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Effects of respiratory muscle training on exercise capacity, quality of life, respiratory and pulmonary function in people with ischaemic heart disease. Systematic review and meta-analysis.

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PROSPERO registration number

CRD42023381388

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1. Abstract

Objective: This systematic review and meta-analysis aimed to evaluate the effects of respiratory muscle training (RMT) on functional exercise capacity, health-related quality of life, respiratory muscle function and pulmonary function in individuals with ischaemic heart disease (IHD).

Methods: Seven electronic databases were searched including MEDLINE, Web of Science, Scopus, PEDro, CINAHL, Science direct and CENTRAL in January 2023. Randomised controlled trials published in English, Spanish or Portuguese conducted to determine the effect of RMT versus passive control and/or sham RMT on the target variables in individuals with IHD, irrespective of age or sex, were included. Two reviewers performed the searches and the extraction of the most relevant data. The quality and risk of bias for each included study was examined by PEDro scale and Cochrane tool.

Results: Thirteen studies (849 participants) were included. The meta-analysis showed a significant increase in peak oxygen consumption (PeakVO_2) (mean difference [MD]=2.18mL·Kg^{-1}·min^{-1} [0.54; 3.83]); inspiratory muscle strength (MD=16.62cmH_2O [12.48; 20.77]); inspiratory muscle endurance (standardised mean difference [SMD]=0.39 [0.19; 0.60]); and expiratory muscle strength (MD=14.52cmH_2O [5.51; 23.53]). There were no benefits on 6-minutes walking distance (MD=37.57m [−36.34; 111.48]); health-related quality of life (SMD=0.22 [−0.16; 0.60]); and pulmonary function (forced vital capacity; MD=2.07% of predicted [−0.90; 5.03]; forced expiratory volume at the first second; MD=−0.75% of predicted [−5.45; 3.95]).

Conclusions: The meta-analysis provided high and moderate-quality evidence that inspiratory muscle training (IMT) improves inspiratory muscle strength and endurance, respectively; and very low-quality evidence for the effects on peakVO_2 and expiratory

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3 muscle strength in individuals with IHD. No superior effects were found in the 6-
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5 minutes walking test, health-related quality of life or pulmonary function compared
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7 with the control group.
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12 **Impact**: The results shown in this systematic review with meta-analysis will provide
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14 clinicians a better understanding of the effects of IMT in people with IHD. IMT could
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16 be integrated into the cardiac rehabilitation management, although more research is
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18 needed.
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21 **Keywords:** Ischemic Heart Disease; Respiratory Muscle Training; Exercise Tolerance;
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23 Health-Related Quality of Life; Respiratory Muscles; Pulmonary Function Test; Meta-
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25 Analysis
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2. Introduction

Among cardiovascular illnesses, ischaemic heart disease (IHD) is the most prevalent, and its incidence continues increasing due to the aging population[1]. IHD is also the leading cause of human suffering, disability and mortality in adults worldwide[1], although with a decline in acute mortality in recent years[2]. Acute myocardial infarction, chronic stable angina, coronary artery disease and ischaemic heart failure are the clinical entities that comprise IHD[1]. IHD is currently considered a major threat to public health and to represent an economic and health care challenge for health systems due to its increasingly negative impact on the population's health[1,2].

The systolic dysfunction present in individuals with IHD impedes the adequate distribution of oxygen and metabolic substrates throughout the body[3], with fatigue and dyspnoea being the primary and most disabling symptoms[4]. In addition to the direct negative effects of these symptoms, studies have detected reductions in exercise tolerance, functionality, and performance in daily activities in individuals with IHD, which leads to the development of sedentary behaviours, resulting in a poorer health-related quality of life (HRQoL)[4–6]. Similar to other cardiovascular diseases, a vicious cycle of inactivity and clinical and functional deterioration is generated, leading to general physical deconditioning and atrophy of the peripheral and respiratory musculature[7,8].

