	**Intervention characteristics** **PR+IMT** • PR: no information • IMT: participants trained with a Threshold inspiratory muscle trainer (Respironics HealthScan, Inc, Cedar Grove, New York, USA). The participants performed the IMT training in a seated position, with the upper limbs supported. The total duration of the respiratory training was 30 min, with sequences of 3 min of training followed by pauses of 2 min. The initial load was equivalent to 30% of the individual's MIP. This load was progressively increased over the first 4 weeks, according to the participant's tolerance, to reach 60% of the MIP. This level was then maintained until the end of the training. **PR:** this group received only PR
Outcomes	Dyspnea Functional exercise capacity: exercise time Respiratory muscle strength: PImax
Notes	

NCT01903772

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion Criteria:** • Patients with COPD • Eligible to participate in an inpatient pulmonary rehabilitation program of 3 weeks • PImax <60 cmH_20 or <50% of the predicted normal value **Exclusion Criteria:** • Major comorbidities preventing successful participation in an 8-week exercise training intervention • use of non-invasive ventilation

NCT01903772 *(Continued)*

Interventions	**Intervention characteristics** **IMT:** Inspiratory Muscle Training Three times daily inspiratory muscle training (2x30 breaths) at an intensity of >50% PImax **Sham IMT:** Twice daily inspiratory muscle training (3x30 breaths) at an intensity of 5 centimeters of water (H2O)
Outcomes	Dyspnea Functional exercise capacity Respiratory muscle strength: PImax Inspiratory muscle endurance capacity
Notes	It is unclear whether the study was completed, and no contact details were found.

NCT02392715

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • COPD demonstrated by spirometry using GOLD criteria • Patient referred by a pneumologist to the ambulatory PR program at the Riviera-Chablais Hospital, Monthey • Patient with maximal inspiratory pressure < 60 cmH20 • Patient > 40 years **Exclusion criteria** • Orthopaedic or neurological troubles that could slant the 6MWD
Interventions	**Intervention characteristics** **PR+IMT:** • PR: general exercise training • IMT: participants trained with a Threshold device 3 times/week with a total of 36 sessions. The training load was increased from 15%-60% of PImax. **PR: (+sham IMT):** this group received general exercise training with a sham IMT set at 5 cmH_2O.
Outcomes	Functional exercise capacity: 6MWD HRQoL: SGRQ Inspiratory muscle strength (PImax)
Notes	

NCT02673242

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • COPD grade 3-4 • Inhabitant of Hedmark (Løten, Våler, Åsnes, Hamar, Elverum) **Exclusion criteria** • Undergoing exercise-based physical therapy treatment • Not able to do IMT physically or mentally
Interventions	**Intervention characteristics** **IMT:** using a Threshold device for 6 weeks **Control/sham:** participants received sham training or another intervention
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD HRQoL: CAT
Notes	

NCT03080662

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • To be eligible for the PR program participants must have stable COPD (at least 4 weeks), inspiratory muscle weakness (PImax < 70%) and pulmonary hyperinflation (TLC > 120%). Patients that have signed informed consent **Exclusion criteria** • Hospitalization within the previous 14 days • Current participation in a rehabilitation program • Locomotor or neurological condition or disability limiting the ability to perform exercise • Lung transplantation or lung volume reduction surgery foreseen within 1 month after discharge
Interventions	**Intervention characteristics** **IMT:** training with ORYGEN DUAL Sham Valve for 5 weeks **Control/sham:** training with the same protocol with no load
Outcomes	

NCT03080662 *(Continued)*

Notes	

NCT03438019

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • Male or female aged > 40 years with a confirmed diagnosis of COPD by a pulmonologist (presence of risk factors and airflow obstruction) • Evidence of inspiratory muscle weakness as defined by the latest ATS/ERS statement on respiratory muscle training **Exclusion criteria** • Refusal to participate in the study • Patients actively undergoing PR • Inability to perform the required manoeuvres (i.e. patients with a cerebrovascular accident or tracheostomy) • Patients not in their stable state (i.e. having an acute exacerbation or within 4 weeks of having one) or the presence of important comorbidities that may confound the interpretation of TIRE (test of incremental respiratory endurance) measures (i.e. decompensated heart failure, diaphragmatic paralysis, prior lung surgery, active cancer treatment, etc.).
Interventions	**Intervention characteristics** **The TIRE IMT group:** will receive a tablet with the TIRE software installed and a PrO2 device through which they will train. Training consists of 6 levels (A-F) with 6 inspirations at each level for a total of 36 breaths. Recovery times between breaths range from 40-5 seconds as the participant advances each level. TIRE data will be stored in the tablet for subsequent interrogation and data retrieval. **The standard IMT group:** will receive a Threshold Inspiratory Muscle Trainer. This device incorporates a flow-independent one-way valve to ensure consistent resistance and features an adjustable specific pressure setting to be set based on MIP values of each participant. Participants will be instructed to perform up to 36 breaths daily. To compare with TIRE training, we will ask participants to perform this within a 30-min session. **The sham IMT group:** will also receive a Threshold device and undergo the exact protocol of group 2 but with minimal resistance applied (7 cm H2O, the lowest in the device).
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD HRQoL: • SGRQ • CAT Respiratory muscle strength: PImax
Notes	

NCT03790410

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** **Inclusion criteria** • Stable COPD • Do not take part in other treatment • Be able to learn the usage of inspiratory muscle trainer **Exclusion criteria** • Acute exacerbation • Balance problems with a neurological cause • The patient unable to cooperate • Participation in pulmonary rehabilitation 3 months before the study • IMT use in the 3 months before the study
Interventions	**Intervention characteristics** **PR+IMT:** PR consists of breathing exercises, bicycle ergometer conditionings, relaxations, and strength and endurance training. IMT consists of strengthening exercises on the diaphragm muscle. **PR:** This group undertook only PR.
Outcomes	Respiratory muscle strength: PImax
Notes	

Newall 1998

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Newall 2000

Methods	Unfound
Participants	Unfound
Interventions	Unfound

Newall 2000 *(Continued)*

Outcomes	Unfound
Notes	Unfound

NTR2990

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Pertuze 1994

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Ramirez Sarmiento 2000

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Reidi 2005

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** Overall

Reidi 2005 *(Continued)*

	• N (randomized/analyzed): 18/unknown • Age mean (SD) in years: 65.1 (6.6) **Inclusion criteria:** FEV1 < 60%
Interventions	**Intervention characteristics** **IMT:** the training was performed through the Threshold set at 30 of PImax. The program consisted of 4 weeks, with 3 weekly sessions where both groups were reassessed weekly **Control/sham:** the training consisted of performing the threshold with or without the natural resistance of the equipment < 7 cmH2O
Outcomes	Respiratory muscle strength: PImax
Notes	

Valderramas 2009

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Vargas 1995

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	
Interventions	**Intervention characteristics** **IMT:** participants used an inexpensive pressure threshold load valve constructed according to the Appropriate Technology principles of the WHO, adjusted at 30% of MIP for 3 months **Control/sham:** this group did not receive any intervention.
Outcomes	Respiratory muscle strength: PImax
Notes	

Vargas 1998

Methods	Unfound

Vargas 1998 *(Continued)*

Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Wang 2004

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** Overall • N (randomized/analyzed): 64
Interventions	**Intervention characteristics** **IMT:** twice a day for 6 months **Control/sham:** no intervention was received
Outcomes	Respiratory function: FEV1 (%pred)
Notes	

Wanke 1994

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Baseline characteristics** PR+IMT • N (randomized/analyzed): 21/unknown PR • N (randomized/analyzed): 21/unknown
Interventions	**Intervention characteristics** **PR+IMT:** • PR: cycle ergometer training for 8 weeks • IMT: for 8 weeks **PR:** cycle ergometer training alone
Outcomes	Functional exercise capacity

Wanke 1994 *(Continued)*

Notes	

Weiner 2006a

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

Wolstenholme 1998

Methods	Unfound
Participants	Unfound
Interventions	Unfound
Outcomes	Unfound
Notes	

6MWD: six-minute walk distance; **12MWD:** 12-minute walk distance; **ATS:** American Thoracic Society; **BDI:** Baseline Dyspnea Index; **BMI:** body mass index; **CAT:** COPD Assessment Test ; **COPD:** chronic obstructive pulmonary disease; **CRQ:** Chronic Respiratory Disease Questionnaire; **ERS:** European Respiratory Society; **FEV1:** forced expiratory volume at 1 second; **GOLD:** Global Initiative for Chronic Obstructive Lung Disease; **HRQoL:** health-related quality of life; **IMT:** inspiratory muscle training; **MIP:** maximal inspiratory pressure; **mMRC:** Modified Medical Research Council; **PImax:** maximal inspiratory pressure; PR: pulmonary rehabilitation; **RCT:** randomized controlled trial; **RV:** residual volume; **SGRQ:** St George's Respiratory Questionnaire; **SWT:** shuttle walk test; **TDI:** Transition Dyspnea Index; **TIRE:** test of incremental respiratory endurance; **WHO:** World Health Organization; **Wmax:** maximum exercise workload

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2020/11/029226

Study name	Effects of inspiratory muscle training vs autogenic drainage in hospitalised COPD patients
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • Diagnosed case of COPD from 4-10 years • Patients of both genders aged between 50-70 years • Smokers and non-smokers • Clinically stable patients **Exclusion criteria**

CTRI/2020/11/029226 *(Continued)*

	• Resting SBP > 200 mm Hg or DBP > 110 mm Hg • Pre-hypertension and hypotension • Diagnosed cases of orthopnea • Diagnosed cases of chronic kidney disease • Injured musculoskeletal or fractured since 3 months.
Interventions	**IMT:** conducted for 30 min with a total of 10 sessions **Control:** this group did not receive any intervention
Outcomes	HRQoL: SGRQ Pulmonary function tests
Starting date	20 November 2020
Contact information	**Sponsorship source:** KLE Academy of Higher Education and Research **Country:** India **Author's name:** Varun Naik **Institution:** Physiotherapy Department Nehru Nagar Belgaum Belgaum **Email:** drvarunnaik@gmail.com **Address:** KARNATAKA 590010 **Clinical trial register:** CTRI/2020/11/029226
Notes	

CTRI/2021/05/033469

Study name	To test the efficacy of inspiratory muscle training device Airofit in reducing breathlessness in COPD patients
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • All patients with spirometry-proven, stable COPD (GOLD stage ≥ 2) screened for inclusion • Patients with MIP < 100% of predicted • Patients aged 35-65 years **Exclusion criteria** • Patients without access to a suitable smartphone or tablet for the duration of intervention • Patients with an inability to read and understand written and verbal instructions in English • Patients with a history of hospitalization during the previous 4 weeks • Patients with severe orthopedic problems during the previous 4 weeks • Patients with diagnosed psychiatric or cognitive disorders • Patients with a progressive neurological or neuromuscular disorder • Patients on the waiting list for lung transplantation • Patients with previous inclusion in a rehabilitation program < 1 year • Patients with previous experience with IMT

CTRI/2021/05/033469 *(Continued)*

	• Patients with underlying bronchiectasis, innate lymphoid cell, post-COVID and post-tuberculosis sequelae • All COPD patients with active COVID status or within 15 days of post-COVID recovery
Interventions	**Intervention characteristics** **IMT (Airofit device group):** the Airofit is a new IMT device, which combines a calibrated inspiratory flow resistance with a pressure transducer and mobile device app. As the user inhales through the device, a pressure load is created; the magnitude of the load is proportional to the rate of air flow, as well as to the flow resistance properties of the load setting. The former has been identified as a limitation of flow-resistive IMT. To overcome the flow-dependency of the training load, the Airofit uses a pressure transducer to communicate with bespoke software, in real time. The measurement of pressure provides the user with instantaneous visual feedback of the pressure created by their inspiratory muscles, i.e. their training effort. The software also provides the user with a personalized visual training intensity target (50% of MIP). A total of 19 patients with a spirometry-proven stable COPD will be enrolled in the experimental arm. **IMT (Powerbreathe device group):** 19 participants will train at a load of 50% of PImax. **Sham IMT:** the participants will use control device 'Breathing pacer'
Outcomes	Inspiratory muscle strength (PImax) Adverse events
Starting date	1 June 2021
Contact information	**Sponsorship source:** Airofit AS Copenhagen, Denmark **Country:** India **Author's name:** Atul Deshmukh **Institution:** Padmashree Dr. D Y Patil University Navi Mumbai **Email:** atul.deshmukh@dypatil.edu **Address:** Centre for Interdisciplinary Research, Ground floor, Central Research Facility, Near Simulation Laboratory Padmashree Dr. D Y Patil Univerisity Campus Sector 7 Nerul Navi Mumbai, MAHARASHTRA, 400706, India
Notes	

CTRI201712010952

Study name	Effect of breathing exercises to improve the strength of respiratory muscles in COPD population
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria:** diagnosed COPD patients **Exclusion criteria:** women with COPD, those unable to comprehend
Interventions	**Intervention :** IMT+PR **Control:** PR

CTRI201712010952 *(Continued)*

Outcomes	6MWD Respiratory muscle strength (PImax) CRQ
Starting date	10 April 2017
Contact information	veenakiran_nambiar@yahoo.co.in
Notes	

De Souza 2019

Study name	Does inspiratory muscle training (IMT) reduce depression in patients with COPD?
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	Patients with COPD presenting with inspiratory muscle weakness
Interventions	**Intervention characteristics** **IMT:** participants trained at 50% of PImax, 2 sessions/d of 30 breaths for 8 weeks, with a weekly face-to-face session **Control/sham:** participants trained at 10% of PImax with a similar protocol
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD Respiratory muscle strength: PImax
Starting date	
Contact information	souzayr@gmail.com
Notes	

Formiga 2020

Study name	Novel versus traditional inspiratory muscle training regimens as home-based, stand-alone therapies in COPD: protocol for a randomized controlled trial
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • Patients > 40 years with a clinical and functional diagnosis of COPD according to GOLD guidelines – stages 1-4

Formiga 2020 *(Continued)*

- Evidence of inspiratory muscle weakness, defined as a MIP ≤ 80 cmH2O and a SMIP ≤ 427 pressure-time units
- The ability to operate a computer, tablet or smartphone independently and follow the training instructions
- Clinical stability with no history of infections or exacerbation of respiratory symptoms for at least 2 months prior to study enrollment
- Non-participation in exercise programs in the past 12 months

Exclusion criteria

- History of lung surgery, lung cancer, as well as individuals with any diagnosed cognitive (i.e. Mini Mental State Examination score < 24), orthopedic, neurological or neuromuscular disorders that might prevent them from appropriately performing the required physical tests and/or completing the study questionnaires
- Patients will not be excluded based upon their current bronchodilator regimen. If they experience acute exacerbations or respiratory infections during the training period, they will be examined by a pneumologist who will decide whether the participant should continue with the training or not.

Interventions	**Intervention characteristics** All groups will train once a day for 8 weeks **TIRE:** participants will use an on-screen training template set at 50% of their MIP and SMIP. The training will consist of 6 levels (A-F) with 6 inspirations per level for up to 36 efforts per session. Preset recovery times between breaths: 60 seconds at level A to 50, 40, 30, 20 and 10 seconds at levels B to F, respectively **Threshold IMT:** participants will train using a one-way spring-loaded valve set at 50% of their MIP. The training will consist of 36 inspirations performed using the device within a 30-min period. **Sham-IMT:** participants will use a one-way spring-loaded valve set to its minimal resistance (−9 cmH2O). The training will consist of 36 inspirations performed using the device within a 30-min period.
Outcomes	Dyspnea: mMRC Respiratory muscle strength: PImax HRQoL: CAT Functional exercise capacity: 6MWD Respiratory muscle strength (PImax) Pulmonary function test
Starting date	1 May 2021
Contact information	dosbaba.filip@fnbrno.cz
Notes	Clinical tiral register: NCT04415788

JPRN-UMIN000039893

Study name	The effectiveness of inspiratory muscle training in patients with chronic obstructive pulmonary disease
Methods	**Study design:** RCT

JPRN-UMIN000039893 *(Continued)*

	Study grouping: parallel-group
Participants	**Inclusion criteria** • Age minimum: 20 years • Age maximum: not applicable • Gender: male **Exclusion criteria** • Participants have no severe and/or unstable cardiac disease, orthopedic disease or mental disorder
Interventions	**Intervention characteristics** **PR+IMT:** • PR: • IMT: 30%-50% of PImax intensity, 30 breaths/session, 2 sessions/d, every day for 3 months **PR +sham IMT:** this group will undergo the same rehabilitation program with an IMT load set at 10% of PImax
Outcomes	Functional exercise capacity: 6MWD HRQoL: CAT Inspiratory muscle strength (PImax)
Starting date	01/11/2016
Contact information	**Sponsorship source:** Akita University Graduate School of Health Sciences **Country:** Japan **Author's name:** Takanobu Shioya **Institution:** Akita University Graduate School of Health Sciences Department of Physical Therapy **Email:** shioya@hos.akita-u.ac.jp **Address:** 1-1-1, Hondo, Akita Japan **Clinical trial register:** JPRN-UMIN000039893
Notes	

JPRN-UMIN000043099

Study name	Effect of inspiratory muscle training on diaphragm and exercise tolerance in patients with COPD
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • Age minimum: 65 years • Age maximum: 85 years • Gender: male and female

JPRN-UMIN000043099 *(Continued)*

	Exclusion criteria • The exclusion criteria include unstable medical conditions that cause or contribute to breathlessness (i.e. metabolic, cardiovascular, or other respiratory diseases) or any other disorders that interfere with exercise testing, such as neuromuscular diseases or musculoskeletal problems
Interventions	**Intervention characteristics** **IMT:** IMT will be performed for 12 weeks **Control:** this group will not receive any intervention
Outcomes	Exercise capacity
Starting date	22 January 2021
Contact information	**Sponsorship source:** Kindai University Hospital **Country:** Japan **Author's name:** Masashi Shiraishi **Institution:** Kindai University Hospital Department of Rehabilitation **Email:** masashi-shiraishi@med.kindai.ac.jp **Address:** 377-2 Onohigashi, Osakasayama-city 589-8511 Japan **Clinical trial register:** JPRN-UMIN000043099
Notes	

NCT04120142

Study name	Effect of inspiratory muscle training during PR on dyspnoea and exercise tolerance in COPD patients
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • COPD diagnosed by pulmonary function testing • Clinically stable • Absence of other obstructive diseases • Signed written consent **Exclusion criteria** • Were previous pneumonectomy or lobectomy in the past 6 months • Spontaneous risk of pneumothorax or rib fracture • Incapacity to follow a standard rehabilitation programme (locomotor deficits, acute cardiac failure and acute exacerbation of COPD at the beginning of the program) • The absence of written informed consent
Interventions	**Intervention characteristics** **PR+IMT:** IMT + aerobic exercise

NCT04120142 *(Continued)*

	PR: aerobic exercise alone
Outcomes	Dyspnea Respiratory muscle strength (PImax)
Starting date	1 February 2019
Contact information	
Notes	

NCT04201522

Study name	The effect of respiratory training on exercise tolerance in COPD (ERTET)
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • Age ≥ 40 years • Chronic airflow obstruction: FEV1/FVC < 0.7, FEV1 of 30%-80%pred, after bronchodilation **Exclusion criteria** • Inability to perform a cycling exercise • Diagnosed of ≥ 1 comorbidities that may limit exercise tolerance: cardiovascular, metabolic, endocrine, gastrointestinal, renal, neurological or rheumatological disease • Recent COPD exacerbation (< 3 months) • Recent cancer • A daily dose of Prednisone > 10 mg • Hypoxemia at rest or during exercise: PaO2 < 60 mmHg or SpO2 ≤ 88% • BMI > 30 kg/m^2 • Pregnancy • Skinfold at intercostal or vastus lateralis muscle > 1.5 cm
Interventions	**Intervention characteristics** **IMT:** participants will train for 6 weeks, 15 min twice daily, 5 d/week at 60% of the peak of minute ventilation, at home by means of a respiratory device (SpiroTiger, Idiag, Fehraltorf, CH) **Control/sham:** participants will undergo the training protocol at rest's minute ventilation
Outcomes	Respiratory muscle strength (PImax)
Starting date	14 March 2017
Contact information	ferid.oueslati@criucpq.ulaval.ca
Notes	

NCT04387318

Study name	Inspiratory muscle training and neuromuscular electrical stimulation in chronic obstructive pulmonary disease
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • Clinical diagnosis of COPD, in stages 2, 3 and 4 according to GOLD criteria • Clinically stable, i.e. absence of infections or exacerbations in the last 3 months • The medical team allows the patient to exercise • Availability of attending the rehabilitation program **Exclusion criteria** • Unstable primary pathologies (cardiovascular, renal, metabolic, psychiatric) • Hemodynamic instability • Nutritional supplementation in the 4 weeks preceding the study • Severe hearing or a visual impairment recorded on patient chart or self-referred • Obesity (BMI > 30 kg/m2) • A neurological or musculoskeletal condition that severely limits mobility and postural control, thus making it impossible to carry out the assessments • Electronic devices, such as heart pacemakers and implantable cardioverter-defibrillator • Skin injuries and infection where electrodes would be placed • Prior participation in pulmonary rehabilitation programs 3 months previous to the study • Vertigo
Interventions	**PR+IMT:** • PR: aerobic and resistance exercise for 8 weeks • IMT: participants will train with POWERbreathe Medic Plus (POWERbreathe International Ltd., England, UK) inspiratory training device for 5 sets of 10 repetitions each, with a 1-minute interval between each set. The initial load set will be 30% of PImax, during the first 2 weeks to allow for an adjustment period. After that, load increases occurred as follows: 35% of PImax in week 3, 40% of PImax in week 4, 45% of PImax in week 5, 50% of PImax at week 6, 55% of PImax in week 7, and 60% of PImax in week 8 **PR:** this group will undergo only the PR protocol described above
Outcomes	HRQoL: SGRQ Respiratory muscle strength (PImax) Respiratory muscle endurance
Starting date	1 October 2019
Contact information	albuisa@gmail.com
Notes	

NCT04802096

Study name	Effects of inspiratory muscle training in addition to pulmonary rehabilitation in patients with moderate to severe COPD exacerbation
Methods	**Study design:** RCT **Study grouping:**parallel-group
Participants	**Inclusion criteria** • Age > 20 years old • Diagnosed as moderate exacerbation of COPD • MIP < 80 cmH2O **Exclusion criteria** • Any clinical diagnosis that will influence the measurement, including any history of neuromyopathy • Angina, acute myocardial infarction in the previous month • Pregnancy • Participated in IMT program in the previous 3 months • Any psychiatric or cognitive disorders, e.g. Mini-Mental State Examination < 24, that will disturb the communication and co-operation of the study
Interventions	**PR+IMT:** • PR: aerobic exercise training, strength training, and education related to airway clearance and drug utilization. All the participants will receive 8-week PR • IMT: the intensity of IMT will be set at 30% of MIP. Participantsin this group will perform 15 breaths/set, 6 sets/d on a daily basis. The intervention will last for 8 weeks **PR:** this group will undergo the same PR program as the intervention group
Outcomes	Functional exercise capacity: 6MWD HRQoL: SGRQ HRQoL: CAT
Starting date	15 March 2021
Contact information	**Sponsorship source:** National Taiwan University Hospital **Country:** Taiwan **Author's name:** Wei-Yu Huang **Institution:** School and Graduate Institute of Physical Therapy of National Taiwan University **Email:** r08428013@ntu.edu.tw **Address:** Taipei, Zhongzheng Dist, Taiwan, 100 **Clinical trial register:** NCT04802096
Notes	

RBR-10nyzcqc

Study name	Effects of Inspiratory Muscle Training on Breathlesness, Exercise Capacity and Postural Control in Patients with COPD
Methods	**Study design:** RCT **Study grouping:**parallel-group
Participants	**Inclusion criteria** • Age> 40 years • Diagnosis of COPD according to GOLD (2016) • Absence of exacerbations in the last 30 days • Presence of inspiratory muscle weakness (PImax <70cmH2O or <70% of predicted) **Exclusion criteria** • Diagnosis of psychiatric or cognitive diseases that compromise the understanding of the study's guidelines • Progressive neurological disease • Neuromuscular disease; Vestibular disorders • Orthopedic changes that compromise the results of field and range tests Presence of other co-morbidities that, at the researcher's discretion, may interfere with the results of the study
Interventions	**IMT:** 22 patients will train at around 50% of their PImax. The training consists of 30 breaths in a row, with deep and strong inspiration (lasting 4-5 minutes), twice a day, every day for 8 weeks. Each week, the patient will return to our center to perform a new manovacuometry and update the load value, maintaining the ~ 50% of the PImax value, and after this update, one of the sessions of the day will be held in person. **Sham IMT:** 16 patients will train at around 10% of their PImax. The training consists of 30 breaths in a row, with deep and strong inspiration (lasting 4-5 minutes), twice a day, every day for 8 weeks. Every week, the patient will return to our center to perform a new manovacuometry, the data will be recorded, however the load will be kept at around 10% of the initial PImax value, after this registration, one of the sessions of the day will be held in person. This value will not make any changes during the study period. After the eight-week protocol, patients will return to perform the initial evaluations and tests again, in the same order they did the first time, and will receive a new medical order for serum vitamin D and calcium measurement for comparison with the first. The CG participants after the study period will undergo the same protocol applied to the IG as treatment.
Outcomes	Dyspnea: mMRC Functional exercise capacity: 6MWD
Starting date	
Contact information	yves.souza@uva.br
Notes	

RBR 42rmqy

Study name	Inspiratory muscle training in chronic obstructive pulmonary disease oxygen-dependent patients: a randomized controlled trial

RBR 42rmqy *(Continued)*

Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**IMT** • N (randomized): 30 **Control/sham** • N (randomized): 30 **Inclusion criteria** • Individuals with COPD • Both genders • Stable clinical condition • Without cardiac disease (heart failure, angina pectoris) • No history of respiratory infection at least 30 days before inclusion of study **Exclusion criteria** • Inability to walk • Inability to do 6MWD • Neuromuscular disease • Non-controlled comorbidies such as arterial hypertension and diabetes mellitus
Interventions	**Intervention characteristics** **IMT:** the experimental group will have 30 individuals that will receive home-based IMT, 7 d/week, over 4 weeks. The daily training will be split into 2 daily sessions (i.e. morning and afternoon). Each daily session will be comprised of four 4-min sets of respiratory training with 1-min rest intervals between each set. The resistance will be provided by the Power Breathe Classic, which allows individuals to exercise the inspiratory muscles during the training session. Training will be individually tailored for each participant. The initial training load for each participant will be set at 50% of his/her PImax. The participants will be trained and instructed to do the exercise program on their own with no supervision. Once a week, during the physical therapist's home visit, the clinician will determine the new values for maximal inspiratory strength, and will adjust the load to 50% of the new values. The device will be covered with opaque material, so that participants will be blinded to the training load. **Control/sham:** the control group with 30 individuals will receive a sham intervention. Sham respiratory muscle training will be delivered using a Power Breathe with no resistance (0 cmH2O) or progression, over the 4-week period, 40 min/d, 7 d/week
Outcomes	HRQoL: ADL Respiratory muscle strength (PImax) Laboratory exercise test: VO2peak
Starting date	30 October 2019
Contact information	viniciusmaldaner@gmail.com
Notes	

TCTR20210604001

Study name	Is single bout of inspiratory muscle training alter blood pressure and cardio autonomics modulation in COPD patients? : a pilot study
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	**Inclusion criteria** • GOLD stage 2-3 COPD patients, which was defined by FEV1 30%-80%pred • Free of acute exacerbation of COPD > 8 weeks before the study • BMI 18.5 kg/m2-29.9 kg/m2 **Exclusion criteria** • History of recent lung surgery, spontaneous pneumothorax or rib fracture < 12 months prior to the study • History of stroke, diabetes, cardiovascular or neuromuscular disorder • Resting blood pressure > 180/110 mmHg or < 90/60 mmHg • Fracture at upper, lower extremity or spine < 6 months prior to the study • Lower extremity and spine pain which was assessed by visual analog scale > 3 • Regular exercise which was defined as having exercise or perform physical activity • Unable to communicate and follow instructions • Resting supplemental oxygen • Age minimum: 40 years • Age maximum: 70 years • Gender: male
Interventions	**Intervention characteristics** **IMT:** participants will perform single session of IMT exercise with 60% of MIP. They will complete 6 breaths/set for 5 sets with 1-min rest between each set **Sham IMT:** participants will undergo the same program described above at no load
Outcomes	
Starting date	11 January 2021
Contact information	**Sponsorship source:** Khon Kaen University Khon Kaen, Thailand **Country:** Thailand **Author's name:** EAKARACH WONGSAYA **Institution:** School of Physical Therapy, Faculty of Associated Medical Sciences, Khon Kaen University **Email:** eakarach.wo@up.ac.th **Address:** 123 School of Physical Therapy, Faculty of Associated Medical Sciences, Khon Kaen University University 40002 Khon Kaen Thailand **Clinical trial register:** TCTR20210604001
Notes	

Tctr 2022

Study name	Effect of inspiratory muscle training on cardiovascular autonomic functions in chronic obstructive pulmonary disease patients
Methods	**Study design:** RCT **Study grouping:** parallel-group
Participants	Patients with COPD
Interventions	**IMT** Home-based IMT will be performed daily using PowerBreathe device. Total eight week of IMT will be provided. The IMT group will start training at 40% of their initial PImax. The new PImax value will be measured every week by the researcher. The training load in each week will be increased continuously over time by adjusting to at least 50% of PImax or gradually increase to the highest tolerable intensity during each of the supervised sessions. The highest tolerable intensity means that the rates of perceived inspiratory effort using a modified Borg dyspnea scale will be the range 4 to 6 of 10 (moderate to very severe). Daily training will consist of 2 sessions of 30 breaths.,The participants will receive only the standard care treatment from the physicians such as pharmacological treatment. They will meet the physician at week 1 and week 8. **Control** This group will not receive any intervention
Outcomes	Dyspnea: • mMRC • BDI-TDI Functional exercise capacity: 6MWD Respiratory muscle strength: PImax Spirometry measurements
Starting date	2022
Contact information	
Notes	

6MWD: six-minute walk distance; **ADL:** activities of daily living; **BMI:** body mass index; **CAT:** Chronic Obstructive Pulmonary Disease Assessment Test; **COPD:** chronic obstructive pulmonary disease; **CRQ:** Chronic respiratory disease questionnaire; **DBP:** diastolic blood pressure; **FEV1:** forced expiratory volume at 1 second; **FVC:** forced vital capacity; **GOLD:** Global Initiative of Chronic Obstructive Lung Disease; **HRQoL:** health-related quality of life; **IMT:** inspiratory muscle training; **MIP:** maximal inspiratory pressure; **mMRC:** Modified Medical Research Council; **PImax:** maximal inspiratory pressure; **PR:** pulmonary rehabilitation; **RCT:** randomized controlled trial; **SBP:** systolic blood pressure; **SGRQ:** St George's Respiratory Questionnaire; **SMIP:** sustained maximal inspiratory pressure; **TIRE:** test of incremental respiratory endurance

RISK OF BIAS

Legend: Low risk of bias High risk of bias Some concerns

Risk of bias for analysis 1.1 Dyspnea: Borg (at submaximal exercise: 50% to 80% of Wmax)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Charususin 2018	✓	✓	✓	✓	✓	✓
Larson 1999	~	✗	✗	✗	~	✗

Risk of bias for analysis 1.2 Dyspnea: Modified Medical Research Council (mMRC)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beaumont 2018	✓	✓	✓	✗	✓	✗
Wang 2017	✓	✓	✓	✗	~	✗

Risk of bias for analysis 1.3 Functional exercise capacity: 6-minute walk distance (6MWD) (meters)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beaumont 2015	~	✓	✓	✓	✓	~
Beaumont 2018	✓	✓	✓	✓	✓	✓
Charususin 2018	✓	✓	✓	✓	✓	✓
De Farias 2019	~	~	✓	✓	~	~
De Farias 2019	~	~	✓	✓	~	~
Dellweg 2017	✓	✓	✓	✓	✓	✓
Mador 2005	~	~	~	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Magadle 2007	~	✓	✓	✓	~	~
Paneroni 2018	✓	✓	✗	✓	✓	✗
Schultz 2018	~	✓	✓	✓	✓	~
Tounsi 2021	✓	✓	✓	✓	✓	✓
Tout 2013	✗	✓	✓	✓	✓	✗
Wang 2017	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.4 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 Short-term (<4 weeks)						
Beaumont 2015	~	✓	✓	✓	✓	~
Dellweg 2017	✓	✓	✓	✓	✓	✓
Paneroni 2018	✓	✓	✗	✓	✓	✗
Schultz 2018	~	✓	✓	✓	✓	~
Subgroup 1.4.2 Medium-term (≥4 weeks and <8 weeks)						
Beaumont 2018	✓	✓	✓	✓	✓	✓
Dellweg 2017	✓	✓	✓	✓	✓	✓
Subgroup 1.4.3 Long-term (≥8 weeks)						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Charususin 2018	✓	✓	✓	✓	✓	✓
De Farias 2019	~	~	✓	✓	~	~
De Farias 2019	~	~	✓	✓	~	~
Mador 2005	~	~	~	✓	~	~
Magadle 2007	~	✓	✓	✓	~	~
Tounsi 2021	✓	✓	✓	✓	✓	✓
Tout 2013	✗	✓	✓	✓	✓	✗
Wang 2017	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.5 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 With respiratory muscle weakness						
Charususin 2018	✓	✓	✓	✓	✓	✓
Dellweg 2017	✓	✓	✓	✓	✓	✓
Tout 2013	✗	✓	✓	✓	✓	✗
Subgroup 1.5.2 Without respiratory muscle weakness						
Beaumont 2015	~	✓	✓	✓	✓	~
Beaumont 2018	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
De Farias 2019	~	~	✓	✓	~	~
De Farias 2019	~	~	✓	✓	~	~
Mador 2005	~	~	~	✓	~	~
Magadle 2007	~	✓	✓	✓	~	~
Paneroni 2018	✓	✓	✗	✓	✓	✗
Schultz 2018	~	✓	✓	✓	✓	~
Tounsi 2021	✓	✓	✓	✓	✓	✓
Wang 2017	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.7 Functional exercise capacity: Wmax (watt)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Charususin 2018	✓	✓	✓	✓	✓	✓
Dekhuijzen 1991	~	✓	✓	✓	✗	✗
Larson 1999	~	✗	✗	✓	~	✗
Mador 2005	~	~	~	✓	~	~
Wang 2017	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.9 Health-related quality of life (HRQoL): St George's Respiratory Questionnaire (SGRQ)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.1 Symptoms						
Beaumont 2018	✓	✓	✓	✗	✓	✗
Tout 2013	✗	✓	✓	✗	~	✗
Subgroup 1.9.2 Activity						
Beaumont 2018	✓	✓	✓	✗	✓	✗
Tout 2013	✗	✓	✓	✗	~	✗
Subgroup 1.9.3 Impact						
Beaumont 2018	✓	✓	✓	✗	✓	✗
Tout 2013	✗	✓	✓	✗	~	✗
Subgroup 1.9.4 Total						
Abedi Yekta 2019	~	✓	✓	✗	✓	✗
Beaumont 2018	✓	✓	✓	✗	✓	✗
Magadle 2007	~	✓	✓	✓	~	~
Majewska-Pul-sakowska 2016	~	✓	✓	✗	~	✗
Schultz 2018	~	✓	✓	✓	✓	~
Tout 2013	✗	✓	✓	✗	~	✗
Wang 2017	✓	✓	✓	✗	~	✗

Risk of bias for analysis 1.10 Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 Dyspnea						
Charususin 2018	✓	✓	✓	✓	✓	✓
Larson 1999	~	✗	✗	~	~	✗
Mador 2005	~	✓	~	✗	~	✗
Subgroup 1.10.2 Fatigue						
Charususin 2018	✓	✓	✓	✓	✓	✓
Larson 1999	~	✗	✗	~	~	✗
Mador 2005	~	✓	~	✗	~	✗
Subgroup 1.10.3 Emotion						
Charususin 2018	✓	✓	✓	✓	✓	✓
Mador 2005	~	✓	~	✗	~	✗
Subgroup 1.10.4 Mastery						
Charususin 2018	✓	✓	✓	✓	✓	✓
Mador 2005	~	✓	~	✗	~	✗

Risk of bias for analysis 1.11 Health-related quality of life (HRQoL): COPD Assessment Test (CAT)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Schultz 2018	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wang 2017	✓	✓	✓	✗	~	✗

Risk of bias for analysis 1.12 Inspiratory muscle strength: PImax (cmH20)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beaumont 2015	~	✓	✓	✓	✓	~
Beaumont 2018	✓	✓	✓	✓	✓	✓
Berry 1996	~	✓	✓	✓	~	~
Charususin 2018	✓	✓	✓	✓	✓	✓
De Farias 2019	~	~	✓	✓	~	~
De Farias 2019	~	~	✓	✓	~	~
Dekhuijzen 1991	~	✓	✓	✓	~	~
Dellweg 2017	✓	✓	✓	✓	✓	✓
Fanfa Bordin 2020	✓	✓	✓	✓	✓	✓
Larson 1999	~	~	✗	✓	~	✗
Mador 2005	~	~	~	✓	~	~
Magadle 2007	~	✓	✓	✓	~	~
Paneroni 2018	✓	✓	✗	✓	✓	✗
Schultz 2018	~	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Tounsi 2021	✓	✓	✓	✓	✓	✓
Wang 2017	✓	✓	✓	✓	~	~
Weiner 1992	~	✓	✓	✓	~	~
Weiner 2000	✗	✓	✓	✓	~	✗

Risk of bias for analysis 1.13 Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: duration of the intervention)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.13.1 Short-term (<4 weeks)						
Beaumont 2015	~	✓	✓	✓	✓	~
Dellweg 2017	✓	✓	✓	✓	✓	✓
Paneroni 2018	✓	✓	✗	✓	✓	✗
Schultz 2018	~	✓	✓	✓	✓	✓
Subgroup 1.13.2 Medium-term (≥ 4 weeks and <8 weeks)						
Beaumont 2018	✓	✓	✓	✓	✓	✓
Dekhuijzen 1991	~	✓	✓	✓	~	~
Dellweg 2017	✓	✓	✓	✓	✓	✓
Weiner 2000	✗	✓	✓	✓	~	✗
Subgroup 1.13.3 Long-term (≥ 8 weeks)						
Berry 1996	~	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Charususin 2018	✓	✓	✓	✓	✓	✓
De Farias 2019	~	~	✓	✓	~	~
De Farias 2019	~	~	✓	✓	~	~
Dekhuijzen 1991	~	✓	✓	✓	~	~
Fanfa Bordin 2020	✓	✓	✓	✓	✓	✓
Larson 1999	~	~	✗	✓	~	✗
Mador 2005	~	~	~	✓	~	~
Magadle 2007	~	✓	✓	✓	~	~
Tounsi 2021	✓	✓	✓	✓	✓	✓
Wang 2017	✓	✓	✓	✓	~	~
Weiner 1992	~	✓	✓	✓	~	~

Risk of bias for analysis 1.14 Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: with or without respiratory muscle weakness)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.14.1 With respiratory muscle weakness						
Charususin 2018	✓	✓	✓	✓	✓	✓
Dekhuijzen 1991	~	✓	✓	✓	~	~
Dellweg 2017	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Weiner 1992						
Weiner 2000						
Subgroup 1.14.2 Without respiratory muscle weakness						
Beaumont 2015						
Beaumont 2018						
De Farias 2019						
De Farias 2019						
Fanfa Bordin 2020						
Larson 1999						
Mador 2005						
Magadle 2007						
Paneroni 2018						
Schultz 2018						
Tounsi 2021						
Wang 2017						

Risk of bias for analysis 2.1 Dyspnea: Borg (at submaximal exercise capacity)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Dacha 2019	✓	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Koppers 2006	~	✓	✓	✓	~	~
Langer 2018	✓	✓	✓	✓	✓	✓
Larson 1999	~	~	✗	✗	~	✗
Petrovic 2012	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.2 Dyspnea: Baseline and Transition Dyspnea Indexes (BDI-TDI)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.2.1 Functional impairment						
Harver 1989	~	✓	✗	✓	~	✗
Weiner 2003	~	✓	✓	✓	✗	✗
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.2.2 Magnitude of task						
Harver 1989	~	✓	✗	✓	~	✗
Weiner 2003	~	✓	✓	✓	✗	✗
Wu 2017	~	✓	✓	✗	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.2.3 Magnitude of effort						
Harver 1989	~	✓	✗	✓	~	✗
Weiner 2003	~	✓	✓	✓	✗	✗
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.2.4 Focal score						
Chuang 2017	~	✓	✗	✗	~	✗
Harver 1989	~	✓	✗	✓	~	✗
Langer 2018	✓	✓	✓	✓	✓	✓
Lisboa 1997	~	✓	✓	✓	~	~
Sanchez Riera 2001	~	✓	✓	✓	✗	✗
Scherer 2000	~	✓	✓	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.3 Dyspnea: Transition Dyspnea Index (TDI): Focal score (subgroup analysis: with or without respiratory muscle weakness)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 With respiratory muscle weakness						
Chuang 2017	~	✓	✗	✗	~	✗
Harver 1989	~	✓	✗	✓	~	✗
Sanchez Riera 2001	~	✓	✓	✓	✗	~
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.3.2 Without respiratory weakness						
Langer 2018	✓	✓	✓	✓	✓	✓
Lisboa 1997	~	✓	✓	✓	~	~
Scherer 2000	~	✓	✓	✓	~	~

Risk of bias for analysis 2.4 Dyspnea: Modified Medical Research Council (mMRC)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Langer 2018	✓	✓	✓	✓	✓	✓
Saka 2021	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✗	~	✗

Risk of bias for analysis 2.5 Functional exercise capacity: 6-minute walk distance (6MWD) (meters)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bavarsad 2015	~	~	✓	✓	~	~
Beckerman 2005	~	✗	✗	✓	~	✗
Chuang 2017	~	✓	✓	✓	~	~
Cutrim 2019	✓	✓	✓	✓	✓	✓
Hill 2006	~	✓	✓	✓	~	~
Hsiao 2003	~	✗	~	✓	~	✗
Hsiao 2003	~	✗	~	✓	~	✗
Koppers 2006	~	✓	✓	✓	~	~
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Lisboa 1997	~	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Saher 2021	~	✗	~	✓	~	✗
Saka 2021	~	✓	✓	✓	~	~
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~

Risk of bias for analysis 2.6 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.6.1 Short-term (<4 weeks)						
Saher 2021	~	✗	~	✓	~	✗
Subgroup 2.6.2 Medium-term (≥4 weeks and <8 weeks)						
Chuang 2017	~	✓	✓	✓	~	~
Koppers 2006	~	✓	✓	✓	~	~
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Lisboa 1997	~	✓	✓	✓	~	~
Subgroup 2.6.3 Long-term (≥8 weeks)						
Bavarsad 2015	~	~	✓	✓	~	~
Beckerman 2005	~	✗	✗	✓	~	~
Cutrim 2019	✓	✓	✓	✓	✓	✓
Hill 2006	~	✓	✓	✓	~	~
Hsiao 2003	~	✗	~	✓	~	✗
Hsiao 2003	~	✗	~	✓	~	✗
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Saka 2021	~	✓	✓	✓	~	~
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Xu 2018	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
ZhouL 2016	✓	~	~	✓	~	~

Risk of bias for analysis 2.7 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.7.1 With respiratory muscle weakness						
Chuang 2017	~	✓	✓	✓	~	~
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Saher 2021	~	✗	~	✓	~	✗
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~
Subgroup 2.7.2 Without respiratory muscle weakness						
Bavarsad 2015	~	~	✓	✓	~	~
Beckerman 2005	~	✗	✗	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Hsiao 2003	~	✗	~	✓	~	✗
Koppers 2006	~	✓	✓	✓	~	~
Lisboa 1997	~	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saka 2021	~	✓	✓	✓	~	~
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Xu 2018	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.9 Functional exercise capacity: Wmax (watt)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hill 2006	~	✓	✓	✓	✓	~
Koppers 2006	~	✓	✓	✓	~	~
Larson 1999	~	✗	✗	✓	~	✗
Lisboa 1997	~	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Sanchez Riera 2001	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~

Risk of bias for analysis 2.12 Health-related quality of life (HRQoL): St George Respiratory Questionnaire (SGRQ)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.12.1 Symptoms						
Berton 2015	~	~	~	✓	~	~
Saka 2021	~	✓	✓	✓	~	~
Subgroup 2.12.2 Activity						
Berton 2015	~	~	~	✓	~	~
Saka 2021	~	✓	✓	✓	~	~
Subgroup 2.12.3 Impact						
Berton 2015	~	~	~	✓	~	~
Saka 2021	~	✓	✓	✓	~	~
Subgroup 2.12.4 Total						
Abedi Yekta 2019	~	✓	~	✗	✓	✗
Beckerman 2005	~	✗	✗	✓	~	✗
Berton 2015	~	~	~	✓	~	~
Majewska-Pul-sakowska 2016	~	✓	✓	✗	~	✗
Saka 2021	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.13 Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.13.1 Dyspnea						
Bustamante 2007	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Larson 1999	~	✗	✗	~	~	✗
Nikoletou 2016	~	~	~	✓	~	~
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.13.2 Fatigue						
Bustamante 2007	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Larson 1999	~	✗	✗	~	~	✗
Nikoletou 2016	~	~	~	✓	~	~
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.13.3 Emotion						
Bustamante 2007	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Nikoletou 2016	~	~	~	✓	~	~
Wu 2017	~	✓	✓	✗	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wu 2017	~	✓	✓	✗	~	✗
Subgroup 2.13.4 Mastery						
Bustamante 2007	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Nikoletou 2016	~	~	~	✓	~	~
Wu 2017	~	✓	✓	✗	~	✗
Wu 2017	~	✓	✓	✗	~	✗

Risk of bias for analysis 2.14 Health-related quality of life (HRQoL): COPD Assessment Test (CAT)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Saka 2021	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.15 Inspiratory muscle strength: PImax (cmH_2O)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beckerman 2005	~	✗	✗	✓	~	✗
Belman 1988	~	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Berton 2015	~	✓	✓	✓	~	~
Bustamante 2007	~	✓	✓	✓	~	~
Chuang 2017	~	✓	✓	✓	~	~
Covey 2001	~	~	~	✓	~	~
Cutrim 2019	✓	✓	✓	✓	✓	✓
Dacha 2019	✓	✓	✓	✓	~	~
Harver 1989	~	✓	✗	✓	~	✗
Heijdra 1996	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~
Hsiao 2003	~	✗	~	✓	~	✗
Hsiao 2003	~	✗	~	✓	~	✗
Kim 1993	~	✓	~	✓	~	~
Koppers 2006	~	✓	✓	✓	~	~
Langer 2018	✓	✓	✓	✓	✓	✓
Larson 1988	✓	✗	~	✓	~	✗
Larson 1999	~	~	✗	✓	~	✗
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Lisboa 1997	~	✓	✓	✓	~	~
Nikoletou 2016	~	~	~	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Petrovic 2012	~	✓	✓	✓	~	~
Preusser 1994	~	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Saher 2021	~	✗	~	✓	~	✗
Saka 2021	~	✓	✓	✓	~	~
Sanchez Riera 2001	~	✓	✓	✓	~	~
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Weiner 2006	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~

Risk of bias for analysis 2.16 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: duration of the intervention)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.16.1 Short-term (<4 weeks)						
Saher 2021	~	✗	~	✓	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.16.2 Medium-term (≥4 weeks and <8 weeks)						
Belman 1988	~	✓	✓	✓	~	~
Bustamante 2007	~	✓	✓	✓	~	~
Chuang 2017	~	✓	✓	✓	~	~
Koppers 2006	~	✓	✓	✓	~	~
Larson 1988	✓	✗	~	✓	~	✗
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Nikoletou 2016	~	~	~	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Subgroup 2.16.3 Long-term (≥8 weeks)						
Beckerman 2005	~	✗	✗	✓	~	✗
Berton 2015	~	✓	✓	✓	~	~
Chuang 2017	~	✓	✓	✓	~	~
Covey 2001	~	~	~	✓	~	~
Cutrim 2019	✓	✓	✓	✓	✓	✓
Dacha 2019	✓	✓	✓	✓	~	~
Harver 1989	~	✓	✗	✓	~	✗
Heijdra 1996	~	✓	✓	✓	~	~
Hill 2006	~	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hsiao 2003	~	✗	~	✓	~	✗
Hsiao 2003	~	✗	~	✓	~	✗
Kim 1993	~	✓	~	✓	~	~
Langer 2018	✓	✓	✓	✓	✓	✓
Larson 1988	✓	✗	~	✓	~	✗
Larson 1999	~	~	✗	✓	~	✗
Lisboa 1997	~	✓	✓	✓	~	~
Petrovic 2012	~	✓	✓	✓	~	~
Preusser 1994	~	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Saka 2021	~	✓	✓	✓	~	~
Sanchez Riera 2001	~	✓	✓	✓	~	~
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Weiner 2006	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~

Risk of bias for analysis 2.17 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: with or without respiratory muscle weakness)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.17.1 With respiratory muscle weakness						
Chuang 2017	~	✓	✓	✓	~	~
Harver 1989	~	✓	✗	✓	~	✗
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Preusser 1994	~	✓	✓	✓	~	~
Saher 2021	~	✗	~	✓	~	✗
Sanchez Riera 2001	~	✓	✓	✓	~	~
Weiner 2006	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~
Subgroup 2.17.2 Without respiratory muscle weakness						
Beckerman 2005	~	✗	✗	✓	~	✗
Belman 1988	~	✓	✓	✓	~	~
Berton 2015	~	✓	✓	✓	~	~
Bustamante 2007	~	✓	✓	✓	~	~
Covey 2001	~	~	~	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Dacha 2019	+	+	+	+	~	~
Hill 2006	~	+	+	+	~	~
Hsiao 2003	~	-	~	+	~	-
Kim 1993	~	+	~	+	~	~
Koppers 2006	~	+	+	+	~	~
Langer 2018	+	+	+	+	+	+
Larson 1999	~	~	-	+	~	-
Lisboa 1997	~	+	+	+	~	~
Nikoletou 2016	~	~	~	+	~	~
Petrovic 2012	~	+	+	+	~	~
Ramirez Sarmiento 2002	~	-	+	+	~	-
Saka 2021	~	+	+	+	~	~
Scherer 2000	~	+	~	+	~	~
Xu 2018	+	+	+	+	+	+

Risk of bias for analysis 2.18 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: method of measurement)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.18.1 Residual Volume (RV)						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beckerman 2005	~	✗	✗	✓	~	✗
Covey 2001	~	~	~	✓	~	~
Cutrim 2019	✓	✓	✓	✓	✓	✓
Heijdra 1996	~	✓	✓	✓	~	~
Hsiao 2003	~	✗	~	✓	~	✗
Hsiao 2003	~	✗	~	✓	~	✗
Kim 1993	~	✓	~	✓	~	~
Koppers 2006	~	✓	✓	✓	~	~
Larson 1988	✓	✗	~	✓	~	✗
Larson 1999	~	~	✗	✓	~	✗
Leelarungrayub 2017	~	✓	✗	✓	~	✗
Saher 2021	~	✗	~	✓	~	✗
Scherer 2000	~	✓	~	✓	~	~
Weiner 2003	~	✓	✓	✓	✗	✗
Weiner 2006	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Wu 2017	~	✓	✓	✓	~	~
Subgroup 2.18.2 Functional Residual Capacity (FRC)						
Belman 1988	~	✓	✓	✓	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Harver 1989	~	✓	✗	✓	~	✗
Hill 2006	~	✓	✓	✓	~	~
Langer 2018	✓	✓	✓	✓	✓	✓
Lisboa 1997	~	✓	✓	✓	~	~
Nikoletou 2016	~	~	~	✓	~	~
Petrovic 2012	~	✓	✓	✓	~	~
Preusser 1994	~	✓	✓	✓	~	~
Sanchez Riera 2001	~	✓	✓	✓	~	~
Subgroup 2.18.3 Not reported						
Berton 2015	~	✓	✓	✓	~	~
Bustamante 2007	~	✓	✓	✓	~	~
Chuang 2017	~	✓	✓	✓	~	~
Dacha 2019	✓	✓	✓	✓	~	~
Ramirez Sarmiento 2002	~	✗	✓	✓	~	✗
Saka 2021	~	✓	✓	✓	~	~
Xu 2018	✓	✓	✓	✓	✓	✓
ZhouL 2016	✓	~	~	✓	~	~

DATA AND ANALYSES

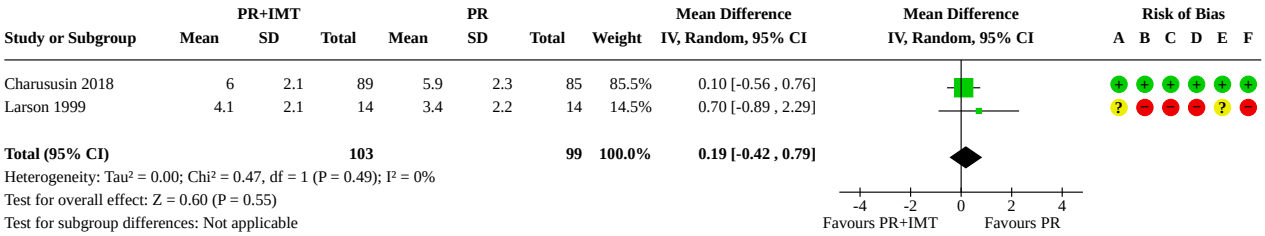
Comparison 1. PR+IMT vs PR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Dyspnea: Borg (at submaximal exercise: 50% to 80% of Wmax)	2	202	Mean Difference (IV, Random, 95% CI)	0.19 [-0.42, 0.79]
1.2 Dyspnea: Modified Medical Research Council (mMRC)	2	204	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.39, 0.14]
1.3 Functional exercise capacity: 6-minute walk distance (6MWD) (meters)	12	1199	Mean Difference (IV, Random, 95% CI)	5.95 [-5.73, 17.63]
1.4 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Short-term (<4 weeks)	4	687	Mean Difference (IV, Random, 95% CI)	10.25 [-24.98, 45.49]
1.4.2 Medium-term (≥4 weeks and <8 weeks)	2	178	Mean Difference (IV, Random, 95% CI)	36.72 [-67.67, 141.11]
1.4.3 Long-term (≥8 weeks)	7	363	Mean Difference (IV, Random, 95% CI)	7.82 [-6.90, 22.54]
1.5 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 With respiratory muscle weakness	3	219	Mean Difference (IV, Random, 95% CI)	31.17 [-10.50, 72.84]
1.5.2 Without respiratory muscle weakness	9	981	Mean Difference (IV, Random, 95% CI)	0.38 [-11.65, 12.42]
1.6 Functional exercise capacity: 12-minute walk distance (12MWD) (meters)	3	80	Mean Difference (IV, Random, 95% CI)	155.77 [-84.53, 396.08]
1.7 Functional exercise capacity: Wmax (watt)	5	326	Mean Difference (IV, Random, 95% CI)	-1.01 [-6.96, 4.94]
1.8 Functional exercise capacity: exercise time (seconds)	3	192	Mean Difference (IV, Random, 95% CI)	58.62 [-25.09, 142.32]
1.9 Health-related quality of life (HRQoL): St George's Respiratory Questionnaire (SGRQ)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 Symptoms	2	169	Mean Difference (IV, Random, 95% CI)	-2.33 [-6.28, 1.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.2 Activity	2	169	Mean Difference (IV, Random, 95% CI)	0.28 [-1.65, 2.20]
1.9.3 Impact	2	169	Mean Difference (IV, Random, 95% CI)	-1.63 [-5.38, 2.11]
1.9.4 Total	7	908	Mean Difference (IV, Random, 95% CI)	0.13 [-0.93, 1.20]
1.10 Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.10.1 Dyspnea	3		Mean Difference (IV, Random, 95% CI)	-0.30 [-1.90, 1.29]
1.10.2 Fatigue	3		Mean Difference (IV, Random, 95% CI)	0.28 [-0.76, 1.31]
1.10.3 Emotion	2		Mean Difference (IV, Random, 95% CI)	-0.63 [-2.53, 1.26]
1.10.4 Mastery	2		Mean Difference (IV, Random, 95% CI)	-0.05 [-1.18, 1.08]
1.11 Health-related quality of life (HRQoL): COPD Assessment Test (CAT)	2	657	Mean Difference (IV, Random, 95% CI)	0.13 [-0.80, 1.06]
1.12 Inspiratory muscle strength: PImax (cmH20)	17	1329	Mean Difference (IV, Random, 95% CI)	11.46 [7.42, 15.50]
1.13 Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: duration of the intervention)	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 Short-term (<4 weeks)	4	687	Mean Difference (IV, Random, 95% CI)	12.63 [4.14, 21.11]
1.13.2 Medium-term (≥ 4 weeks and <8 weeks)	4	233	Mean Difference (IV, Random, 95% CI)	12.27 [3.75, 20.79]
1.13.3 Long-term (≥ 8 weeks)	11	478	Mean Difference (IV, Random, 95% CI)	11.52 [5.50, 17.53]
1.14 Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: with or without respiratory muscle weakness)	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 With respiratory muscle weakness	5	282	Mean Difference (IV, Random, 95% CI)	14.84 [11.35, 18.34]
1.14.2 Without respiratory muscle weakness	11	1031	Mean Difference (IV, Random, 95% CI)	10.57 [5.23, 15.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.15 Laboratory exercise test: VO2peak (L/min)	5	313	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.05, 0.03]
1.16 Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)	2	52	Std. Mean Difference (IV, Random, 95% CI)	1.22 [-0.18, 2.62]
1.17 Respiratory muscle endurance time: Tlim (seconds) (sustained ventilation according to PImax)	3	236	Mean Difference (IV, Random, 95% CI)	84.63 [-50.77, 220.02]
1.18 Respiratory muscle endurance time: Tlim (seconds) (sustained ventilation according to MVV)	2	51	Mean Difference (IV, Random, 95% CI)	477.69 [215.43, 739.94]
1.19 Maximal voluntary ventilation (MVV)	3	93	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.02, 0.83]
1.20 Respiratory function: forced expiratory volume at 1 second (FEV1) (%Pred)	6	173	Mean Difference (IV, Random, 95% CI)	0.77 [-1.72, 3.26]
1.21 Respiratory function: forced expiratory volume at 1 second (FEV1) (Liters)	6	889	Mean Difference (IV, Random, 95% CI)	0.04 [-0.04, 0.13]

Analysis 1.1. Comparison 1: PR+IMT vs PR, Outcome 1: Dyspnea: Borg (at submaximal exercise: 50% to 80% of Wmax)

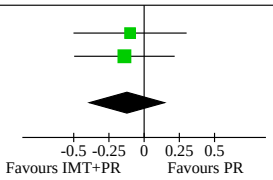


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: PR+IMT vs PR, Outcome 2: Dyspnea: Modified Medical Research Council (mMRC)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Beaumont 2018	-0.9	1.2	74	-0.8	1.3	75	44.1%	-0.10 [-0.50 , 0.30]
Wang 2017	-0.47	0.68	28	-0.33	0.67	27	55.9%	-0.14 [-0.50 , 0.22]
Total (95% CI)			**102**			**102**	**100.0%**	**-0.12 [-0.39 , 0.14]**

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

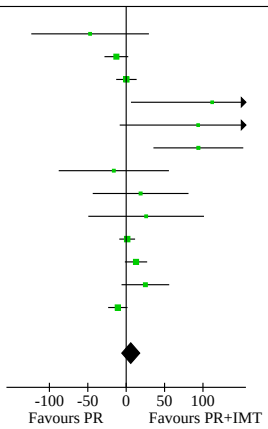


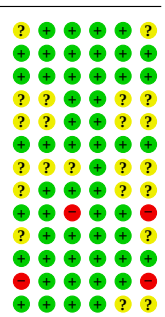
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: PR+IMT vs PR, Outcome 3: Functional exercise capacity: 6-minute walk distance (6MWD) (meters)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Beaumont 2015	437.3	123.6	16	484.3	101.5	18	2.1%	-47.00 [-123.59 , 29.59]
Beaumont 2018	23.4	51.2	74	36.2	44.9	75	14.3%	-12.80 [-28.27 , 2.67]
Charususin 2018 (1)	407.3	44.0886	87	407	44.0886	82	15.3%	0.30 [-13.00 , 13.60]
De Farias 2019 (2)	484	110.5	12	372	97.3	5	1.1%	112.00 [6.25 , 217.75]
De Farias 2019 (3)	465.7	86	9	372	97.3	5	1.2%	93.70 [-8.43 , 195.83]
Dellweg 2017	290	75	15	196	85	14	3.3%	94.00 [35.49 , 152.51]
Mador 2005	427.6	110.76	15	443.7	85.53	14	2.3%	-16.10 [-87.86 , 55.66]
Magadle 2007	359	84.18	14	340.2	81.12	13	3.0%	18.80 [-43.56 , 81.16]
Paneroni 2018	504	65.1	12	478	106	10	2.1%	26.00 [-49.32 , 101.32]
Schultz 2018	85.3	62.8	300	83.99	65.74	302	16.7%	1.31 [-8.96 , 11.58]
Tounsi 2021	42.6	25.4	16	29.8	15.2	16	14.8%	12.80 [-1.70 , 27.30]
Tout 2013	413.5	5.61	10	388.5	49.78	10	8.1%	25.00 [-6.05 , 56.05]
Wang 2017	21.68	23.86	28	32.55	23.85	27	15.6%	-10.87 [-23.48 , 1.74]
Total (95% CI)			**608**			**591**	**100.0%**	**5.95 [-5.73 , 17.63]**

Heterogeneity: Tau² = 185.65; Chi² = 30.87, df = 12 (P = 0.002); I² = 61%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



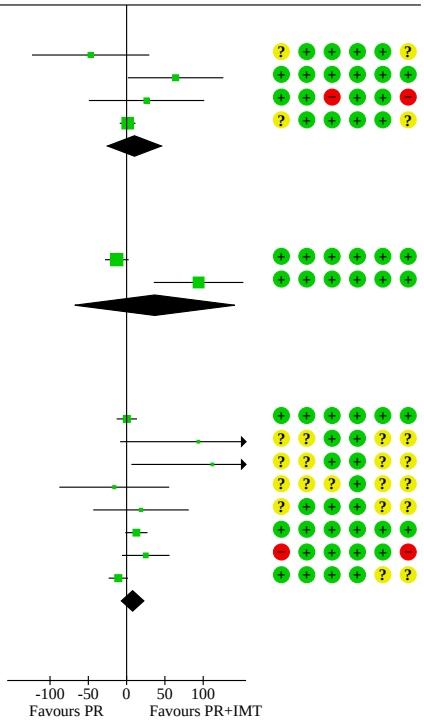


Footnotes
(1) Data from adjusted analysis
(2) Threshold device
(3) Normocapnic hyperpnea device

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: PR+IMT vs PR, Outcome 4: Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Short-term (<4 weeks)								
Beaumont 2015	437.3	123.6	16	484.3	101.5	18	15.0%	-47.00 [-123.59 , 29.59]
Dellweg 2017	237	84	15	173	87	14	19.8%	64.00 [1.68 , 126.32]
Paneroni 2018	504	65.1	12	478	106	10	15.4%	26.00 [-49.32 , 101.32]
Schultz 2018	85.3	62.8	300	83.99	65.74	302	49.8%	1.31 [-8.96 , 11.58]
Subtotal (95% CI)			**343**			**344**	**100.0%**	**10.25 [-24.98 , 45.49]**
Heterogeneity: Tau² = 621.99; Chi² = 5.77, df = 3 (P = 0.12); I² = 48%								
Test for overall effect: Z = 0.57 (P = 0.57)								
1.4.2 Medium-term (≥4 weeks and <8 weeks)								
Beaumont 2018	23.4	51.2	74	36.2	44.9	75	53.6%	-12.80 [-28.27 , 2.67]
Dellweg 2017	290	75	15	196	85	14	46.4%	94.00 [35.49 , 152.51]
Subtotal (95% CI)			**89**			**89**	**100.0%**	**36.72 [-67.67 , 141.11]**
Heterogeneity: Tau² = 5226.43; Chi² = 11.96, df = 1 (P = 0.0005); I² = 92%								
Test for overall effect: Z = 0.69 (P = 0.49)								
1.4.3 Long-term (≥8 weeks)								
Charususin 2018 (1)	407.3	44.0886	87	407	44.0886	82	25.0%	0.30 [-13.00 , 13.60]
De Farias 2019 (2)	465.7	86	9	372	97.3	5	1.9%	93.70 [-8.43 , 195.83]
De Farias 2019 (3)	484	110.5	12	372	97.3	5	1.8%	112.00 [6.25 , 217.75]
Mador 2005	427.6	110.76	15	443.7	85.53	14	3.7%	-16.10 [-87.86 , 55.66]
Magadle 2007	359	84.18	14	340.2	81.12	13	4.7%	18.80 [-43.56 , 81.16]
Tounsi 2021	42.6	25.4	16	29.8	15.2	16	24.1%	12.80 [-1.70 , 27.30]
Tout 2013	413.5	5.61	10	388.5	49.78	10	13.1%	25.00 [-6.05 , 56.05]
Wang 2017	21.68	23.86	28	32.55	23.85	27	25.6%	-10.87 [-23.48 , 1.74]
Subtotal (95% CI)			**191**			**172**	**100.0%**	**7.82 [-6.90 , 22.54]**
Heterogeneity: Tau² = 179.22; Chi² = 16.07, df = 7 (P = 0.02); I² = 56%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Test for subgroup differences: Chi² = 0.30, df = 2 (P = 0.86), I² = 0%								



Footnotes

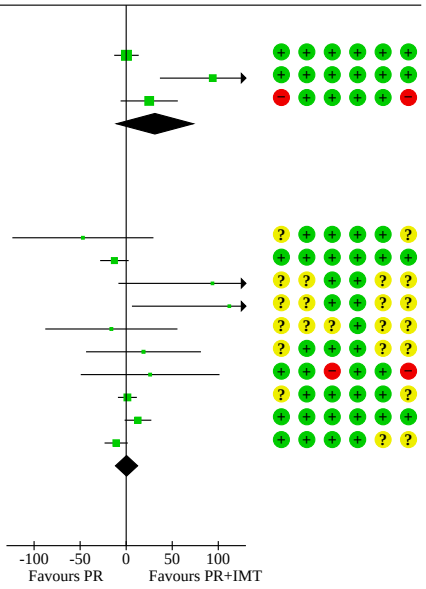
(1) Data from adjusted analysis
(2) Normocapnic hyperpnea
(3) Threshold device

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: PR+IMT vs PR, Outcome 5: Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 With respiratory muscle weakness								
Charususin 2018 (1)	407.3	44.0886	87	407	44.0886	82	41.4%	0.30 [-13.00 , 13.60]
Dellweg 2017	290	75	15	196	85	15	23.8%	94.00 [36.63 , 151.37]
Tout 2013	413.5	5.61	10	388.5	49.78	10	34.9%	25.00 [-6.05 , 56.05]
Subtotal (95% CI)			**112**			**107**	**100.0%**	**31.17 [-10.50 , 72.84]**
Heterogeneity: Tau² = 1045.88; Chi² = 11.07, df = 2 (P = 0.004); I² = 82%								
Test for overall effect: Z = 1.47 (P = 0.14)								
1.5.2 Without respiratory muscle weakness								
Beaumont 2015	437.3	123.6	16	484.3	101.5	18	2.3%	-47.00 [-123.59 , 29.59]
Beaumont 2018	23.4	51.2	74	36.2	44.9	75	19.8%	-12.80 [-28.27 , 2.67]
De Farias 2019 (2)	465.7	86	9	372	97.3	5	1.3%	93.70 [-8.43 , 195.83]
De Farias 2019 (3)	484	110.5	12	372	97.3	5	1.2%	112.00 [6.25 , 217.75]
Mador 2005	427.6	110.76	15	443.7	85.53	14	2.6%	-16.10 [-87.86 , 55.66]
Magadle 2007	359	84.18	14	340.2	81.12	13	3.3%	18.80 [-43.56 , 81.16]
Paneroni 2018	504	65.1	12	478	106	10	2.3%	26.00 [-49.32 , 101.32]
Schultz 2018	85.3	62.8	300	83.99	65.74	302	24.2%	1.31 [-8.96 , 11.58]
Tounsi 2021	42.6	25.4	16	29.8	15.2	16	20.6%	12.80 [-1.70 , 27.30]
Wang 2017	21.68	23.86	28	32.55	23.85	27	22.3%	-10.87 [-23.48 , 1.74]
Subtotal (95% CI)			**496**			**485**	**100.0%**	**0.38 [-11.65 , 12.42]**
Heterogeneity: Tau² = 128.00; Chi² = 18.38, df = 9 (P = 0.03); I² = 51%								
Test for overall effect: Z = 0.06 (P = 0.95)								
Test for subgroup differences: Chi² = 1.94, df = 1 (P = 0.16), I² = 48.3%								

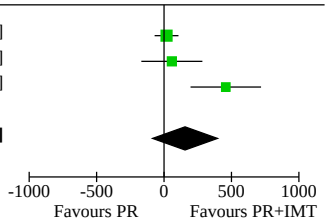


Footnotes
(1) Data from adjusted analysis
(2) Normocapnic hyperpnea device
(3) Threshold device

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: PR+IMT vs PR, Outcome 6: Functional exercise capacity: 12-minute walk distance (12MWD) (meters)

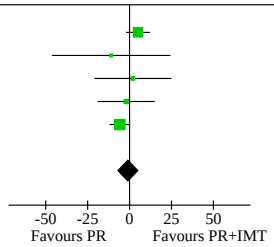
Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Berry 1996	984.5	86.7	7	965.9	93	9	40.5%	18.60 [-69.81 , 107.01]
Dekhuijzen 1991	1309	376	20	1251	354	20	31.1%	58.00 [-168.33 , 284.33]
Weiner 1992	1170	353.3	12	712	297.9	12	28.4%	458.00 [196.53 , 719.47]
Total (95% CI)			**39**			**41**	**100.0%**	**155.77 [-84.53 , 396.08]**
Heterogeneity: Tau² = 35071.69; Chi² = 9.74, df = 2 (P = 0.008); I² = 79%								
Test for overall effect: Z = 1.27 (P = 0.20)								
Test for subgroup differences: Not applicable								

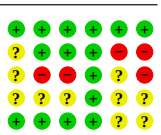


Analysis 1.7. Comparison 1: PR+IMT vs PR, Outcome 7: Functional exercise capacity: Wmax (watt)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Charususin 2018	64	26	89	59	22	85	37.3%	5.00 [-2.15 , 12.15]
Dekhuijzen 1991	116	59	20	127	55	20	2.7%	-11.00 [-46.35 , 24.35]
Larson 1999	77	32	14	75	30	14	6.2%	2.00 [-20.98 , 24.98]
Mador 2005	65	27.11	15	67	19.36	14	10.6%	-2.00 [-19.06 , 15.06]
Wang 2017	6.1	11.7	28	11.86	11.7	27	43.2%	-5.76 [-11.95 , 0.43]
Total (95% CI)			**166**			**160**	**100.0%**	**-1.01 [-6.96 , 4.94]**

Heterogeneity: Tau² = 11.42; Chi² = 5.36, df = 4 (P = 0.25); I² = 25%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



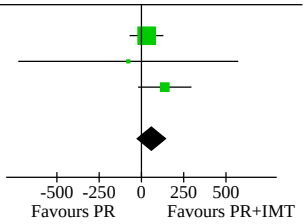


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: PR+IMT vs PR, Outcome 8: Functional exercise capacity: exercise time (seconds)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Charususin 2018 (1)	496	309	72	466	292	67	70.2%	30.00 [-69.91 , 129.91]
Mador 2005 (2)	1470	975.6	15	1548	808.2	14	1.7%	-78.00 [-728.37 , 572.37]
Weiner 1992 (3)	720	207.2	12	582	186.6	12	28.2%	138.00 [-19.77 , 295.77]
Total (95% CI)			**99**			**93**	**100.0%**	**58.62 [-25.09 , 142.32]**

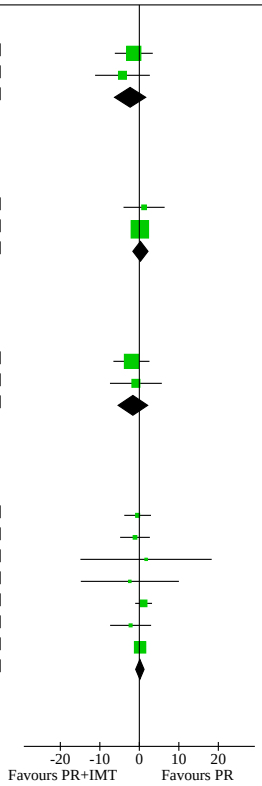
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Footnotes
(1) Cycling at 80% of Wmax (data from adjusted analysis)
(2) Cycling at 60 to 70% of Wmax
(3) Cycling at 40% of Wmax

Analysis 1.9. Comparison 1: PR+IMT vs PR, Outcome 9: Health-related quality of life (HRQoL): St George's Respiratory Questionnaire (SGRQ)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
1.9.1 Symptoms									
Beaumont 2018	-4.8	15.1	74	-3.4	14.8	75	67.6%	-1.40 [-6.20 , 3.40]	+ + + − + −
Tout 2013	31.23	7.93	10	35.5	7.88	10	32.4%	-4.27 [-11.20 , 2.66]	− + + − ? −
Subtotal (95% CI)			**84**			**85**	**100.0%**	**-2.33 [-6.28 , 1.62]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%									
Test for overall effect: Z = 1.16 (P = 0.25)									
1.9.2 Activity									
Beaumont 2018	-9.1	14.7	74	-10.3	17.6	75	13.7%	1.20 [-4.00 , 6.40]	+ + + − + −
Tout 2013	17.11	2.45	10	16.98	2.27	10	86.3%	0.13 [-1.94 , 2.20]	− + + − ? −
Subtotal (95% CI)			**84**			**85**	**100.0%**	**0.28 [-1.65 , 2.20]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%									
Test for overall effect: Z = 0.28 (P = 0.78)									
1.9.3 Impact									
Beaumont 2018	-12.1	13.7	74	-10.1	14.7	75	67.4%	-2.00 [-6.56 , 2.56]	+ + + − + −
Tout 2013	31.23	8.16	10	32.1	6.75	10	32.6%	-0.87 [-7.43 , 5.69]	− + + − ? −
Subtotal (95% CI)			**84**			**85**	**100.0%**	**-1.63 [-5.38 , 2.11]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%									
Test for overall effect: Z = 0.85 (P = 0.39)									
1.9.4 Total									
Abedi Yekta 2019	-5.5	3.54	15	-5.07	5.48	14	9.9%	-0.43 [-3.81 , 2.95]	? + + − + −
Beaumont 2018	-10.1	10.9	74	-9	12.5	75	8.0%	-1.10 [-4.86 , 2.66]	+ + + − + −
Magadle 2007	55.5	24	16	53.8	23.2	15	0.4%	1.70 [-14.92 , 18.32]	? + + + ? ?
Majewska-Pulsakowska 2016	48.2	17.1	13	50.6	12.6	9	0.7%	-2.40 [-14.82 , 10.02]	? + + − ? −
Schultz 2018	-9.42	13.44	300	-10.5	13.22	302	25.0%	1.08 [-1.05 , 3.21]	? + + + + ?
Tout 2013	25.92	6.12	10	28.13	5.71	10	4.2%	-2.21 [-7.40 , 2.98]	− + + − ? −
Wang 2017	-3.32	2.8	28	-3.51	2.8	27	51.7%	0.19 [-1.29 , 1.67]	+ + + − ? −
Subtotal (95% CI)			**456**			**452**	**100.0%**	**0.13 [-0.93 , 1.20]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 6 (P = 0.89); I² = 0%									
Test for overall effect: Z = 0.25 (P = 0.81)									
Test for subgroup differences: Chi² = 2.19, df = 3 (P = 0.53), I² = 0%									

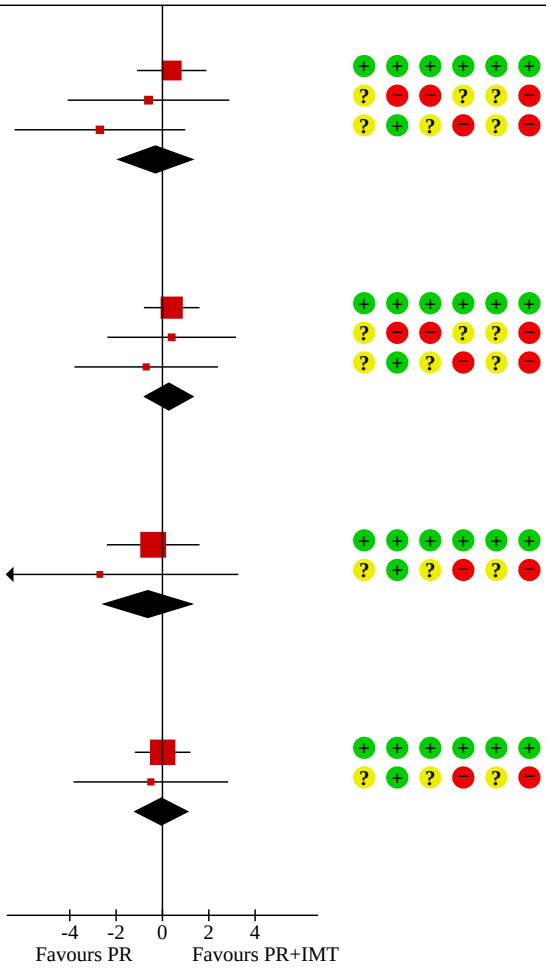


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: PR+IMT vs PR, Outcome 10: Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Dyspnea				
Charususin 2018	0.4	0.7653	64.9%	0.40 [-1.10 , 1.90]
Larson 1999	-0.6	1.78	18.4%	-0.60 [-4.09 , 2.89]
Mador 2005	-2.7	1.8788	16.7%	-2.70 [-6.38 , 0.98]
Subtotal (95% CI)			**100.0%**	**-0.30 [-1.90 , 1.29]**
Heterogeneity: Tau² = 0.44; Chi² = 2.42, df = 2 (P = 0.30); I² = 17%				
Test for overall effect: Z = 0.37 (P = 0.71)				
1.10.2 Fatigue				
Charususin 2018	0.4	0.6123	74.8%	0.40 [-0.80 , 1.60]
Larson 1999	0.4	1.4165	14.0%	0.40 [-2.38 , 3.18]
Mador 2005	-0.7	1.5811	11.2%	-0.70 [-3.80 , 2.40]
Subtotal (95% CI)			**100.0%**	**0.28 [-0.76 , 1.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%				
Test for overall effect: Z = 0.52 (P = 0.60)				
1.10.3 Emotion				
Charususin 2018	-0.4	1.0204	89.9%	-0.40 [-2.40 , 1.60]
Mador 2005	-2.7	3.048	10.1%	-2.70 [-8.67 , 3.27]
Subtotal (95% CI)			**100.0%**	**-0.63 [-2.53 , 1.26]**
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%				
Test for overall effect: Z = 0.65 (P = 0.51)				
1.10.4 Mastery				
Charususin 2018	0.01	0.6123	88.6%	0.01 [-1.19 , 1.21]
Mador 2005	-0.5	1.7029	11.4%	-0.50 [-3.84 , 2.84]
Subtotal (95% CI)			**100.0%**	**-0.05 [-1.18 , 1.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%				
Test for overall effect: Z = 0.08 (P = 0.93)				
Test for subgroup differences: Chi² = 0.83, df = 3 (P = 0.84), I² = 0%				



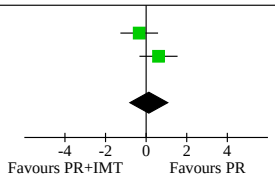
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: PR+IMT vs PR, Outcome 11: Health-related quality of life (HRQoL): COPD Assessment Test (CAT)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Schultz 2018	-3.76	5.76	300	-3.42	5.85	302	50.3%	-0.34 [-1.27 , 0.59]	? + + + + ?
Wang 2017	-2.39	1.79	28	-3	1.76	27	49.7%	0.61 [-0.33 , 1.55]	+ + + - ? -
Total (95% CI)			**328**			**329**	**100.0%**	**0.13 [-0.80 , 1.06]**	

Heterogeneity: Tau² = 0.22; Chi² = 1.99, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

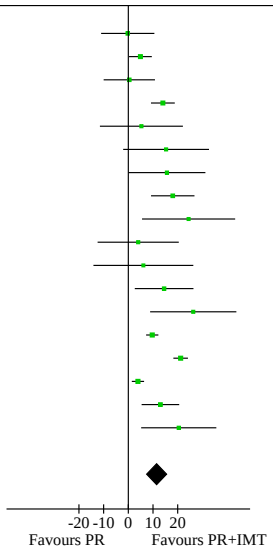


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: PR+IMT vs PR, Outcome 12: Inspiratory muscle strength: PImax (cmH20)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Beaumont 2015	85.38	15.75	16	85.61	16.3	18	5.5%	-0.23 [-11.01 , 10.55]	? + + + + ?
Beaumont 2018	14.8	14.9	74	9.9	13.8	75	8.2%	4.90 [0.29 , 9.51]	+ + + + + +
Berry 1996	79	10.3	7	78.6	10.8	9	5.7%	0.40 [-9.99 , 10.79]	? + + + ? ?
Charususin 2018	75	19	89	61	13	85	8.1%	14.00 [9.18 , 18.82]	+ + + + + +
De Farias 2019 (1)	90	18.5	12	84.7	15	5	3.5%	5.30 [-11.51 , 22.11]	? ? + + ? ?
De Farias 2019 (2)	100	17.4	9	84.7	15	5	3.4%	15.30 [-2.08 , 32.68]	? ? + + ? ?
Dekhuijzen 1991	81.2	27.53	20	65.56	22.5	20	3.9%	15.64 [0.06 , 31.22]	? + + + ? ?
Dellweg 2017	55	11	15	37	13	14	6.4%	18.00 [9.20 , 26.80]	+ + + + + +
Fanfa Bordin 2020	95.12	20.5	12	70.7	24	10	3.1%	24.42 [5.56 , 43.28]	+ + + + + +
Larson 1999	90	16	14	86	27	14	3.6%	4.00 [-12.44 , 20.44]	? ? - + ? -
Mador 2005	76.3	32.53	15	70.2	22.44	14	2.8%	6.10 [-14.13 , 26.33]	? ? ? + ? ?
Magadle 2007	81.2	16	14	66.7	15.5	13	5.1%	14.50 [2.62 , 26.38]	? + + + ? ?
Paneroni 2018	107.6	22.9	12	81.3	18.9	10	3.4%	26.30 [8.83 , 43.77]	+ + - + + -
Schultz 2018	18.66	16.11	300	8.97	14.89	302	8.8%	9.69 [7.21 , 12.17]	? + + + + +
Tounsi 2021	22.9	5.8	16	1.7	1.6	16	8.7%	21.20 [18.25 , 24.15]	+ + + + + +
Wang 2017	5.2	4.7	28	1.3	4.7	27	8.8%	3.90 [1.42 , 6.38]	+ + + + ? ?
Weiner 1992	57.8	10	12	44.8	9	12	6.9%	13.00 [5.39 , 20.61]	? + + + ? ?
Weiner 2000	77.5	17.5	11	57.07	11.4	4	4.0%	20.43 [5.21 , 35.65]	- + + + ? -
Total (95% CI)			**676**			**653**	**100.0%**	**11.46 [7.42 , 15.50]**	

Heterogeneity: Tau² = 46.42; Chi² = 105.61, df = 17 (P < 0.00001); I² = 84%
Test for overall effect: Z = 5.56 (P < 0.00001)
Test for subgroup differences: Not applicable

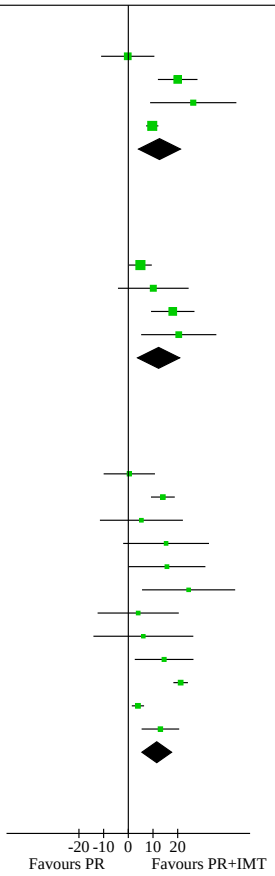


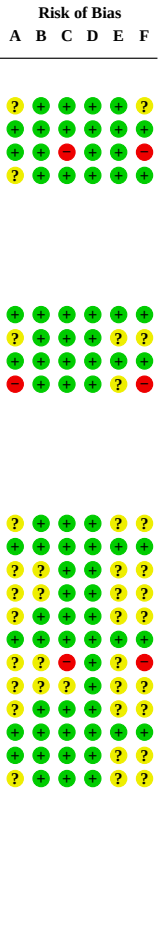
Footnotes
(1) Threshold device
(2) Normocapnic hyperpnea

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.13. Comparison 1: PR+IMT vs PR, Outcome 13: Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: duration of the intervention)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 Short-term (<4 weeks)								
Beaumont 2015	85.38	15.75	16	85.61	16.3	18	22.9%	-0.23 [-11.01 , 10.55]
Dellweg 2017	52	11	15	32	11	14	27.5%	20.00 [11.99 , 28.01]
Paneroni 2018	107.6	22.9	12	81.3	18.9	10	14.3%	26.30 [8.83 , 43.77]
Schultz 2018	18.66	16.11	300	8.97	14.89	302	35.3%	9.69 [7.21 , 12.17]
Subtotal (95% CI)			**343**			**344**	**100.0%**	**12.63 [4.14 , 21.11]**
Heterogeneity: Tau² = 51.54; Chi² = 12.75, df = 3 (P = 0.005); I² = 76%								
Test for overall effect: Z = 2.92 (P = 0.004)								
1.13.2 Medium-term (≥ 4 weeks and <8 weeks)								
Beaumont 2018	14.8	14.9	74	9.9	13.8	75	35.7%	4.90 [0.29 , 9.51]
Dekhuijzen 1991	71.3	25.5	20	61.18	20.4	20	18.8%	10.12 [-4.19 , 24.43]
Dellweg 2017	55	11	15	37	13	14	28.0%	18.00 [9.20 , 26.80]
Weiner 2000	77.5	17.5	11	57.07	11.4	4	17.5%	20.43 [5.21 , 35.65]
Subtotal (95% CI)			**120**			**113**	**100.0%**	**12.27 [3.75 , 20.79]**
Heterogeneity: Tau² = 47.44; Chi² = 9.22, df = 3 (P = 0.03); I² = 67%								
Test for overall effect: Z = 2.82 (P = 0.005)								
1.13.3 Long-term (≥ 8 weeks)								
Berry 1996	79	10.3	7	78.6	10.8	9	9.1%	0.40 [-9.99 , 10.79]
Charususin 2018	75	19	89	61	13	85	11.5%	14.00 [9.18 , 18.82]
De Farias 2019 (1)	90	18.5	12	84.7	15	5	6.3%	5.30 [-11.51 , 22.11]
De Farias 2019 (2)	100	17.4	9	84.7	15	5	6.1%	15.30 [-2.08 , 32.68]
Dekhuijzen 1991	81.2	27.53	20	65.56	22.5	20	6.8%	15.64 [0.06 , 31.22]
Fanfa Bordin 2020	95.12	20.5	12	70.7	24	10	5.6%	24.42 [5.56 , 43.28]
Larson 1999	90	16	14	86	27	14	6.4%	4.00 [-12.44 , 20.44]
Mador 2005	76.3	32.53	15	70.2	22.44	14	5.2%	6.10 [-14.13 , 26.33]
Magadle 2007	81.2	16	14	66.7	15.5	13	8.4%	14.50 [2.62 , 26.38]
Tounsi 2021	22.9	5.8	16	1.7	1.6	16	12.1%	21.20 [18.25 , 24.15]
Wang 2017	5.2	4.7	28	1.3	4.7	27	12.2%	3.90 [1.42 , 6.38]
Weiner 1992	57.8	10	12	44.8	9	12	10.4%	13.00 [5.39 , 20.61]
Subtotal (95% CI)			**248**			**230**	**100.0%**	**11.52 [5.50 , 17.53]**
Heterogeneity: Tau² = 75.76; Chi² = 87.15, df = 11 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 3.75 (P = 0.0002)								
Test for subgroup differences: Chi² = 0.05, df = 2 (P = 0.98), I² = 0%								





Footnotes

(1) Threshold device

(2) Normocapnic hyperpnea

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviations from intended interventions

(C) Bias due to missing outcome data

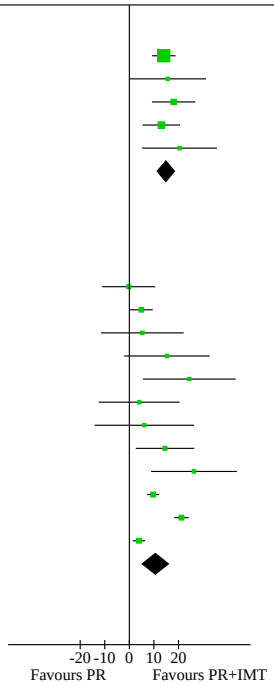
(D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

Analysis 1.14. Comparison 1: PR+IMT vs PR, Outcome 14: Inspiratory muscle strength: PImax (cmH2O) (subgroup analysis: with or without respiratory muscle weakness)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
1.14.1 With respiratory muscle weakness								
Charususin 2018	75	19	89	61	13	85	52.7%	14.00 [9.18 , 18.82]
Dekhuijzen 1991	81.2	27.53	20	65.56	22.5	20	5.0%	15.64 [0.06 , 31.22]
Dellweg 2017	55	11	15	37	13	14	15.8%	18.00 [9.20 , 26.80]
Weiner 1992	57.8	10	12	44.8	9	12	21.1%	13.00 [5.39 , 20.61]
Weiner 2000	77.5	17.5	11	57.07	11.4	4	5.3%	20.43 [5.21 , 35.65]
Subtotal (95% CI)			**147**			**135**	**100.0%**	**14.84 [11.35 , 18.34]**
Heterogeneity: Tau² = 0.00; Chi² = 1.37, df = 4 (P = 0.85); I² = 0%								
Test for overall effect: Z = 8.32 (P < 0.00001)								
1.14.2 Without respiratory muscle weakness								
Beaumont 2015	85.38	15.75	16	85.61	16.3	18	8.7%	-0.23 [-11.01 , 10.55]
Beaumont 2018	14.8	14.9	74	9.9	13.8	75	12.2%	4.90 [0.29 , 9.51]
De Farias 2019 (1)	90	18.5	12	84.7	15	5	5.8%	5.30 [-11.51 , 22.11]
De Farias 2019 (2)	100	17.4	9	84.7	15	5	5.5%	15.30 [-2.08 , 32.68]
Fanfa Bordin 2020	95.12	20.5	12	70.7	24	10	5.0%	24.42 [5.56 , 43.28]
Larson 1999	90	16	14	86	27	14	5.9%	4.00 [-12.44 , 20.44]
Mador 2005	76.3	32.53	15	70.2	22.44	14	4.6%	6.10 [-14.13 , 26.33]
Magadle 2007	81.2	16	14	66.7	15.5	13	8.0%	14.50 [2.62 , 26.38]
Paneroni 2018	107.6	22.9	12	81.3	18.9	10	5.5%	26.30 [8.83 , 43.77]
Schultz 2018	18.66	16.11	300	8.97	14.89	302	13.0%	9.69 [7.21 , 12.17]
Tounsi 2021	22.9	5.8	16	1.7	1.6	16	12.9%	21.20 [18.25 , 24.15]
Wang 2017	5.2	4.7	28	1.3	4.7	27	13.0%	3.90 [1.42 , 6.38]
Subtotal (95% CI)			**522**			**509**	**100.0%**	**10.57 [5.23 , 15.91]**
Heterogeneity: Tau² = 55.50; Chi² = 94.26, df = 11 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 3.88 (P = 0.0001)								
Test for subgroup differences: Chi² = 1.72, df = 1 (P = 0.19), I² = 41.8%								



Footnotes

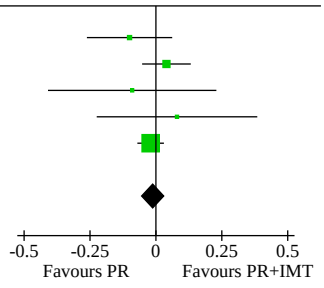
(1) Threshold device
(2) Normocapnic hyperpnea

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.15. Comparison 1: PR+IMT vs PR, Outcome 15: Laboratory exercise test: VO2peak (L/min)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Berry 1996 (1)	1.1	0.15	7	1.2	0.18	9	6.7%	-0.10 [-0.26 , 0.06]
Charususin 2018	1	0.3	89	0.96	0.32	85	20.6%	0.04 [-0.05 , 0.13]
Dekhuijzen 1991	1.37	0.53	20	1.46	0.5	20	1.7%	-0.09 [-0.41 , 0.23]
Larson 1999	1.33	0.44	14	1.25	0.38	14	1.9%	0.08 [-0.22 , 0.38]
Wang 2017	0.12	0.09	28	0.14	0.1	27	69.1%	-0.02 [-0.07 , 0.03]
Total (95% CI)			**158**			**155**	**100.0%**	**-0.01 [-0.05 , 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 3.03, df = 4 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								
Test for subgroup differences: Not applicable								



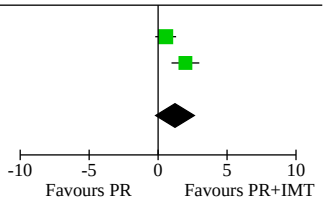
Footnotes

(1) We used the mean weight of each group to convert from ml/kg/min to L/min

Analysis 1.16. Comparison 1: PR+IMT vs PR, Outcome 16: Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Std. Mean Difference IV, Random, 95% CI
Larson 1999	68	15	14	58	20	14	52.8%	0.55 [-0.21 , 1.31]
Weiner 1992	79.6	8.31	12	60.7	10.04	12	47.2%	1.98 [0.97 , 2.99]
Total (95% CI)			**26**			**26**	**100.0%**	**1.22 [-0.18 , 2.62]**

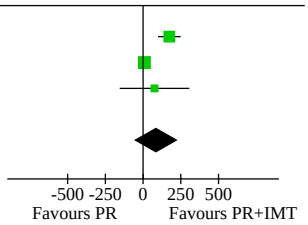
Heterogeneity: Tau² = 0.82; Chi² = 4.95, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1: PR+IMT vs PR, Outcome 17: Respiratory muscle endurance time: Tlim (seconds) (sustained ventilation according to PImax)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Charususin 2018 (1)	592.8	270	89	418.8	234	85	38.1%	174.00 [99.03 , 248.97]
Dekhuijzen 1991 (2)	158	29	20	149	33	20	42.8%	9.00 [-10.25 , 28.25]
Paneroni 2018 (3)	337.3	210.6	12	261.6	318.6	10	19.2%	75.70 [-154.93 , 306.33]
Total (95% CI)			**121**			**115**	**100.0%**	**84.63 [-50.77 , 220.02]**

Heterogeneity: Tau² = 11064.83; Chi² = 17.68, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable

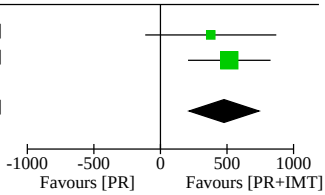


Footnotes
(1) Breathing against 50-60% of PImax
(2) Breathing against 70% of PImax
(3) Breathing against 30% of PImax

Analysis 1.18. Comparison 1: PR+IMT vs PR, Outcome 18: Respiratory muscle endurance time: Tlim (seconds) (sustained ventilation according to MVV)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Mador 2005 (1)	1686	534	15	1308	785.4	14	28.4%	378.00 [-114.23 , 870.23]
Paneroni 2018 (2)	840	444	12	322.8	292.8	10	71.6%	517.20 [207.30 , 827.10]
Total (95% CI)			**27**			**24**	**100.0%**	**477.69 [215.43 , 739.94]**

Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 3.57 (P = 0.0004)
Test for subgroup differences: Not applicable

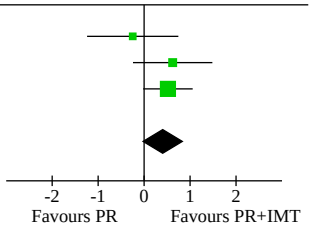


Footnotes
(1) Sustained ventilation at 70% of MVV
(2) Sustained ventilation at 60-75% of MVV

Analysis 1.19. Comparison 1: PR+IMT vs PR, Outcome 19: Maximal voluntary ventilation (MVV)

Study or Subgroup	PR Mean	PR SD	PR Total	PR+IMT Mean	PR+IMT SD	PR+IMT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Berry 1996	57.9	14.81	7	61.9	15.6	9	18.0%	-0.25 [-1.24 , 0.74]
Paneroni 2018	61.4	26.1	12	47.5	14	10	23.7%	0.62 [-0.24 , 1.48]
Wang 2017	4.14	6.19	28	0.9	6.13	27	58.3%	0.52 [-0.02 , 1.06]
Total (95% CI)			**47**			**46**	**100.0%**	**0.40 [-0.02 , 0.83]**

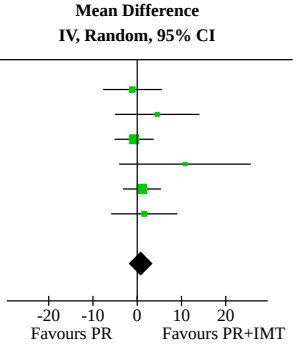
Heterogeneity: Tau² = 0.01; Chi² = 2.07, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 1.86 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: PR+IMT vs PR, Outcome 20: Respiratory function: forced expiratory volume at 1 second (FEV1) (%Pred)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Berry 1996	47	6.6	7	48.1	6.9	9	14.0%	-1.10 [-7.75 , 5.55]
Dellweg 2017	37.8	13.6	15	33.3	12.7	14	6.8%	4.50 [-5.07 , 14.07]
Magadle 2007	46.5	5.98	14	47.2	5.76	13	31.6%	-0.70 [-5.13 , 3.73]
Majewska-Pulsakowska 2016	61.9	21	13	51.1	14.6	9	2.8%	10.80 [-4.08 , 25.68]
Wang 2017	1.23	8.1	28	0.16	8.1	27	33.8%	1.07 [-3.21 , 5.35]
Weiner 1992	35.2	9	12	33.6	9.7	12	11.1%	1.60 [-5.89 , 9.09]
Total (95% CI)			**89**			**84**	**100.0%**	**0.77 [-1.72 , 3.26]**

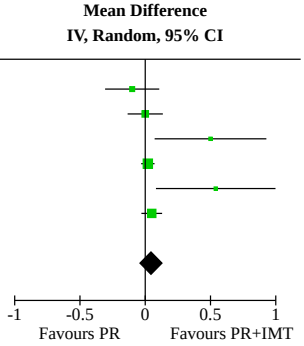
Heterogeneity: Tau² = 0.00; Chi² = 3.12, df = 5 (P = 0.68); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: PR+IMT vs PR, Outcome 21: Respiratory function: forced expiratory volume at 1 second (FEV1) (Liters)

Study or Subgroup	PR+IMT Mean	PR+IMT SD	PR+IMT Total	PR Mean	PR SD	PR Total	Weight	Mean Difference IV, Random, 95% CI
Berry 1996	1.39	0.21	7	1.49	0.21	9	11.6%	-0.10 [-0.31 , 0.11]
Charususin 2018	1.1	0.4	89	1.1	0.5	85	19.4%	0.00 [-0.13 , 0.13]
Majewska-Pulsakowska 2016	1.8	0.7	13	1.3	0.3	9	3.5%	0.50 [0.07 , 0.93]
Schultz 2018	0.21	0.33	300	0.19	0.31	302	33.7%	0.02 [-0.03 , 0.07]
Tout 2013	1.44	0.57	10	0.9	0.47	10	3.1%	0.54 [0.08 , 1.00]
Wang 2017	0.06	0.15	28	0.01	0.15	27	28.7%	0.05 [-0.03 , 0.13]
Total (95% CI)			**447**			**442**	**100.0%**	**0.04 [-0.04 , 0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 11.49, df = 5 (P = 0.04); I² = 56%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable



Comparison 2. IMT vs control/sham

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Dyspnea: Borg (at submaximal exercise capacity)	6	144	Mean Difference (IV, Random, 95% CI)	-0.94 [-1.36, -0.51]
2.2 Dyspnea: Baseline and Transition Dyspnea Indexes (BDI-TDI)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2.1 Functional impairment	3	95	Mean Difference (IV, Random, 95% CI)	0.88 [0.51, 1.25]
2.2.2 Magnitude of task	3	95	Mean Difference (IV, Random, 95% CI)	0.73 [0.35, 1.12]
2.2.3 Magnitude of effort	3	95	Mean Difference (IV, Random, 95% CI)	0.86 [0.42, 1.30]
2.2.4 Focal score	8	238	Mean Difference (IV, Random, 95% CI)	2.98 [2.07, 3.89]
2.3 Dyspnea: Transition Dyspnea Index (TDI): Focal score (subgroup analysis: with or without respiratory muscle weakness)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 With respiratory muscle weakness	4	152	Mean Difference (IV, Random, 95% CI)	3.52 [2.55, 4.49]
2.3.2 Without respiratory weakness	3	70	Mean Difference (IV, Random, 95% CI)	2.28 [1.10, 3.46]
2.4 Dyspnea: Modified Medical Research Council (mMRC)	4	150	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-0.76, -0.43]
2.5 Functional exercise capacity: 6-minute walk distance (6MWD) (meters)	16	501	Mean Difference (IV, Random, 95% CI)	35.71 [25.68, 45.74]
2.6 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)	16		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.6.1 Short-term (<4 weeks)	1	34	Mean Difference (IV, Random, 95% CI)	33.06 [23.05, 43.07]
2.6.2 Medium-term (≥4 weeks and <8 weeks)	4	131	Mean Difference (IV, Random, 95% CI)	31.15 [1.50, 60.81]
2.6.3 Long-term (≥8 weeks)	11	336	Mean Difference (IV, Random, 95% CI)	38.47 [22.75, 54.20]
2.7 Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.7.1 With respiratory muscle weakness	5	178	Mean Difference (IV, Random, 95% CI)	33.74 [25.08, 42.40]
2.7.2 Without respiratory muscle weakness	11	291	Mean Difference (IV, Random, 95% CI)	29.80 [12.86, 46.73]

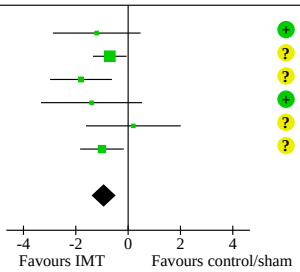
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.8 Functional exercise capacity: 12-minute walk distance (12MWD) (meters)	3	101	Mean Difference (IV, Random, 95% CI)	-33.31 [-158.10, 91.48]
2.9 Functional exercise capacity: Wmax (watt)	7	206	Mean Difference (IV, Random, 95% CI)	0.66 [-6.44, 7.76]
2.10 Functional exercise capacity: exercise time (seconds)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.11 Functional exercise capacity: shuttle walk test (SWT) (meters)	2	57	Mean Difference (IV, Random, 95% CI)	-7.45 [-92.74, 77.83]
2.12 Health-related quality of life (HRQoL): St George Respiratory Questionnaire (SGRQ)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.12.1 Symptoms	2	53	Mean Difference (IV, Random, 95% CI)	-2.10 [-3.50, -0.71]
2.12.2 Activity	2	53	Mean Difference (IV, Random, 95% CI)	-9.86 [-15.08, -4.63]
2.12.3 Impact	2	53	Mean Difference (IV, Random, 95% CI)	-6.06 [-13.76, 1.65]
2.12.4 Total	6	182	Mean Difference (IV, Random, 95% CI)	-3.85 [-8.18, 0.48]
2.13 Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.13.1 Dyspnea	5	178	Mean Difference (IV, Random, 95% CI)	1.63 [0.23, 3.03]
2.13.2 Fatigue	5	178	Mean Difference (IV, Random, 95% CI)	1.32 [0.08, 2.55]
2.13.3 Emotion	4	163	Mean Difference (IV, Random, 95% CI)	2.64 [0.82, 4.46]
2.13.4 Mastery	4	154	Mean Difference (IV, Random, 95% CI)	1.57 [0.07, 3.06]
2.14 Health-related quality of life (HRQoL): COPD Assessment Test (CAT)	2	86	Mean Difference (IV, Random, 95% CI)	-2.97 [-3.85, -2.10]
2.15 Inspiratory muscle strength: PImax (cmH_2O)	32	916	Mean Difference (IV, Random, 95% CI)	14.57 [9.85, 19.29]
2.16 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: duration of the intervention)	32		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.16.1 Short-term (<4 weeks)	1	34	Mean Difference (IV, Random, 95% CI)	12.60 [6.94, 18.26]
2.16.2 Medium-term (≥4 weeks and <8 weeks)	8	223	Mean Difference (IV, Random, 95% CI)	11.89 [6.76, 17.02]
2.16.3 Long-term (≥8 weeks)	26	748	Mean Difference (IV, Random, 95% CI)	15.02 [9.26, 20.78]
2.17 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: with or without respiratory muscle weakness)	28		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.17.1 With respiratory muscle weakness	10	323	Mean Difference (IV, Random, 95% CI)	11.08 [7.51, 14.64]
2.17.2 Without respiratory muscle weakness	19	499	Mean Difference (IV, Random, 95% CI)	13.82 [5.36, 22.29]
2.18 Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: method of measurement)	32		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.18.1 Residual Volume (RV)	15	466	Mean Difference (IV, Random, 95% CI)	12.63 [8.46, 16.81]
2.18.2 Functional Residual Capacity (FRC)	9	206	Mean Difference (IV, Random, 95% CI)	11.87 [7.33, 16.41]
2.18.3 Not reported	8	244	Mean Difference (IV, Random, 95% CI)	19.52 [4.63, 34.41]
2.19 Laboratory exercise test: VO_2peak	11	286	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.05, 0.57]
2.20 Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)	8	179	Mean Difference (IV, Random, 95% CI)	9.71 [4.93, 14.50]
2.21 Respiratory muscle endurance time: T_{lim} (seconds)	10	260	Mean Difference (IV, Random, 95% CI)	270.57 [182.44, 358.71]
2.22 Maximal voluntary ventilation (MVV)	2	36	Std. Mean Difference (IV, Random, 95% CI)	0.99 [0.28, 1.69]
2.23 Respiratory function: forced expiratory volume at 1 second (FEV1) (%pred)	10	314	Mean Difference (IV, Random, 95% CI)	2.62 [0.20, 5.04]
2.24 Respiratory function: forced expiratory volume at 1 second (FEV1) (Liters)	12	362	Mean Difference (IV, Random, 95% CI)	0.04 [-0.06, 0.14]

Analysis 2.1. Comparison 2: IMT vs control/sham, Outcome 1: Dyspnea: Borg (at submaximal exercise capacity)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Dacha 2019 (1)	-0.2	1.2	6	1	1.4	4	6.5%	-1.20 [-2.87 , 0.47]	+	+	+	+	?	?
Hill 2006 (2)	0.8	0.6	16	1.5	1.2	17	44.0%	-0.70 [-1.34 , -0.06]	?	+	+	+	?	?
Koppers 2006 (2)	5.4	1.3	18	7.2	2.2	18	13.0%	-1.80 [-2.98 , -0.62]	?	+	+	+	?	?
Langer 2018 (3)	-1.8	2.3	10	-0.4	2.1	10	4.9%	-1.40 [-3.33 , 0.53]	+	+	+	+	+	+
Larson 1999 (4)	5.3	2.2	13	5.1	2.4	12	5.5%	0.20 [-1.61 , 2.01]	?	?	−	−	?	−
Petrovic 2012 (5)	5	0.9	10	6	1	10	26.1%	-1.00 [-1.83 , -0.17]	?	+	+	−	?	−
Total (95% CI)			**73**			**71**	**100.0%**	**-0.94 [-1.36 , -0.51]**						

Heterogeneity: Tau² = 0.00; Chi² = 4.43, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.32 (P < 0.0001)
Test for subgroup differences: Not applicable

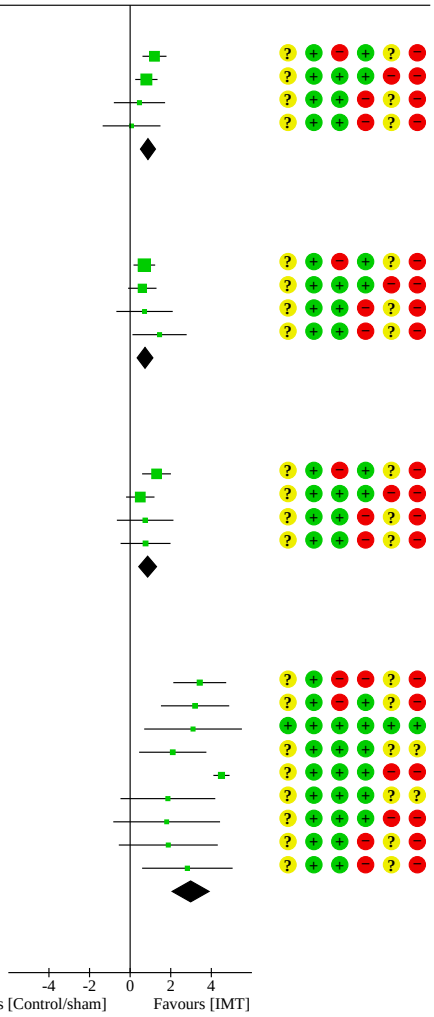


Footnotes
(1) Isotime at 70%-80% of Wmax
(2) 50% of Wmax
(3) Isotime at 75% of Wmax
(4) at 25%-50% of Wmax
(5) 75% of Wmax

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: IMT vs control/sham, Outcome 2: Dyspnea: Baseline and Transition Dyspnea Indexes (BDI-TDI)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
2.2.1 Functional impairment								
Harver 1989	1.3	0.9	10	0.1	0.3	9	39.2%	1.20 [0.61 , 1.79]
Weiner 2003	2.4	0.56	8	1.6	0.56	8	45.5%	0.80 [0.25 , 1.35]
Wu 2017 (1)	0.71	1.1	21	0.25	1.89	10	8.6%	0.46 [-0.80 , 1.72]
Wu 2017 (2)	0.32	1.8	19	0.25	1.89	10	6.8%	0.07 [-1.35 , 1.49]
Subtotal (95% CI)			**58**			**37**	**100.0%**	**0.88 [0.51 , 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%								
Test for overall effect: Z = 4.65 (P < 0.00001)								
2.2.2 Magnitude of task								
Harver 1989	0.8	0.8	10	0.1	0.3	9	53.0%	0.70 [0.17 , 1.23]
Weiner 2003	2.5	0.84	8	1.9	0.56	8	30.8%	0.60 [-0.10 , 1.30]
Wu 2017 (2)	0.21	1.36	19	-0.5	2.01	10	7.8%	0.71 [-0.68 , 2.10]
Wu 2017 (1)	0.95	1.12	21	-0.5	2.01	10	8.5%	1.45 [0.12 , 2.78]
Subtotal (95% CI)			**58**			**37**	**100.0%**	**0.73 [0.35 , 1.12]**
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 3 (P = 0.74); I² = 0%								
Test for overall effect: Z = 3.70 (P = 0.0002)								
2.2.3 Magnitude of effort								
Harver 1989	1.4	1.1	10	0.1	0.3	9	38.2%	1.30 [0.59 , 2.01]
Weiner 2003	2.4	0.84	8	1.9	0.56	8	39.2%	0.50 [-0.20 , 1.20]
Wu 2017 (2)	0.84	1.8	19	0.1	1.83	10	9.9%	0.74 [-0.65 , 2.13]
Wu 2017 (1)	0.86	1.11	21	0.1	1.83	10	12.7%	0.76 [-0.47 , 1.99]
Subtotal (95% CI)			**58**			**37**	**100.0%**	**0.86 [0.42 , 1.30]**
Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 3 (P = 0.47); I² = 0%								
Test for overall effect: Z = 3.86 (P = 0.0001)								
2.2.4 Focal score								
Chuang 2017	9	2.27	27	5.57	2.65	28	14.3%	3.43 [2.13 , 4.73]
Harver 1989	3.5	2.5	10	0.3	1	9	12.0%	3.20 [1.52 , 4.88]
Langer 2018	4.3	2.2	10	1.2	3.2	10	8.4%	3.10 [0.69 , 5.51]
Lisboa 1997	3.8	1.89	10	1.7	1.89	10	12.1%	2.10 [0.44 , 3.76]
Sanchez Riera 2001 (3)	4.7	0.6	9	0.2	0.11	9	19.6%	4.50 [4.10 , 4.90]
Scherer 2000	4.66	4	15	2.8	2.3	15	8.7%	1.86 [-0.48 , 4.20]
Weiner 2003	7.3	2.82	8	5.5	2.54	8	7.5%	1.80 [-0.83 , 4.43]
Wu 2017 (2)	1.58	2.93	19	-0.3	3.31	10	8.3%	1.88 [-0.56 , 4.32]
Wu 2017 (1)	2.52	2.04	21	-0.3	3.31	10	9.1%	2.82 [0.59 , 5.05]
Subtotal (95% CI)			**129**			**109**	**100.0%**	**2.98 [2.07 , 3.89]**
Heterogeneity: Tau² = 1.06; Chi² = 23.07, df = 8 (P = 0.003); I² = 65%								
Test for overall effect: Z = 6.42 (P < 0.00001)								



Footnotes

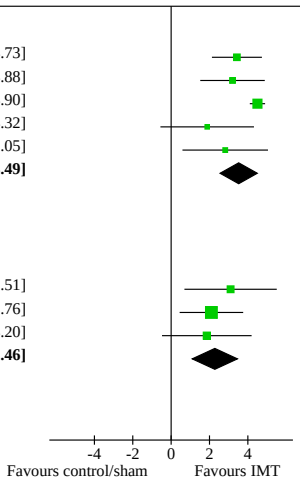
(1) Pflex device
(2) Threshold device
(3) This study did not report the BDI score.

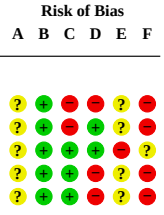
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: IMT vs control/sham, Outcome 3: Dyspnea: Transition Dyspnea Index (TDI): Focal score (subgroup analysis: with or without respiratory muscle weakness)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 With respiratory muscle weakness								
Chuang 2017	9	2.27	27	5.57	2.65	28	22.6%	3.43 [2.13 , 4.73]
Harver 1989	3.5	2.5	10	0.3	1	9	17.8%	3.20 [1.52 , 4.88]
Sanchez Riera 2001	4.7	0.6	9	0.2	0.11	9	35.8%	4.50 [4.10 , 4.90]
Wu 2017 (1)	1.58	2.93	19	-0.3	3.31	10	11.2%	1.88 [-0.56 , 4.32]
Wu 2017 (2)	2.52	2.04	21	-0.3	3.31	10	12.6%	2.82 [0.59 , 5.05]
Subtotal (95% CI)			**86**			**66**	**100.0%**	**3.52 [2.55 , 4.49]**
Heterogeneity: Tau² = 0.64; Chi² = 9.74, df = 4 (P = 0.05); I² = 59%								
Test for overall effect: Z = 7.12 (P < 0.00001)								
2.3.2 Without respiratory weakness								
Langer 2018	4.3	2.2	10	1.2	3.2	10	24.0%	3.10 [0.69 , 5.51]
Lisboa 1997	3.8	1.89	10	1.7	1.89	10	50.6%	2.10 [0.44 , 3.76]
Scherer 2000	4.66	4	15	2.8	2.3	15	25.5%	1.86 [-0.48 , 4.20]
Subtotal (95% CI)			**35**			**35**	**100.0%**	**2.28 [1.10 , 3.46]**
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.74); I² = 0%								
Test for overall effect: Z = 3.79 (P = 0.0002)								
Test for subgroup differences: Chi² = 2.55, df = 1 (P = 0.11), I² = 60.8%								



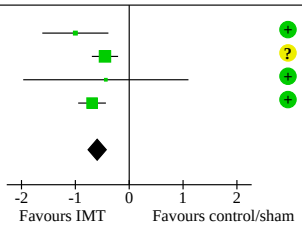


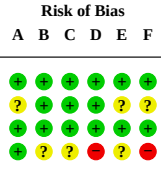
Footnotes
(1) Threshold device
(2) Pflex device

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: IMT vs control/sham, Outcome 4: Dyspnea: Modified Medical Research Council (mMRC)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Fixed, 95% CI
Langer 2018 (1)	-0.6	0.7	10	0.4	0.7	10	7.6%	-1.00 [-1.61 , -0.39]
Saka 2021	-0.5	0.51	20	-0.05	0.22	20	48.1%	-0.45 [-0.69 , -0.21]
Xu 2018	-0.304	2.68	23	0.13	2.628	23	1.2%	-0.43 [-1.97 , 1.10]
ZhouL 2016	2.06	0.33	22	2.75	0.52	22	43.1%	-0.69 [-0.95 , -0.43]
Total (95% CI)			**75**			**75**	**100.0%**	**-0.59 [-0.76 , -0.43]**
Heterogeneity: Chi² = 3.60, df = 3 (P = 0.31); I² = 17%								
Test for overall effect: Z = 6.90 (P < 0.00001)								
Test for subgroup differences: Not applicable								





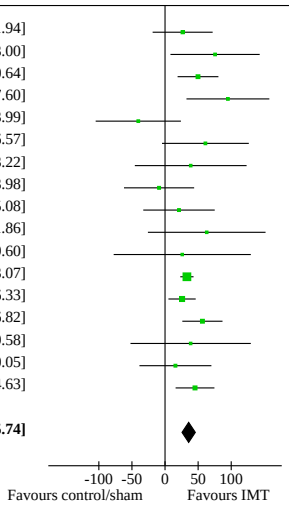
Footnotes
(1) The scale is from 1 to 5

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: IMT vs control/sham, Outcome 5: Functional exercise capacity: 6-minute walk distance (6MWD) (meters)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Bavarsad 2015	491	68.44	15	464.4	57.82	15	4.4%	26.60 [-18.74 , 71.94]	? ? + + ? ?
Beckerman 2005	326	96.48	17	250.4	94.28	14	2.1%	75.60 [8.20 , 143.00]	? - - + ? -
Chuang 2017	266.15	48.69	27	216.34	66.84	28	8.5%	49.81 [18.98 , 80.64]	? + + + ? ?
Cutrim 2019	486	74.56	11	391	75.25	11	2.4%	95.00 [32.40 , 157.60]	+ + + + + +
Hill 2006	472.8	104.3	16	513.2	82.4	17	2.3%	-40.40 [-104.79 , 23.99]	? + + + ? ?
Hsiao 2003 (1)	481.8	49	10	420.8	66.3	5	2.2%	61.00 [-4.57 , 126.57]	? - ? + ? -
Hsiao 2003 (2)	459.6	98.8	10	420.8	66.3	5	1.4%	38.80 [-45.62 , 123.22]	? - ? + ? -
Koppers 2006	535	77	18	544	85	18	3.3%	-9.00 [-61.98 , 43.98]	? + + + ? ?
Leelarungrayub 2017	340	55.97	10	318.9	66.72	10	3.2%	21.10 [-32.88 , 75.08]	? + - + ? -
Lisboa 1997	417	107.51	10	354	94.86	10	1.2%	63.00 [-25.86 , 151.86]	? + + + ? ?
Ramirez Sarmiento 2002	433	81	7	407	114	7	0.9%	26.00 [-77.60 , 129.60]	? - + + ? -
Saher 2021	239.82	9.36	17	206.76	18.87	17	30.3%	33.06 [23.05 , 43.07]	? - ? + ? -
Saka 2021	42.8	26.51	20	17.06	38.78	20	15.4%	25.74 [5.15 , 46.33]	? + + + ? ?
Scherer 2000	69.38	42.4	15	12.9	42.4	15	8.7%	56.48 [26.14 , 86.82]	? + ? + ? ?
Weiner 2003	326.2	106.63	8	287.5	76.36	8	1.2%	38.70 [-52.18 , 129.58]	? + + + - -
Xu 2018	24.17	88.05	23	8.47	99.65	23	3.2%	15.70 [-38.65 , 70.05]	+ + + + + +
ZhouL 2016	284.9	56.6	22	239.6	41.5	22	9.2%	45.30 [15.97 , 74.63]	+ ? ? + ? ?
Total (95% CI)			**256**			**245**	**100.0%**	**35.71 [25.68 , 45.74]**	

Heterogeneity: Tau² = 60.27; Chi² = 18.94, df = 16 (P = 0.27); I² = 16%
Test for overall effect: Z = 6.98 (P < 0.00001)
Test for subgroup differences: Not applicable

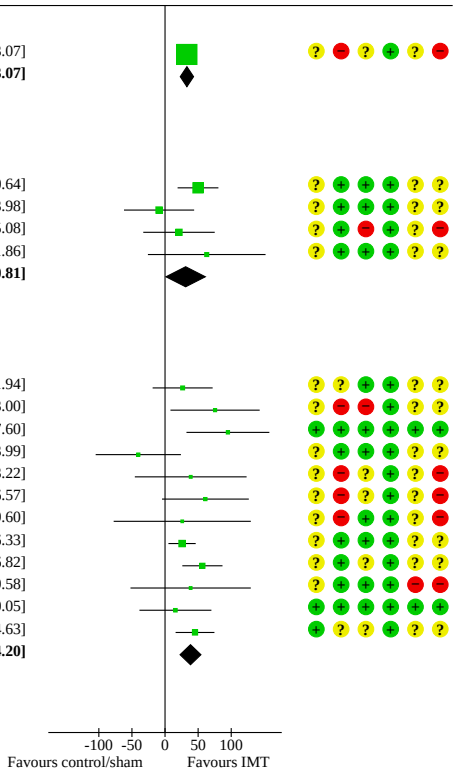


Footnotes
(1) Threshold device
(2) Incentive spirometer

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: IMT vs control/sham, Outcome 6: Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: duration of the intervention)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/sham Mean	Control/sham SD	Control/sham Total	Weight	Mean Difference IV, Random, 95% CI
2.6.1 Short-term (<4 weeks)								
Saher 2021	239.82	9.36	17	206.76	18.87	17	100.0%	33.06 [23.05 , 43.07]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**33.06 [23.05 , 43.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.47 (P < 0.00001)								
2.6.2 Medium-term (≥4 weeks and <8 weeks)								
Chuang 2017	266.15	48.69	27	216.34	66.84	28	44.7%	49.81 [18.98 , 80.64]
Koppers 2006	535	77	18	544	85	18	23.0%	-9.00 [-61.98 , 43.98]
Leelarungrayub 2017	340	55.97	10	318.9	66.72	10	22.4%	21.10 [-32.88 , 75.08]
Lisboa 1997	417	107.51	10	354	94.86	10	9.9%	63.00 [-25.86 , 151.86]
Subtotal (95% CI)			**65**			**66**	**100.0%**	**31.15 [1.50 , 60.81]**
Heterogeneity: Tau² = 264.50; Chi² = 4.17, df = 3 (P = 0.24); I² = 28%								
Test for overall effect: Z = 2.06 (P = 0.04)								
2.6.3 Long-term (≥8 weeks)								
Bavarsad 2015	491	68.44	15	464.4	57.82	15	9.2%	26.60 [-18.74 , 71.94]
Beckerman 2005	326	96.48	17	250.4	94.28	14	4.8%	75.60 [8.20 , 143.00]
Cutrim 2019	486	74.56	11	391	75.25	11	5.4%	95.00 [32.40 , 157.60]
Hill 2006	472.8	104.3	16	513.2	82.4	17	5.2%	-40.40 [-104.79 , 23.99]
Hsiao 2003 (1)	459.6	98.8	10	420.8	66.3	5	3.2%	38.80 [-45.62 , 123.22]
Hsiao 2003 (2)	481.8	49	10	420.8	66.3	5	5.0%	61.00 [-4.57 , 126.57]
Ramirez Sarmiento 2002	433	81	7	407	114	7	2.2%	26.00 [-77.60 , 129.60]
Saka 2021	42.8	26.51	20	17.06	38.78	20	23.2%	25.74 [5.15 , 46.33]
Scherer 2000	69.38	42.4	15	12.9	42.4	15	15.8%	56.48 [26.14 , 86.82]
Weiner 2003	326.2	106.63	8	287.5	76.36	8	2.8%	38.70 [-52.18 , 129.58]
Xu 2018	24.17	88.05	23	8.47	99.65	23	6.9%	15.70 [-38.65 , 70.05]
ZhouL 2016	284.9	56.6	22	239.6	41.5	22	16.5%	45.30 [15.97 , 74.63]
Subtotal (95% CI)			**174**			**162**	**100.0%**	**38.47 [22.75 , 54.20]**
Heterogeneity: Tau² = 167.40; Chi² = 14.50, df = 11 (P = 0.21); I² = 24%								
Test for overall effect: Z = 4.79 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%								



Footnotes

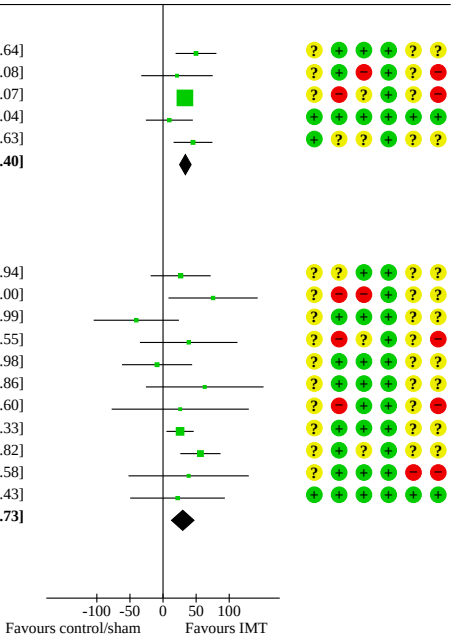
(1) Incentive spirometer
(2) Threshold device

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.7. Comparison 2: IMT vs control/sham, Outcome 7: Functional exercise capacity: 6-minute walk distance (6MWD) (meters) (subgroup analysis: with or without respiratory muscle weakness)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
2.7.1 With respiratory muscle weakness									
Chuang 2017	266.15	48.69	27	216.34	66.84	28	7.9%	49.81 [18.98 , 80.64]	? + + + ? ?
Leelarungrayub 2017	340	55.97	10	318.9	66.72	10	2.6%	21.10 [-32.88 , 75.08]	? + − + ? −
Saher 2021	239.82	9.36	17	206.76	18.87	17	74.8%	33.06 [23.05 , 43.07]	? − ? + ? −
Xu 2018	23.286	48.85	14	13.727	41.58	11	6.0%	9.56 [-25.92 , 45.04]	+ + + + + +
ZhouL 2016	284.9	56.6	22	239.6	41.5	22	8.7%	45.30 [15.97 , 74.63]	+ ? ? + ? ?
Subtotal (95% CI)			**90**			**88**	**100.0%**	**33.74 [25.08 , 42.40]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 4 (P = 0.45); I² = 0%									
Test for overall effect: Z = 7.63 (P < 0.00001)									
2.7.2 Without respiratory muscle weakness									
Bavarsad 2015	491	68.44	15	464.4	57.82	15	11.1%	26.60 [-18.74 , 71.94]	? ? + + ? ?
Beckerman 2005	326	96.48	17	250.4	94.28	14	5.6%	75.60 [8.20 , 143.00]	? − − + ? ?
Hill 2006	472.8	104.3	16	513.2	82.4	17	6.1%	-40.40 [-104.79 , 23.99]	? + + + ? ?
Hsiao 2003 (1)	459.6	98.8	10	420.8	66.3	10	4.8%	38.80 [-34.95 , 112.55]	? − ? + ? −
Koppers 2006	535	77	18	544	85	18	8.6%	-9.00 [-61.98 , 43.98]	? + + + ? ?
Lisboa 1997	417	107.51	10	354	94.86	10	3.4%	63.00 [-25.86 , 151.86]	? + + + ? ?
Ramirez Sarmiento 2002	433	81	7	407	114	7	2.5%	26.00 [-77.60 , 129.60]	? − + + ? −
Saka 2021	42.8	26.51	20	17.06	38.78	20	29.8%	25.74 [5.15 , 46.33]	? + + + ? ?
Scherer 2000	69.38	42.4	15	12.9	42.4	15	19.7%	56.48 [26.14 , 86.82]	? + ? + ? ?
Weiner 2003	326.2	106.63	8	287.5	76.36	8	3.3%	38.70 [-52.18 , 129.58]	? + + + − −
Xu 2018	25.55	77.37	9	3.667	89.5	12	5.1%	21.88 [-49.67 , 93.43]	+ + + + + +
Subtotal (95% CI)			**145**			**146**	**100.0%**	**29.80 [12.86 , 46.73]**	
Heterogeneity: Tau² = 139.76; Chi² = 12.22, df = 10 (P = 0.27); I² = 18%									
Test for overall effect: Z = 3.45 (P = 0.0006)									
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%									

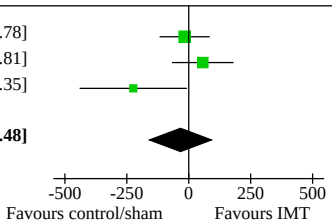


Footnotes
(1) Incentive spirometer

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.8. Comparison 2: IMT vs control/sham, Outcome 8: Functional exercise capacity: 12-minute walk distance (12MWD) (meters)

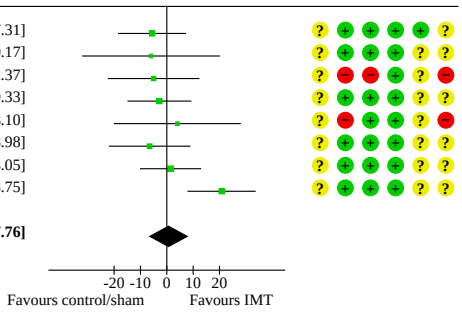
Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Kim 1993	823.2	169.4	39	839.7	206.3	22	42.0%	-16.50 [-117.78 , 84.78]
Larson 1988	849.4	142.3	8	792.7	133.2	12	36.9%	56.70 [-67.41 , 180.81]
Preusser 1994	624	278	12	848	215	8	21.1%	-224.00 [-440.65 , -7.35]
Total (95% CI)			**59**			**42**	**100.0%**	**-33.31 [-158.10 , 91.48]**
Heterogeneity: Tau² = 6980.99; Chi² = 4.86, df = 2 (P = 0.09); I² = 59%								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Not applicable								



Analysis 2.9. Comparison 2: IMT vs control/sham, Outcome 9: Functional exercise capacity: Wmax (watt)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Hill 2006	64.4	14.6	16	70	22.6	17	15.3%	-5.60 [-18.51 , 7.31]
Koppers 2006	120	38	18	126	42	18	5.9%	-6.00 [-32.17 , 20.17]
Larson 1999	68	17	13	73	26	12	10.9%	-5.00 [-22.37 , 12.37]
Lisboa 1997	32.7	14.23	10	35.5	13.43	10	16.3%	-2.80 [-14.93 , 9.33]
Ramirez Sarmiento 2002	86	23	7	82	23	7	6.8%	4.00 [-20.10 , 28.10]
Sanchez Riera 2001	52	15.4	9	58.5	18	9	12.5%	-6.50 [-21.98 , 8.98]
Wu 2017 (1)	67.63	16.07	19	66.2	14.68	10	17.0%	1.43 [-10.19 , 13.05]
Wu 2017 (2)	87	21.56	21	66.2	14.68	10	15.3%	20.80 [7.85 , 33.75]
Total (95% CI)			**113**			**93**	**100.0%**	**0.66 [-6.44 , 7.76]**

Heterogeneity: Tau² = 42.12; Chi² = 12.06, df = 7 (P = 0.10); I² = 42%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



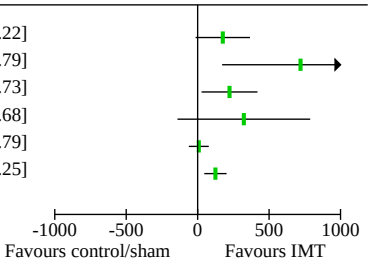
Footnotes
(1) Threshold device
(2) Pflex device

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.10. Comparison 2: IMT vs control/sham, Outcome 10: Functional exercise capacity: exercise time (seconds)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Mean Difference IV, Random, 95% CI
Berton 2015 (1)	191	247	7	15	65	6	176.00 [-14.22 , 366.22]
Koppers 2006 (2)	1680	840	18	960	840	18	720.00 [171.21 , 1268.79]
Langer 2018 (1)	277	303	10	54	89	10	223.00 [27.27 , 418.73]
Scherer 2000 (3)	529.1	793.96	15	205.8	460.11	15	323.30 [-141.08 , 787.68]
Wu 2017 (4)	405.58	96.57	19	397.55	88.1	10	8.03 [-61.73 , 77.79]
Wu 2017 (5)	522.05	129.41	21	397.55	88.1	10	124.50 [46.75 , 202.25]

Test for subgroup differences: Not applicable

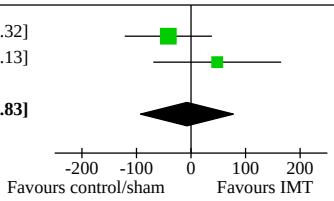


Footnotes
(1) Cycling at 75% of Wmax
(2) Cycling at 50% of Wmax
(3) Exericse time on treadmill which was set to 80% of the inclination and to 100% of the speed reached at VO2peak
(4) Incremental cycle test (Threshold device)
(5) Incremental cycle test (Pflex device)

Analysis 2.11. Comparison 2: IMT vs control/sham, Outcome 11: Functional exercise capacity: shuttle walk test (SWT) (meters)

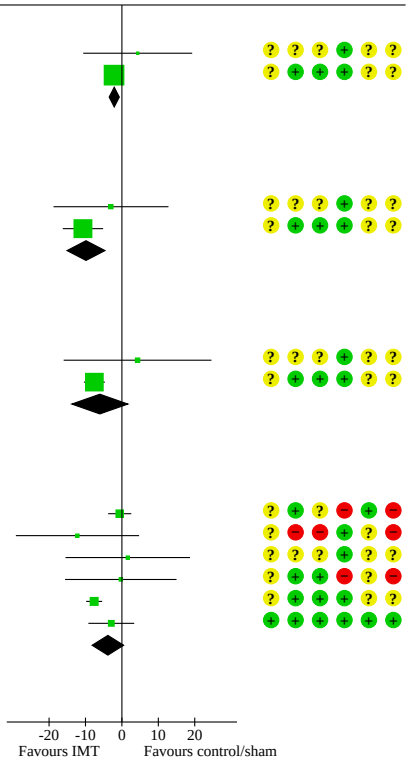
Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Nikoletou 2016	218.4	92.7	21	260	150.2	18	61.9%	-41.60 [-121.52 , 38.32]
Sanchez Riera 2001	541	112	9	493	140	9	38.1%	48.00 [-69.13 , 165.13]
Total (95% CI)			**30**			**27**	**100.0%**	**-7.45 [-92.74 , 77.83]**

Heterogeneity: Tau² = 1397.03; Chi² = 1.53, df = 1 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: IMT vs control/sham, Outcome 12: Health-related quality of life (HRQoL): St George Respiratory Questionnaire (SGRQ)

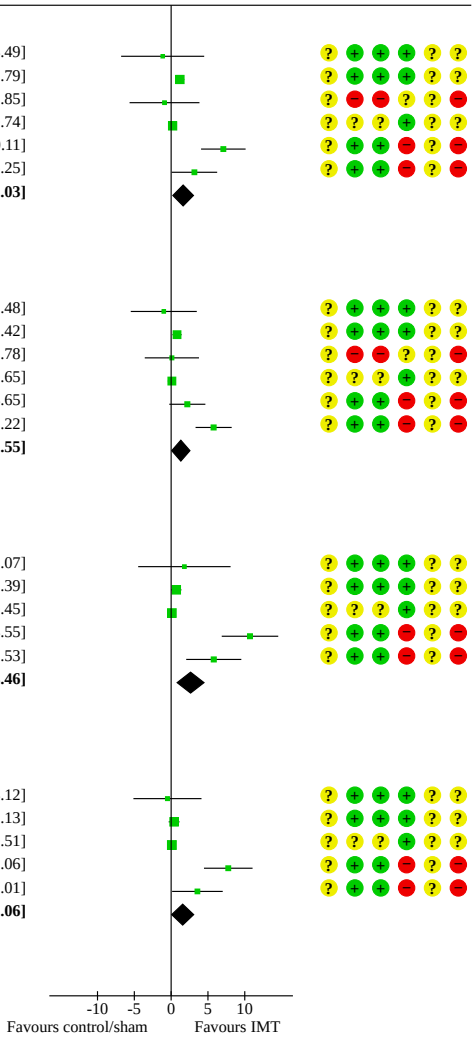
Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
2.12.1 Symptoms									
Berton 2015	50.74	12.2	7	46.4	14.9	6	0.9%	4.34 [-10.62 , 19.30]	? ? ? + ? ?
Saka 2021	-2.47	3.02	20	-0.31	1.05	20	99.1%	-2.16 [-3.56 , -0.76]	? + + + ? ?
Subtotal (95% CI)			**27**			**26**	**100.0%**	**-2.10 [-3.50 , -0.71]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%									
Test for overall effect: Z = 2.96 (P = 0.003)									
2.12.2 Activity									
Berton 2015	64.9	16.9	7	67.9	12	6	11.0%	-3.00 [-18.78 , 12.78]	? ? ? + ? ?
Saka 2021	-13.32	11.81	20	-2.62	4.48	20	89.0%	-10.70 [-16.24 , -5.16]	? + + + ? ?
Subtotal (95% CI)			**27**			**26**	**100.0%**	**-9.86 [-15.08 , -4.63]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%									
Test for overall effect: Z = 3.70 (P = 0.0002)									
2.12.3 Impact									
Berton 2015	39.9	21.6	7	35.6	15.6	6	12.6%	4.30 [-15.99 , 24.59]	? ? ? + ? ?
Saka 2021	-6.69	5.46	20	0.86	3.66	20	87.4%	-7.55 [-10.43 , -4.67]	? + + + ? ?
Subtotal (95% CI)			**27**			**26**	**100.0%**	**-6.06 [-13.76 , 1.65]**	
Heterogeneity: Tau² = 15.53; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%									
Test for overall effect: Z = 1.54 (P = 0.12)									
2.12.4 Total									
Abedi Yekta 2019	-4.79	5.55	16	-4.19	3.23	15	29.8%	-0.60 [-3.77 , 2.57]	? + ? − + −
Beckerman 2005	49.1	24.32	17	61.3	23.57	14	5.5%	-12.20 [-29.11 , 4.71]	? − − + ? −
Berton 2015	49	17.7	7	47.4	13.7	6	5.4%	1.60 [-15.49 , 18.69]	? ? ? + ? ?
Majewska-Pulsakowska 2016	47.2	16	8	47.5	19.4	13	6.5%	-0.30 [-15.60 , 15.00]	? + + − ? −
Saka 2021	-8.01	4.19	20	-0.39	2.74	20	32.5%	-7.62 [-9.81 , -5.43]	? + + + ? ?
Xu 2018	-3.087	11.649	23	-0.174	10.085	23	20.3%	-2.91 [-9.21 , 3.38]	+ + + + + +
Subtotal (95% CI)			**91**			**91**	**100.0%**	**-3.85 [-8.18 , 0.48]**	
Heterogeneity: Tau² = 13.78; Chi² = 14.90, df = 5 (P = 0.01); I² = 66%									
Test for overall effect: Z = 1.74 (P = 0.08)									
Test for subgroup differences: Chi² = 8.88, df = 3 (P = 0.03), I² = 66.2%									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.13. Comparison 2: IMT vs control/sham, Outcome 13: Health-related quality of life (HRQoL): Chronic Respiratory Disease Questionnaire (CRQ)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
2.13.1 Dyspnea									
Bustamante 2007	14.25	5.66	12	15.4	7.49	10	5.2%	-1.15 [-6.79 , 4.49]	? + + + ? ?
Hill 2006	4.9	0.7	16	3.7	1	17	31.0%	1.20 [0.61 , 1.79]	? + + + ? ?
Larson 1999	21.8	6.5	12	22.7	5.3	12	6.9%	-0.90 [-5.65 , 3.85]	? - - ? ? -
Nikoletou 2016	0.6	0.8	21	0.4	0.9	18	31.3%	0.20 [-0.34 , 0.74]	? ? ? + ? ?
Wu 2017 (1)	27.19	2.73	21	20.1	4.5	10	13.0%	7.09 [4.07 , 10.11]	? + + - ? -
Wu 2017 (2)	23.26	2.97	19	20.1	4.5	10	12.6%	3.16 [0.07 , 6.25]	? + + - ? -
Subtotal (95% CI)			**101**			**77**	**100.0%**	**1.63 [0.23 , 3.03]**	
Heterogeneity: Tau² = 1.55; Chi² = 26.37, df = 5 (P < 0.0001); I² = 81%									
Test for overall effect: Z = 2.28 (P = 0.02)									
2.13.2 Fatigue									
Bustamante 2007	19.7	4.85	12	20.7	5.72	10	6.1%	-1.00 [-5.48 , 3.48]	? + + + ? ?
Hill 2006	4.8	0.8	16	4	1	17	28.7%	0.80 [0.18 , 1.42]	? + + + ? ?
Larson 1999	19.8	4.7	12	19.7	4.5	12	8.3%	0.10 [-3.58 , 3.78]	? - - ? ? -
Nikoletou 2016	0.5	1.1	21	0.4	0.6	18	29.1%	0.10 [-0.45 , 0.65]	? ? ? + ? ?
Wu 2017 (2)	19.1	2.78	19	16.9	3.4	10	13.9%	2.20 [-0.25 , 4.65]	? + + - ? -
Wu 2017 (1)	22.67	2.93	21	16.9	3.4	10	13.9%	5.77 [3.32 , 8.22]	? + + - ? -
Subtotal (95% CI)			**101**			**77**	**100.0%**	**1.32 [0.08 , 2.55]**	
Heterogeneity: Tau² = 1.29; Chi² = 22.89, df = 5 (P = 0.0004); I² = 78%									
Test for overall effect: Z = 2.09 (P = 0.04)									
2.13.3 Emotion									
Bustamante 2007	38.5	7.65	12	36.7	10.1	19	6.8%	1.80 [-4.47 , 8.07]	? + + + ? ?
Hill 2006	5.6	0.8	16	4.9	1.2	17	32.3%	0.70 [0.01 , 1.39]	? + + + ? ?
Nikoletou 2016	0.3	0.7	21	0.2	0.4	18	33.4%	0.10 [-0.25 , 0.45]	? ? ? + ? ?
Wu 2017 (1)	38.81	3.5	21	28.1	5.7	10	13.5%	10.71 [6.87 , 14.55]	? + + - ? -
Wu 2017 (2)	33.89	2.74	19	28.1	5.7	10	14.0%	5.79 [2.05 , 9.53]	? + + - ? -
Subtotal (95% CI)			**89**			**74**	**100.0%**	**2.64 [0.82 , 4.46]**	
Heterogeneity: Tau² = 2.56; Chi² = 39.24, df = 4 (P < 0.00001); I² = 90%									
Test for overall effect: Z = 2.84 (P = 0.005)									
2.13.4 Mastery									
Bustamante 2007	22.3	4.94	12	22.8	5.94	10	8.0%	-0.50 [-5.12 , 4.12]	? + + + ? ?
Hill 2006	5.7	0.8	16	5.3	1.3	17	32.4%	0.40 [-0.33 , 1.13]	? + + + ? ?
Nikoletou 2016	0.3	0.6	21	0.2	0.7	18	34.3%	0.10 [-0.31 , 0.51]	? ? ? + ? ?
Wu 2017 (1)	22.71	2.3	21	14.95	5.08	10	12.9%	7.76 [4.46 , 11.06]	? + + - ? -
Wu 2017 (2)	18.52	3.06	19	14.95	5.08	10	12.3%	3.57 [0.13 , 7.01]	? + + - ? -
Subtotal (95% CI)			**89**			**65**	**100.0%**	**1.57 [0.07 , 3.06]**	
Heterogeneity: Tau² = 1.65; Chi² = 24.21, df = 4 (P < 0.0001); I² = 83%									
Test for overall effect: Z = 2.06 (P = 0.04)									
Test for subgroup differences: Chi² = 1.42, df = 3 (P = 0.70), I² = 0%									



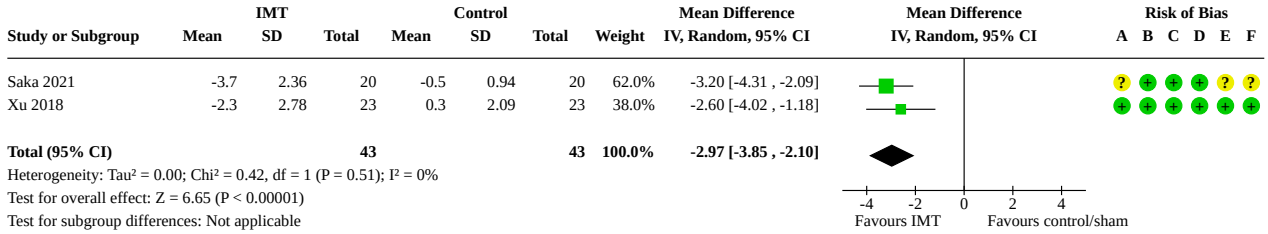
Footnotes

(1) Pflex device
(2) Threshold device

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.14. Comparison 2: IMT vs control/sham, Outcome 14: Health-related quality of life (HRQoL): COPD Assessment Test (CAT)



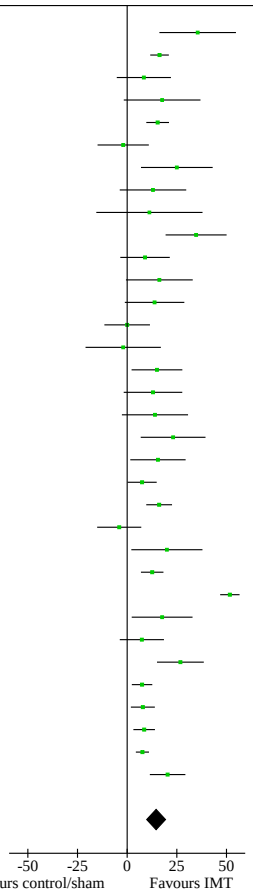
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.15. Comparison 2: IMT vs control/sham, Outcome 15: Inspiratory muscle strength: PImax (cmH_2O)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Beckerman 2005	101.1	29.27	17	65.6	25.44	14	2.3%	35.50 [16.23 , 54.77]	? - - + ? -
Belman 1988	21.3	5.736	8	5	3.788	9	3.6%	16.30 [11.62 , 20.98]	? + + + ? ?
Berton 2015	112.1	12.8	7	103.7	12.24	6	2.8%	8.40 [-5.23 , 22.03]	? + + + ? ?
Bustamante 2007	104.3	22.4	12	86.7	23.5	10	2.3%	17.60 [-1.71 , 36.91]	? + + + ? ?
Chuang 2017	48.56	10.18	27	33.21	11.4	28	3.5%	15.35 [9.64 , 21.06]	? + + + ? ?
Covey 2001	75	17	12	77	17	15	2.9%	-2.00 [-14.90 , 10.90]	? ? ? + ? ?
Cutrim 2019	84	26	11	59	16	11	2.4%	25.00 [6.96 , 43.04]	+ + + + + +
Dacha 2019	94	20	6	81	5	4	2.5%	13.00 [-3.74 , 29.74]	+ + + + ? ?
Harver 1989	94.5	27.9	10	83.3	31.2	9	1.7%	11.20 [-15.53 , 37.93]	? + - + ? -
Heijdra 1996	93.8	20.3	10	59.1	14.2	10	2.7%	34.70 [19.35 , 50.05]	? + + + ? ?
Hill 2006	80.7	17.8	16	71.7	18.7	17	3.0%	9.00 [-3.45 , 21.45]	? + + + ? ?
Hsiao 2003 (1)	26.8	19.4	10	10.6	13.4	5	2.5%	16.20 [-0.61 , 33.01]	? - ? + ? -
Hsiao 2003 (2)	24.4	15	10	10.6	13.4	5	2.7%	13.80 [-1.18 , 28.78]	? - ? + ? -
Kim 1993	78	25	40	78	22	26	3.1%	0.00 [-11.47 , 11.47]	? + ? + ? ?
Koppers 2006	73	28	18	75	30	18	2.3%	-2.00 [-20.96 , 16.96]	? + + + ? ?
Langer 2018	21	16	10	6	13	10	2.9%	15.00 [2.22 , 27.78]	+ + + + + +
Larson 1988	73	19	10	60	15	11	2.7%	13.00 [-1.74 , 27.74]	+ - ? + ? -
Larson 1999	100	25	13	86	17	12	2.5%	14.00 [-2.65 , 30.65]	? ? - + ? -
Leelarungrayub 2017	84	22.35	10	60.87	13.88	10	2.6%	23.13 [6.82 , 39.44]	? + - + ? -
Lisboa 1997	93	17.39	10	77.5	14.23	10	2.8%	15.50 [1.57 , 29.43]	? + + + ? ?
Nikoletou 2016	9.6	10.87	21	2.09	12.338	18	3.4%	7.51 [0.15 , 14.87]	? ? ? + ? ?
Petrovic 2012	93.3	7.4	10	77.2	7.4	10	3.5%	16.10 [9.61 , 22.59]	? + + + ? ?
Preusser 1994	42	17	12	46	8	8	3.1%	-4.00 [-15.10 , 7.10]	? + + + ? ?
Ramirez Sarmiento 2002	99	22	7	79	10	7	2.4%	20.00 [2.10 , 37.90]	? - + + ? -
Saher 2021	54.8	8.03	17	42.2	8.79	17	3.5%	12.60 [6.94 , 18.26]	? - ? + ? -
Saka 2021	54.45	10	20	2.75	4.88	20	3.6%	51.70 [46.82 , 56.58]	? + + + ? ?
Sanchez Riera 2001	66.1	15.8	9	48.5	17.3	9	2.7%	17.60 [2.29 , 32.91]	? + + + ? ?
Scherer 2000	19.7	16.65	15	12.3	14.33	15	3.1%	7.40 [-3.72 , 18.52]	? + ? + ? ?
Weiner 2003	85.8	12.16	8	59	11.87	8	3.0%	26.80 [15.02 , 38.58]	? + + + - -
Weiner 2006	58.7	7.85	14	51.2	5.91	14	3.6%	7.50 [2.35 , 12.65]	? + + + ? ?
Wu 2017 (3)	45.11	8.71	21	37.21	7.66	10	3.5%	7.90 [1.87 , 13.93]	? + + + ? ?
Wu 2017 (1)	45.77	5.84	19	37.21	7.66	10	3.6%	8.56 [3.13 , 13.99]	? + + + ? ?
Xu 2018	9.83	6.857	23	2.15	4.3	23	3.7%	7.68 [4.37 , 10.99]	+ + + + + +
ZhouL 2016	75.65	19.35	22	55.29	9.15	22	3.3%	20.36 [11.42 , 29.30]	+ ? ? + ? ?
Total (95% CI)			**485**			**431**	**100.0%**	**14.57 [9.85 , 19.29]**	

Heterogeneity: Tau² = 155.22; Chi² = 310.19, df = 33 (P < 0.00001); I² = 89%
Test for overall effect: Z = 6.05 (P < 0.00001)
Test for subgroup differences: Not applicable

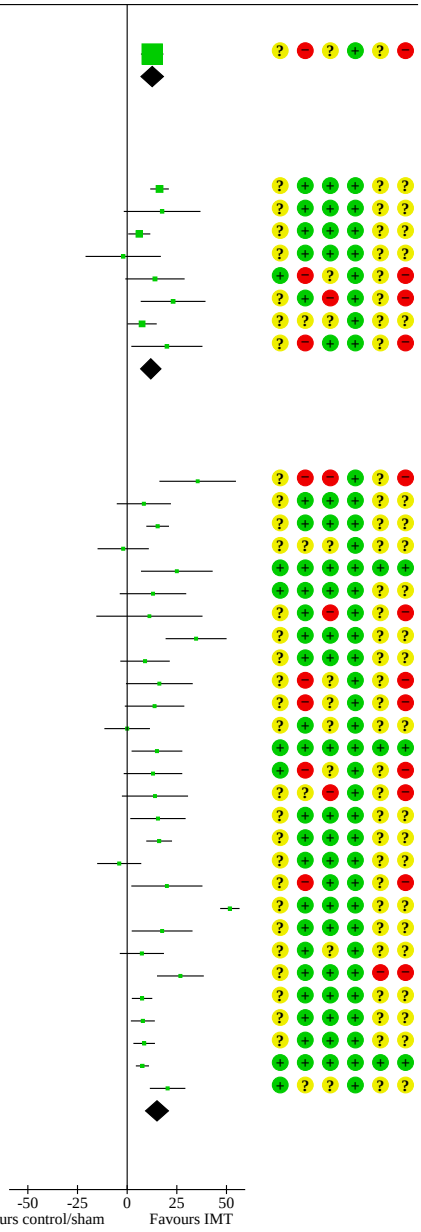


Footnotes
(1) Threshold device
(2) Incentive spirometer
(3) Pflex device

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.16. Comparison 2: IMT vs control/sham, Outcome 16: Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: duration of the intervention)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
2.16.1 Short-term (<4 weeks)								
Saher 2021	54.8	8.03	17	42.2	8.79	17	100.0%	12.60 [6.94 , 18.26]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**12.60 [6.94 , 18.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.36 (P < 0.0001)								
2.16.2 Medium-term (≥4 weeks and <8 weeks)								
Belman 1988	21.3	5.736	8	5	3.788	9	24.5%	16.30 [11.62 , 20.98]
Bustamante 2007	104.3	22.4	12	86.7	23.5	10	5.7%	17.60 [-1.71 , 36.91]
Chuang 2017	39.56	10.02	27	33.46	10.98	28	22.6%	6.10 [0.55 , 11.65]
Koppers 2006	73	28	18	75	30	18	5.9%	-2.00 [-20.96 , 16.96]
Larson 1988	75	18	10	61	16	10	8.5%	14.00 [-0.93 , 28.93]
Leelarungrayub 2017	84	22.35	10	60.87	13.88	10	7.5%	23.13 [6.82 , 39.44]
Nikoletou 2016	9.6	10.87	21	2.09	12.388	18	18.8%	7.51 [0.14 , 14.88]
Ramirez Sarmiento 2002	99	22	7	79	10	7	6.5%	20.00 [2.10 , 37.90]
Subtotal (95% CI)			**113**			**110**	**100.0%**	**11.89 [6.76 , 17.02]**
Heterogeneity: Tau² = 22.26; Chi² = 14.02, df = 7 (P = 0.05); I² = 50%								
Test for overall effect: Z = 4.54 (P < 0.00001)								
2.16.3 Long-term (≥8 weeks)								
Beckerman 2005	101.1	29.27	17	65.6	25.44	14	2.9%	35.50 [16.23 , 54.77]
Berton 2015	112.1	12.8	7	103.7	12.24	6	3.5%	8.40 [-5.23 , 22.03]
Chuang 2017	48.56	10.18	27	33.21	11.4	28	4.2%	15.35 [9.64 , 21.06]
Covey 2001	75	17	12	77	17	15	3.6%	-2.00 [-14.90 , 10.90]
Cutrim 2019	84	26	11	59	16	11	3.0%	25.00 [6.96 , 43.04]
Dacha 2019	94	20	6	81	5	4	3.2%	13.00 [-3.74 , 29.74]
Harver 1989	94.5	27.9	10	83.3	31.2	9	2.2%	11.20 [-15.53 , 37.93]
Heijdra 1996	93.8	20.3	10	59.1	14.2	10	3.3%	34.70 [19.35 , 50.05]
Hill 2006	80.7	17.8	16	71.7	18.7	17	3.6%	9.00 [-3.45 , 21.45]
Hsiao 2003 (1)	26.8	19.4	10	10.6	13.4	5	3.2%	16.20 [-0.61 , 33.01]
Hsiao 2003 (2)	24.4	15	10	10.6	13.4	5	3.4%	13.80 [-1.18 , 28.78]
Kim 1993	78	25	40	78	22	26	3.7%	0.00 [-11.47 , 11.47]
Langer 2018	21	16	10	6	13	10	3.6%	15.00 [2.22 , 27.78]
Larson 1988	73	19	10	60	15	11	3.4%	13.00 [-1.74 , 27.74]
Larson 1999	100	25	13	86	17	12	3.2%	14.00 [-2.65 , 30.65]
Lisboa 1997	93	17.39	10	77.5	14.23	10	3.5%	15.50 [1.57 , 29.43]
Petrovic 2012	93.3	7.4	10	77.2	7.4	10	4.1%	16.10 [9.61 , 22.59]
Preusser 1994	42	17	12	46	8	8	3.7%	-4.00 [-15.10 , 7.10]
Ramirez Sarmiento 2002	99	22	7	79	10	7	3.1%	20.00 [2.10 , 37.90]
Saka 2021	54.45	10	20	2.75	4.88	20	4.2%	51.70 [46.82 , 56.58]
Sanchez Riera 2001	66.1	15.8	9	48.5	17.3	9	3.3%	17.60 [2.29 , 32.91]
Scherer 2000	19.7	16.65	15	12.3	14.33	15	3.7%	7.40 [-3.72 , 18.52]
Weiner 2003	85.8	12.16	8	59	11.87	8	3.7%	26.80 [15.02 , 38.58]
Weiner 2006	58.7	7.85	14	51.2	5.91	14	4.2%	7.50 [2.35 , 12.65]
Wu 2017 (3)	45.11	8.71	21	37.21	7.66	10	4.1%	7.90 [1.87 , 13.93]
Wu 2017 (1)	45.77	5.84	19	37.21	7.66	10	4.2%	8.56 [3.13 , 13.99]
Xu 2018	9.83	6.85	23	2.15	4.3	23	4.3%	7.68 [4.37 , 10.99]
ZhouL 2016	75.65	19.35	22	55.29	9.15	22	3.9%	20.36 [11.42 , 29.30]
Subtotal (95% CI)			**399**			**349**	**100.0%**	**15.02 [9.26 , 20.78]**
Heterogeneity: Tau² = 198.85; Chi² = 301.25, df = 27 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.67, df = 2 (P = 0.72), I² = 0%								



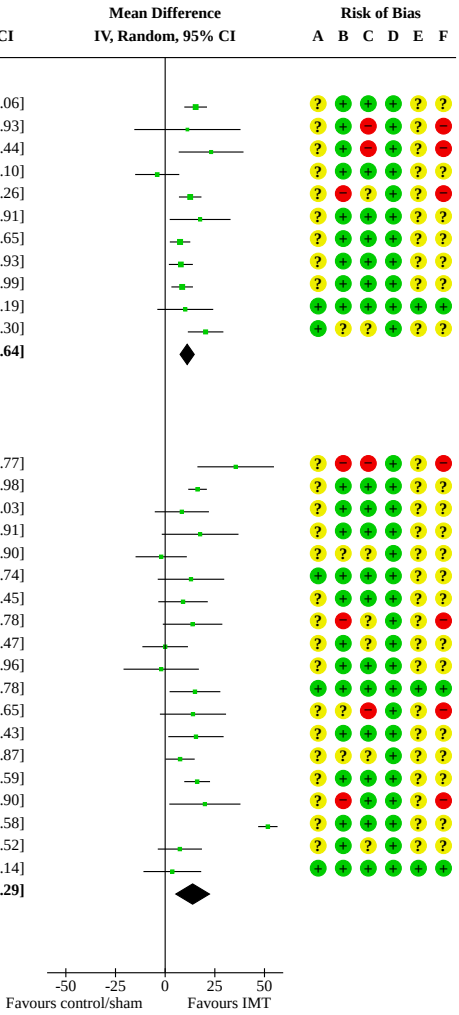
Footnotes

(1) Threshold device
(2) Incentive spirometer
(3) Pflex device

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.17. Comparison 2: IMT vs control/sham, Outcome 17: Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: with or without respiratory muscle weakness)



Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
2.17.1 With respiratory muscle weakness														
Chuang 2017	48.56	10.18	27	33.21	11.4	28	13.7%	15.35 [9.64 , 21.06]	?	+	+	+	?	?
Harver 1989	94.5	27.9	10	83.3	31.2	9	1.6%	11.20 [-15.53 , 37.93]	?	+	−	+	?	−
Leelarungrayub 2017	84	22.35	10	60.87	13.88	10	3.9%	23.13 [6.82 , 39.44]	?	+	−	+	?	−
Preusser 1994	42	17	12	46	8	8	6.9%	-4.00 [-15.10 , 7.10]	?	+	+	+	?	?
Saher 2021	54.8	8.03	17	42.2	8.79	17	13.7%	12.60 [6.94 , 18.26]	?	−	?	+	?	−
Sanchez Riera 2001	66.1	15.8	9	48.5	17.3	9	4.3%	17.60 [2.29 , 32.91]	?	+	+	+	?	?
Weiner 2006	58.7	7.85	14	51.2	5.91	14	14.6%	7.50 [2.35 , 12.65]	?	+	+	+	?	?
Wu 2017 (1)	45.11	8.71	21	37.21	7.66	10	13.1%	7.90 [1.87 , 13.93]	?	+	+	+	?	?
Wu 2017 (2)	45.77	5.84	19	37.21	7.66	10	14.1%	8.56 [3.13 , 13.99]	?	+	+	+	?	?
Xu 2018	12.7	23	14	2.576	12.3	11	4.9%	10.12 [-3.95 , 24.19]	+	+	+	+	+	+
ZhouL 2016	75.65	19.35	22	55.29	9.15	22	9.0%	20.36 [11.42 , 29.30]	+	?	?	+	?	?
Subtotal (95% CI)			**175**			**148**	**100.0%**	**11.08 [7.51 , 14.64]**						
Heterogeneity: Tau² = 15.69; Chi² = 20.13, df = 10 (P = 0.03); I² = 50%														
Test for overall effect: Z = 6.09 (P < 0.00001)														
2.17.2 Without respiratory muscle weakness														
Beckerman 2005	101.1	29.27	17	65.6	25.44	14	4.6%	35.50 [16.23 , 54.77]	?	−	−	+	?	−
Belman 1988	21.3	5.736	8	5	3.788	9	6.0%	16.30 [11.62 , 20.98]	?	+	+	+	?	?
Berton 2015	112.1	12.8	7	103.7	12.24	6	5.3%	8.40 [-5.23 , 22.03]	?	+	+	+	?	?
Bustamante 2007	104.3	22.4	12	86.7	23.5	10	4.6%	17.60 [-1.71 , 36.91]	?	+	+	+	?	?
Covey 2001	75	17	12	77	17	15	5.3%	-2.00 [-14.90 , 10.90]	?	?	?	+	?	?
Dacha 2019	94	20	6	81	5	4	4.9%	13.00 [-3.74 , 29.74]	+	+	+	+	?	?
Hill 2006	80.7	17.8	16	71.7	18.7	17	5.4%	9.00 [-3.45 , 21.45]	?	+	+	+	?	?
Hsiao 2003 (3)	24.4	15	10	10.6	13.4	5	5.1%	13.80 [-1.18 , 28.78]	?	−	?	+	?	−
Kim 1993	78	25	40	78	22	26	5.5%	0.00 [-11.47 , 11.47]	?	+	?	+	?	?
Koppers 2006	73	28	18	75	30	18	4.7%	-2.00 [-20.96 , 16.96]	?	+	+	+	?	?
Langer 2018	21	16	10	6	13	10	5.3%	15.00 [2.22 , 27.78]	+	+	+	+	+	+
Larson 1999	100	25	13	86	17	12	4.9%	14.00 [-2.65 , 30.65]	?	?	−	+	?	−
Lisboa 1997	93	17.39	10	77.5	14.23	10	5.2%	15.50 [1.57 , 29.43]	?	+	+	+	?	?
Nikoletou 2016	9.6	10.87	21	2.09	12.338	18	5.8%	7.51 [0.15 , 14.87]	?	?	?	+	?	?
Petrovic 2012	93.3	7.4	10	77.2	7.4	10	5.9%	16.10 [9.61 , 22.59]	?	+	+	+	?	?
Ramirez Sarmiento 2002	99	22	7	79	10	7	4.8%	20.00 [2.10 , 37.90]	?	−	+	+	?	−
Saka 2021	54.45	10	20	2.75	4.88	20	6.0%	51.70 [46.82 , 56.58]	?	+	+	+	?	?
Scherer 2000	19.7	16.65	15	12.3	14.33	15	5.5%	7.40 [-3.72 , 18.52]	?	+	?	+	?	?
Xu 2018	5.367	16.67	9	1.758	17.01	12	5.2%	3.61 [-10.92 , 18.14]	+	+	+	+	+	+
Subtotal (95% CI)			**261**			**238**	**100.0%**	**13.82 [5.36 , 22.29]**						
Heterogeneity: Tau² = 306.06; Chi² = 226.02, df = 18 (P < 0.00001); I² = 92%														
Test for overall effect: Z = 3.20 (P = 0.001)														
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² = 0%														

Footnotes

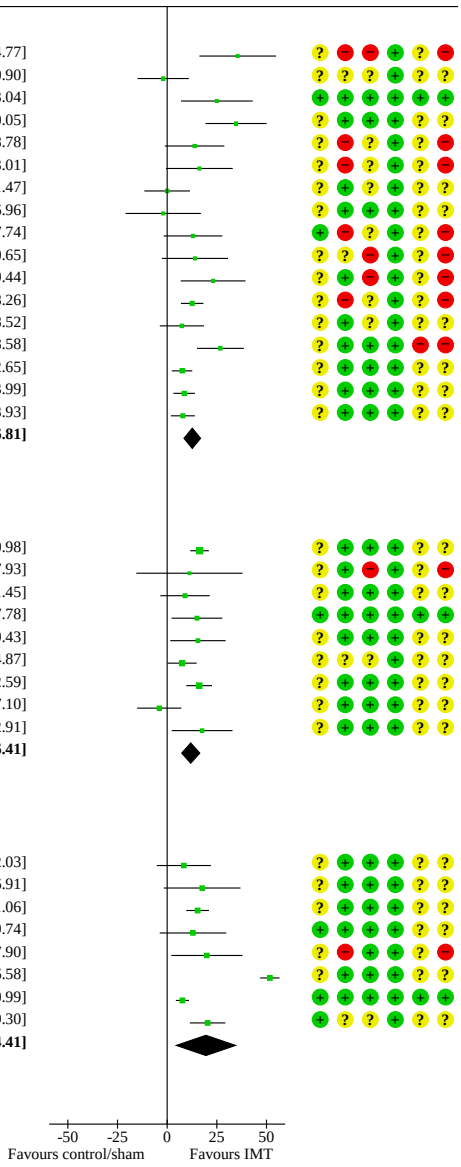
(1) Pflex device
(2) Threshold device
(3) Incentive spirometer

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.18. Comparison 2: IMT vs control/sham, Outcome 18: Inspiratory muscle strength: PImax (cmH_2O) (subgroup analysis: method of measurement)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
2.18.1 Residual Volume (RV)									
Beckerman 2005	101.1	29.27	17	65.6	25.44	14	3.4%	35.50 [16.23 , 54.77]	? - - + ? -
Covey 2001	75	17	12	77	17	15	5.5%	-2.00 [-14.90 , 10.90]	? ? ? + ? ?
Cutrim 2019	84	26	11	59	16	11	3.7%	25.00 [6.96 , 43.04]	+ + + + + +
Heijdra 1996	93.8	20.3	10	59.1	14.2	10	4.5%	34.70 [19.35 , 50.05]	? + + + ? ?
Hsiao 2003 (1)	24.4	15	10	10.6	13.4	5	4.7%	13.80 [-1.18 , 28.78]	? - ? + ? -
Hsiao 2003 (2)	26.8	19.4	10	10.6	13.4	5	4.0%	16.20 [-0.61 , 33.01]	? - ? + ? -
Kim 1993	78	25	40	78	22	26	6.2%	0.00 [-11.47 , 11.47]	? + ? + ? ?
Koppers 2006	73	28	18	75	30	18	3.4%	-2.00 [-20.96 , 16.96]	? + + + ? ?
Larson 1988	73	19	10	60	15	11	4.8%	13.00 [-1.74 , 27.74]	+ - ? + ? -
Larson 1999	100	25	13	86	17	12	4.1%	14.00 [-2.65 , 30.65]	? ? - + ? -
Leelarungrayub 2017	84	22.35	10	60.87	13.88	10	4.2%	23.13 [6.82 , 39.44]	? + - + ? -
Saher 2021	54.8	8.03	17	42.2	8.79	17	9.7%	12.60 [6.94 , 18.26]	? - ? + ? -
Scherer 2000	19.7	16.65	15	12.3	14.33	15	6.4%	7.40 [-3.72 , 18.52]	? + ? + ? ?
Weiner 2003	85.8	12.16	8	59	11.87	8	6.1%	26.80 [15.02 , 38.58]	? + + + - -
Weiner 2006	58.7	7.85	14	51.2	5.91	14	10.0%	7.50 [2.35 , 12.65]	? + + + ? ?
Wu 2017 (2)	45.77	5.84	19	37.21	7.66	10	9.8%	8.56 [3.13 , 13.99]	? + + + ? ?
Wu 2017 (3)	45.11	8.71	21	37.21	7.66	10	9.4%	7.90 [1.87 , 13.93]	? + + + ? ?
Subtotal (95% CI)			**255**			**211**	**100.0%**	**12.63 [8.46 , 16.81]**	
Heterogeneity: Tau² = 38.55; Chi² = 40.87, df = 16 (P = 0.0006); I² = 61%									
Test for overall effect: Z = 5.93 (P < 0.00001)									
2.18.2 Functional Residual Capacity (FRC)									
Belman 1988	21.3	5.736	8	5	3.788	9	21.3%	16.30 [11.62 , 20.98]	? + + + ? ?
Harver 1989	94.5	27.9	10	83.3	31.2	9	2.6%	11.20 [-15.53 , 37.93]	? + - + ? -
Hill 2006	80.7	17.8	16	71.7	18.7	17	9.0%	9.00 [-3.45 , 21.45]	? + + + ? ?
Langer 2018	21	16	10	6	13	10	8.7%	15.00 [2.22 , 27.78]	+ + + + + +
Lisboa 1997	93	17.39	10	77.5	14.23	10	7.7%	15.50 [1.57 , 29.43]	? + + + ? ?
Nikoletou 2016	9.6	10.87	21	2.09	12.338	18	16.0%	7.51 [0.15 , 14.87]	? ? ? + ? ?
Petrovic 2012	93.3	7.4	10	77.2	7.4	10	17.7%	16.10 [9.61 , 22.59]	? + + + ? ?
Preusser 1994	42	17	12	46	8	8	10.4%	-4.00 [-15.10 , 7.10]	? + + + ? ?
Sanchez Riera 2001	66.1	15.8	9	48.5	17.3	9	6.7%	17.60 [2.29 , 32.91]	? + + + ? ?
Subtotal (95% CI)			**106**			**100**	**100.0%**	**11.87 [7.33 , 16.41]**	
Heterogeneity: Tau² = 19.40; Chi² = 14.91, df = 8 (P = 0.06); I² = 46%									
Test for overall effect: Z = 5.13 (P < 0.00001)									
2.18.3 Not reported									
Berton 2015	112.1	12.8	7	103.7	12.24	6	12.3%	8.40 [-5.23 , 22.03]	? + + + ? ?
Bustamante 2007	104.3	22.4	12	86.7	23.5	10	11.1%	17.60 [-1.71 , 36.91]	? + + + ? ?
Chuang 2017	48.56	10.18	27	33.21	11.4	28	13.4%	15.35 [9.64 , 21.06]	? + + + ? ?
Dacha 2019	94	20	6	81	5	4	11.7%	13.00 [-3.74 , 29.74]	+ + + + ? ?
Ramirez Sarmiento 2002	99	22	7	79	10	7	11.4%	20.00 [2.10 , 37.90]	? - + + ? -
Saka 2021	54.45	10	20	2.75	4.88	20	13.5%	51.70 [46.82 , 56.58]	? + + + ? ?
Xu 2018	9.83	6.857	23	2.15	4.3	23	13.6%	7.68 [4.37 , 10.99]	+ + + + + +
ZhouL 2016	75.65	19.35	22	55.29	9.15	22	13.0%	20.36 [11.42 , 29.30]	+ ? ? + ? ?
Subtotal (95% CI)			**124**			**120**	**100.0%**	**19.52 [4.63 , 34.41]**	
Heterogeneity: Tau² = 421.84; Chi² = 221.67, df = 7 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 2.57 (P = 0.01)									
Test for subgroup differences: Chi² = 0.93, df = 2 (P = 0.63), I² = 0%									



Footnotes

(1) Incentive spirometer
(2) Threshold device
(3) Pflex device

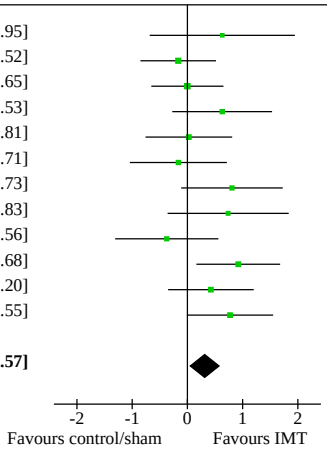
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.19. Comparison 2: IMT vs control/sham, Outcome 19: Laboratory exercise test: VO_2peak

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI
Dacha 2019	1.32	0.47	6	1.03	0.3	4	3.7%	0.63 [-0.68 , 1.95]
Hill 2006	0.868	0.219	16	0.913	0.301	17	11.7%	-0.17 [-0.85 , 0.52]
Koppers 2006	19.9	4.7	18	19.9	5.1	18	12.6%	0.00 [-0.65 , 0.65]
Langer 2018	0.01	0.05	10	-0.03	0.07	10	7.3%	0.63 [-0.27 , 1.53]
Larson 1999	1.3	0.31	13	1.29	0.42	12	9.3%	0.03 [-0.76 , 0.81]
Lisboa 1997	0.75	0.19	10	0.78	0.16	10	7.7%	-0.16 [-1.04 , 0.71]
Petrovic 2012	1.9	0.24	10	1.71	0.21	10	7.1%	0.81 [-0.11 , 1.73]
Ramirez Sarmiento 2002	15	5	7	12	2	7	5.1%	0.74 [-0.36 , 1.83]
Sanchez Riera 2001	1.1	0.2	9	1.2	0.3	9	6.9%	-0.37 [-1.31 , 0.56]
Scherer 2000	2.5	2.32	15	-0.3	3.48	15	9.9%	0.92 [0.16 , 1.68]
Wu 2017 (1)	0.88	0.13	19	0.82	0.15	10	9.5%	0.43 [-0.35 , 1.20]
Wu 2017 (2)	0.95	0.17	21	0.82	0.15	10	9.4%	0.77 [-0.01 , 1.55]
Total (95% CI)			**154**			**132**	**100.0%**	**0.31 [0.05 , 0.57]**

Heterogeneity: Tau² = 0.03; Chi² = 12.74, df = 11 (P = 0.31); I² = 14%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable

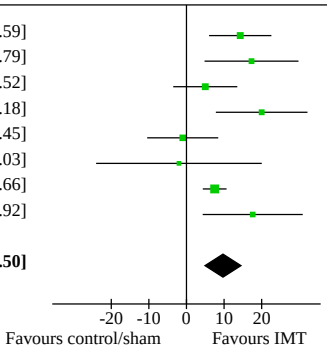


Footnotes
(1) Threshold device
(2) Pflex device

Analysis 2.20. Comparison 2: IMT vs control/sham, Outcome 20: Respiratory muscle endurance: respiratory muscle endurance pressure (P_{thmax}) (cmH_2O)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Belman 1988	50	8.7	8	35.7	8.7	9	15.1%	14.30 [6.01 , 22.59]
Hill 2006	60.1	18	16	42.8	18.6	17	9.6%	17.30 [4.81 , 29.79]
Koppers 2006	31	14	18	26	12	18	14.7%	5.00 [-3.52 , 13.52]
Larson 1999	69	15	13	49	16	12	9.9%	20.00 [7.82 , 32.18]
Preusser 1994	34	15	12	35	6	8	13.3%	-1.00 [-10.45 , 8.45]
Ramirez Sarmiento 2002	39	22	7	41	20	7	4.0%	-2.00 [-24.03 , 20.03]
Sanchez Riera 2001	27.5	4.2	9	20	2.4	9	24.6%	7.50 [4.34 , 10.66]
Weiner 2003	59.52	13.85	8	41.9	13.29	8	8.8%	17.62 [4.32 , 30.92]
Total (95% CI)			**91**			**88**	**100.0%**	**9.71 [4.93 , 14.50]**

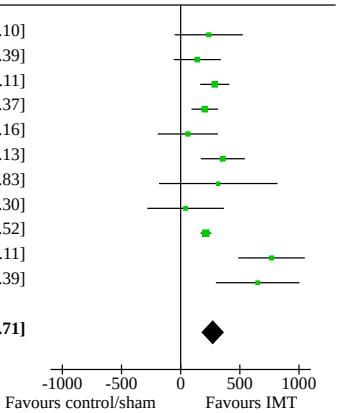
Heterogeneity: Tau² = 21.61; Chi² = 14.81, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 3.98 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.21. Comparison 2: IMT vs control/sham, Outcome 21: Respiratory muscle endurance time: T_{lim} (seconds)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Bustamante 2007 (1)	639.6	330	12	402.6	354	10	6.3%	237.00 [-51.10 , 525.10]
Hill 2007 (2)	836.4	154.8	16	696	387	17	9.7%	140.40 [-58.59 , 339.39]
Hsiao 2003 (3)	264	192	10	-24	36	5	14.0%	288.00 [164.89 , 411.11]
Hsiao 2003 (4)	180	174	10	-24	36	5	14.7%	204.00 [91.63 , 316.37]
Kim 1993 (1)	417.6	351.6	39	357	558.6	23	7.4%	60.60 [-192.96 , 314.16]
Langer 2018 (5)	467	259	10	111	152	10	10.4%	356.00 [169.87 , 542.13]
Larson 1988 (1)	726	732	9	408	240	10	2.7%	318.00 [-182.83 , 818.83]
Nikoletou 2016 (6)	62.33	373.94	6	20.75	126.1	4	5.4%	41.58 [-282.14 , 365.30]
Petrovic 2012 (7)	467.4	58.2	10	253.8	43.2	10	18.3%	213.60 [168.68 , 258.52]
Ramirez Sarmiento 2002 (8)	1320	360	7	552	120	7	6.5%	768.00 [486.89 , 1049.11]
Scherer 2000 (9)	883.8	681.6	15	233.4	148.2	15	4.7%	650.40 [297.41 , 1003.39]
Total (95% CI)			**144**			**116**	**100.0%**	**270.57 [182.44 , 358.71]**

Heterogeneity: Tau² = 10507.44; Chi² = 26.76, df = 10 (P = 0.003); I² = 63%
Test for overall effect: Z = 6.02 (P < 0.00001)
Test for subgroup differences: Not applicable

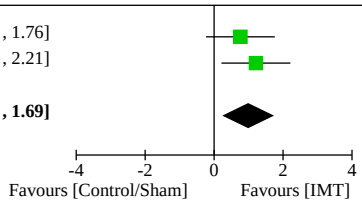


Footnotes
(1) Breathing against 66% of PImax
(2) Breathing against ≈80% of PImax
(3) Breathing against 70% of PImax (Threshold device)
(4) Breathing against 70% of PImax (resistive device) Incentive spirometer
(5) Breathing against 50-60% of PImax
(6) Breathing against 50% of Poesmax
(7) Breathing against 60% of PImax
(8) Breathing against 80% of PImax
(9) Sustained ventilation at 66% or 75% of MVV

Analysis 2.22. Comparison 2: IMT vs control/sham, Outcome 22: Maximal voluntary ventilation (MVV)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Std. Mean Difference IV, Random, 95% CI
Belman 1988	54	19.79	8	40	15	9	50.1%	0.76 [-0.23 , 1.76]
Harver 1989	47.2	13.4	10	31.6	10.9	9	49.9%	1.21 [0.21 , 2.21]
Total (95% CI)			**18**			**18**	**100.0%**	**0.99 [0.28 , 1.69]**

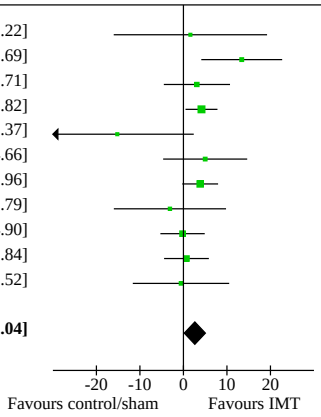
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 2.23. Comparison 2: IMT vs control/sham, Outcome 23: Respiratory function: forced expiratory volume at 1 second (FEV1) (%pred)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Bavarsad 2015	65	26.15	15	63.4	22.99	15	1.8%	1.60 [-16.02 , 19.22]
Harver 1989	45.5	9.5	10	32.1	11.6	10	5.8%	13.40 [4.11 , 22.69]
Hill 2006	35.7	12.7	16	32.6	9.2	17	8.2%	3.10 [-4.51 , 10.71]
Leelarungrayub 2017	65.3	2.62	10	61.15	5.31	10	21.3%	4.15 [0.48 , 7.82]
Majewska-Pulsakowska 2016	50.1	20.4	8	65.3	19.2	13	1.8%	-15.20 [-32.77 , 2.37]
Ramirez Sarmiento 2002	34	11	7	29	7	7	5.5%	5.00 [-4.66 , 14.66]
Saka 2021	4.3	8.47	20	0.45	4.05	20	18.9%	3.85 [-0.26 , 7.96]
Scherer 2000	0.6	20.52	15	3.7	15.1	15	3.3%	-3.10 [-15.99 , 9.79]
Wu 2017 (1)	53.3	5.13	19	53.5	7.33	10	14.7%	-0.20 [-5.30 , 4.90]
Wu 2017 (2)	54.2	5.63	21	53.5	7.33	10	14.5%	0.70 [-4.44 , 5.84]
Xu 2018	-0.82	21.58	23	-0.26	16.4	23	4.3%	-0.56 [-11.64 , 10.52]
Total (95% CI)			**164**			**150**	**100.0%**	**2.62 [0.20 , 5.04]**

Heterogeneity: Tau² = 3.68; Chi² = 13.15, df = 10 (P = 0.22); I² = 24%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable

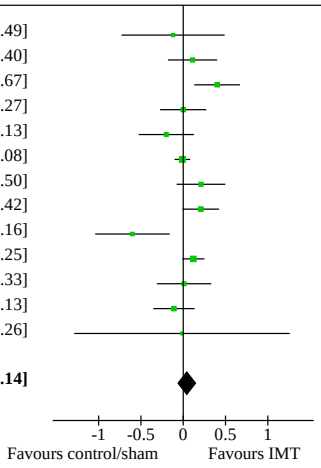


Footnotes
(1) Threshold device
(2) Pflex device

Analysis 2.24. Comparison 2: IMT vs control/sham, Outcome 24: Respiratory function: forced expiratory volume at 1 second (FEV1) (Liters)

Study or Subgroup	IMT Mean	IMT SD	IMT Total	Control/Sham Mean	Control/Sham SD	Control/Sham Total	Weight	Mean Difference IV, Random, 95% CI
Bavarsad 2015	1.9	0.91	15	2.02	0.79	15	2.5%	-0.12 [-0.73 , 0.49]
Belman 1988	1	0.14	8	0.89	0.42	9	7.4%	0.11 [-0.18 , 0.40]
Harver 1989	1.3	0.3	10	0.9	0.3	9	8.1%	0.40 [0.13 , 0.67]
Hill 2006	1	0.4	16	1	0.4	17	8.0%	0.00 [-0.27 , 0.27]
Koppers 2006	1.6	0.5	18	1.8	0.5	18	6.4%	-0.20 [-0.53 , 0.13]
Langer 2018	0.01	0.1	10	0.02	0.11	10	15.8%	-0.01 [-0.10 , 0.08]
Leelarungrayub 2017	1.85	0.22	10	1.64	0.41	10	7.5%	0.21 [-0.08 , 0.50]
Lisboa 1997	1	0.31	10	0.792	0.16	10	10.1%	0.21 [-0.01 , 0.42]
Majewska-Pulsakowska 2016	1.1	0.5	8	1.7	0.5	13	4.2%	-0.60 [-1.04 , -0.16]
Saka 2021	0.13	0.27	20	0.01	0.13	20	14.0%	0.12 [-0.01 , 0.25]
Wu 2017 (1)	1.83	0.54	21	1.82	0.36	10	6.5%	0.01 [-0.31 , 0.33]
Wu 2017 (2)	1.71	0.22	19	1.82	0.36	10	9.0%	-0.11 [-0.35 , 0.13]
Xu 2018	-0.02	2.5	23	-0.005	1.86	23	0.6%	-0.01 [-1.29 , 1.26]
Total (95% CI)			**188**			**174**	**100.0%**	**0.04 [-0.06 , 0.14]**

Heterogeneity: Tau² = 0.02; Chi² = 25.27, df = 12 (P = 0.01); I² = 53%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Footnotes
(1) Pflex device
(2) Threshold device

APPENDICES

Appendix 1. Database search strategies

Database/search platform/date of last search	Search strategy	Results
Airways Register (via Cochrane Register of Studies) Date of most recent search: 19 October 2022	1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All AND INSEGMENT 2 MeSH DESCRIPTOR Bronchitis, Chronic AND INSEGMENT 3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) AND INSEGMENT 4 COPD:MISC1 AND INSEGME 5 (COPD OR AECOPD):TI,AB,KW AND INSEGMENT 6 #1 OR #2 OR #3 OR #4 OR #5 AND INSEGMENT 7 MESH DESCRIPTOR Breathing Exercises AND INSEGMENT 8 MESH DESCRIPTOR Respiratory Muscles EXPLODE ALL AND INSEGMENT 9 MESH DESCRIPTOR Exercise Tolerance AND INSEGMENT 10 (IMT or RMT):ti,ab AND INSEGMENT 11 ((inspiratory or ventilat* or respiratory) NEAR3 (muscle or resistance) NEAR3 (train* or strength* or endur*)) AND INSEGMENT 12 (threshold NEAR2 (load or device*)) AND INSEGMENT 13 (resist* NEAR2 device*) AND INSEGMENT 14 isocapnic hyperpnea AND INSEGMENT 15 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #14 OR #13 16 #6 AND #15 17 INREGISTER 18 #16 AND #17	Oct 2020=937 Aug 2021=44 Oct 2022=265 (together with CENTRAL)
CENTRAL (via Cochrane Register of Studies) Date of most recent search: 19 October 2022	1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All AND CENTRAL:TARGET 2 MeSH DESCRIPTOR Bronchitis, Chronic AND CENTRAL:TARGET 3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) AND CENTRAL:TARGET 4 COPD:MISC1 AND CENTRAL:TARGET 5 (COPD OR AECOPD):TI,AB,KW AND CENTRAL:TARGET 6 #1 OR #2 OR #3 OR #4 OR #5 AND CENTRAL:TARGET 7 MESH DESCRIPTOR Breathing Exercises AND CENTRAL:TARGET 8 MESH DESCRIPTOR Respiratory Muscles EXPLODE ALL AND CENTRAL:TARGET 9 MESH DESCRIPTOR Exercise Tolerance AND CENTRAL:TARGET 10 (IMT or RMT):ti,ab AND CENTRAL:TARGET 11 ((inspiratory or ventilat* or respiratory) NEAR3 (muscle or resistance) NEAR3 (train* or strength* or endur*)) AND CENTRAL:TARGET 12 (threshold NEAR2 (load or device*)) AND CENTRAL:TARGET 13 (resist* NEAR2 device*) AND CENTRAL:TARGET 14 isocapnic hyperpnea AND CENTRAL:TARGET 15 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #14 OR #13 AND CENTRAL:TARGET 16 #6 AND #15 AND CENTRAL:TARGET	Oct 2020=1239 Aug 2021=69 Oct 2022=265 (together with the Airways Register)

(Continued)

	17 CENTRAL:TARGET 18 #16 AND #17 AND CENTRAL:TARGET	
MEDLINE (Ovid) ALL Date of most recent search: 20 October 2022	1 Lung Diseases, Obstructive/ 2 exp Pulmonary Disease, Chronic Obstructive/ 3 emphysema$.tw. 4 (chronic$ adj3 bronchiti$).tw. 5 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 6 (COPD or AECOPD or AECB).ti,ab. 7 or/1-6 8 Breathing Exercises/ 9 exp Respiratory Muscles/ 10 Exercise Tolerance/ 11 Muscle Strength/ 12 (IMT or RMT).ti,ab. 13 ((inspiratory or ventilat$ or respiratory) adj3 (muscle or resistance) adj3 (train$ or strength$ or endur$)).tw. 14 (threshold adj2 (load or device$)).tw. 15 (resist$ adj2 device$).tw. 16 isocapnic hyperpnea.tw. 17 or/8-16 18 (controlled clinical trial or randomized controlled trial).pt. 19 (randomized or randomised).ab,ti. 20 placebo.ab,ti. 21 randomly.ab,ti. 22 trial.ab,ti. 23 groups.ab,ti. 24 or/18-23 25 Animals/ 26 Humans/ 27 25 not (25 and 26) 28 24 not 27 29 7 and 17 and 28	Oct 2020=1609 Aug 2021=86 Oct 2022=172
Embase (Ovid) Date of most recent search: 20 October 2022	1 Chronic Obstructive Lung Disease/ 2 Obstructive Airway Disease/ 3 Chronic Bronchitis/ 4 Lung Emphysema/ 5 emphysema$.tw. 6 (chronic$ adj3 bronchiti$).tw. 7 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 8 (COPD or AECOPD or AECB).ti,ab. 9 or/1-8 10 breathing exercise/ 11 breathing muscle/ 12 exercise tolerance/ 13 muscle strength/ 14 (IMT or RMT).ti,ab. 15 ((inspiratory or ventilat$ or respiratory) adj3 (muscle or resistance) adj3 (train$ or strength$ or endur$)).tw. 16 (threshold adj2 (load or device$)).tw. 17 (resist$ adj2 device$).tw. 18 isocapnic hyperpnea.tw. 19 or/10-18 20 Randomized Controlled Trial/ 21 randomization/ 22 controlled clinical trial/ 23 Double Blind Procedure/	Oct 2020=2093 Aug 2021=146 Oct 2022=251

(Continued)

	24 Single Blind Procedure/ 25 Crossover Procedure/ 26 (clinica$ adj3 trial$).tw. 27 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method $)).tw. 28 exp Placebo/ 29 placebo$.ti,ab. 30 random$.ti,ab. 31 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 32 (crossover$ or cross-over$).ti,ab. 33 or/20-32 34 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 35 human/ or normal human/ or human cell/ 36 34 and 35 37 34 not 36 38 33 not 37 39 9 and 19 and 38	
CINHAL (EBSCO) Date of most recent search: 19 October 2022	S41 S7 AND S17 AND S40 S40 S39 NOT S38 S39 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 S38 S36 NOT S37 S37 (MH "Human") S36 S33 OR S34 OR S35 S35 TI (animal model*) S34 (MH "Animal Studies") S33 (MH "Animals+") S32 AB (cluster W3 RCT) S31 MH (crossover design) OR MH (comparative studies) S30 AB (control W5 group) S29 PT (Randomized Controlled Trial) S28 (MH "Placebos") S27 MH ("sample size") AND AB (assigned OR allocated OR control) S26 TI (trial) S25 AB (random*) S24 TI (randomised OR randomized) S23 (MH "Cluster Sample") S22 (MH "Pretest-Posttest Design") S21 (MH "Random Assignment") S20 (MH "Single-Blind Studies") S19 (MH "Double-Blind Studies") S18 (MH "Randomized Controlled Trials") S17 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 S16 isocapnic hyperpnea S15 resist* N2 device* S14 threshold* N2 (load or device*) S13 (inspiratory or ventilat* or respiratory) N3 (muscle or resistance) N3 (train* or strength* or endur*) S12 AB (IMT or RMT) or TI (IMT or RMT) S11 (MH "Muscle Strength") S10 (MH "Exercise Tolerance" S9 (MH "Respiratory Muscles+") S8 (MH "Breathing Exercises") S7 S1 or S2 or S3 or S4 or S5 or S6 S6 COPD or COAD or COBD or AECB S5 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) and (obstruct*) and (disease*) S4 chronic bronchitis S3 "emphysema*"	Oct 2020=182 Aug 2021=22 Oct 2022=76

(Continued)

	S2 (MH "Lung Diseases, Obstructive") S1 (MH "Pulmonary Disease, Chronic Obstructive+")	
PsycINFO (Ovid) Date of most recent search: 19 October 2022	1 exp Chronic Obstructive Pulmonary Disease/ 2 emphysema$.tw. 3 (chronic$ adj3 bronchiti$).tw. 4 (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw. 5 (COPD or AECOPD or AECB).ti,ab. 6 or/1-5 7 ((inspiratory or ventilat$ or respiratory) adj3 (muscle or resistance) adj3 (train$ or strength$ or endur$)).tw. 8 (IMT or RMT).ti,ab. 9 (threshold adj2 (load or device$)).tw. 10 (resist$ adj2 device$).tw. 11 isocapnic hyperpnea.tw. 12 or/7-11 13 random$.tw. 14 (clinical adj5 trial$).tw. 15 (control$ adj5 trial$).tw. 16 ((clinical or control$ or comparativ$) adj5 (study or studies)).tw. 17 placebo$.tw. 18 (single blind$ or single-blind$).tw. 19 (double blind$ or double-blind$).tw. 20 (triple blind$ or triple-blind$).tw. 21 or/13-20 22 6 and 12 and 21	Oct 2020=10 August 2021=1 Oct 2022=3
PEDro Date of most recent search: 20 October 2022	Abstract & title: inspiratory muscle copd random* Topic: chronic respiratory disease Method: Clinical trial When searching: Match all search terms (AND)	Oct 2020=81 Aug 2021=1 Oct 2022=5
ClinicalTrials.gov Date of most recent search: 20 October 2022	Study type: Interventional Condition: COPD Intervention: inspiratory muscle training OR threshold load OR threshold device OR resistive device	Oct 2020=58 Aug 2021=6

(Continued)

		Oct 2022=12
WHO trials portal Date of most recent search: 20 October 2022	Condition: COPD Intervention: inspiratory muscle training OR threshold load OR threshold device OR resistive device	Oct 2020=347 Aug 2021=2 Oct 2022=9

HISTORY

Protocol first published: Issue 11, 2020

CONTRIBUTIONS OF AUTHORS

Conception of the review: OA/WF
Co-ordination of the review: OA
Search and collection of studies for inclusion in the review: OA/WF
Data extraction: OA/AK
Assessment of the risk of bias in the included studies: OA/TL
Analysis of data: OA/AK
Assessment of certainty in the body of evidence: OA/TL
Interpretation of data: WF/SK
Writing the review: OA
Clinical and statistical comments: RG/AR

Contributions of editorial team

Sally Spencer (Co-ordinating Editor) edited the review; advised on methodology, interpretation and content; and approved the review prior to publication.
Rebecca Fortescue (Co-ordinating Editor) checked the data in the review.
Anne Holland (Contact Editor): edited the review; and advised on methodology, interpretation and content.
Emma Dennett (Deputy Co-ordinating Editor): advised on methodology, interpretation and content; and edited the review.
Emma Jackson (Managing Editor): co-ordinated the editorial process; conducted peer review; obtained translations; and edited the plain language summary and reference sections of the review.
Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; and edited the search methods section.

Vittoria Lutje (Freelance Information Specialist): ran the updated search.

Kayleigh Kew (Freelance Editor): edited the review and advised on methodology.

DECLARATIONS OF INTEREST

OA: none known
RG: none known
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TL: none known
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because few studies used the Borg scale and reported it at different levels of effort, we decided to replace it with PImax for subgroup analysis. The 6MWD and PImax are respectively clinical and physiological outcomes, and we believed that analysing both outcomes together would present an opportunity to check for the possible correlation between them.

Because many RCTs were included, we conducted a sensitivity analysis by keeping just the studies at an overall low risk of bias.

We conducted a sensitivity analysis by removing (Preusser 1994) because we noticed large differences in baseline data between the two groups.

We did not use Robvis to generate weighted bar plots because it was possible to create them with Revman Web, and finally we kept just the PRISMA flow diagram and funnel plots.