In addition to cardiovascular abnormalities, stable individuals with chronic IHD present mild-to-moderate structural and functional respiratory muscle impairments[5]. Respiratory muscle atrophy presents important implications for exercise intolerance by triggering the activation of the respiratory metaboreflex in individuals with cardiovascular diseases[7,9]. Activation of the respiratory metaboreflex involves an increase in sympathetic outflow resulting in a sequence of cardiovascular changes that include a preferential redistribution of blood flow, favouring respiratory muscle perfusion and decreasing locomotor muscle

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perfusion, which in turn decreases exercise tolerance due to peripheral muscle fatigue[10,11]. Up to 72% of the most severely affected patients have limitations in daily activities due to respiratory fatigue, leading to depression, anxiety and psychological distress[12]. Thus, reversing respiratory muscle weakness should be considered a primary therapeutic target in IHD.

Clinical practice guidelines refer to exercise as the "polypill" because of its multiple beneficial effects on the physiology of the cardiovascular system, giving it the highest level of recommendation in the management of IHD[13]. Respiratory muscle training (RMT) is becoming increasingly popular in cardiac rehabilitation programs, given that it is an inexpensive and well-tolerated exercise option in individuals with cardiovascular disease[14]. RMT has demonstrated improvements in respiratory muscle strength, exercise tolerance, dyspnoea, and HRQoL in other populations, such as individuals with chronic obstructive pulmonary disease (COPD), stroke, healthy individuals and even individuals with heart failure[15–18]. Although several randomised controlled trials (RCTs) have recently been published evaluating the effects of inspiratory muscle training (IMT) in individuals with IHD, no systematic review summarising all the evidence has been conducted. Therefore, the objective of this review was to evaluate the effects of RMT on functional exercise capacity, HRQoL, respiratory muscle function and pulmonary function in individuals with IHD.

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3. Methods

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration guidelines[19]. It is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[20]. The protocol was registered in PROSPERO (CRD42023381388).

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Data Sources and Searches

The Russell-Rose et al.[21] guidelines were applied to the search strategy. MEDLINE, Web of Science, Scopus, PEDro, CINAHL, Science direct and CENTRAL electronic databases were searched without date restriction up to January 20, 2023. The search string was adapted to each database according to the data in **Appendix A.** Bibliographies included in previously published reviews were screened. Corresponding authors were e-mailed when clinical or methodological concerns emerged. Two independent reviewers conducted the search based on the same methodology (RFG and ILUV). Disagreements were resolved by consensus including a third reviewer (TdC).

Study Selection

The selection criteria for eligible studies were based on clinical and methodological considerations stated in the population-interventions-comparison-outcomes of interest-study design strategy[22].

Population: Individuals with IHD diagnosed by medical history evaluation, imaging techniques and/or exercise capacity tests were included. Evidence supports that there are no differences in clinical outcomes between individuals with stable IHD with or without revascularization surgery if they received optimal treatment[23], so individuals were included if they were optimally treated, regardless of whether or not they had undergone revascularization surgery. No age or sex limitations were imposed.

Intervention and comparison: The experimental intervention was RMT applied through threshold or resistive loading devices. IMT, expiratory muscle training (EMT) or combined respiratory muscle training (IMT+EMT) modalities were included. The comparisons should have allowed the determination of the absolute

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effect attributable to the RMT. Thus, valid comparisons were: 1) RMT in isolation versus passive control; and 2) RMT in isolation versus sham RMT. The inclusion of an additional standard care to the comparisons was allowed, if performed under the same protocol in both study arms. Studies that performed an RMT prior to a surgical intervention were included, as long as they provided pre-post data from the prehabilitation period for the purpose of ensuring comparability between study interventions.

Outcomes: The outcomes of interest were functional exercise capacity, HRQoL, respiratory muscle function and pulmonary function; therefore all included studies were required to assess at least one of these outcomes. Functional exercise capacity was measured by maximum and submaximal exercise tests (i.e., peak oxygen consumption [Peak VO_2] or 6-minute walk distance [6MWD], respectively). HRQoL had to be measured by valid and reliable patient reported outcomes measures such as the EuroQol-5D questionnaire (EQ-5D-5L), 12 or 36-Item Short Form Survey (SF-12 or SF-36), or the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Respiratory muscle function included: 1) Respiratory muscle strength measured by the maximal static mouth inspiratory (MIP) and expiratory pressures (MEP); and 2) Inspiratory muscular endurance (IME) was measured by the highest load that could be sustained for at least 1 min (maximal sustained inspiratory pressure in cmH_2O [Pm_{peak}]) or by its relative value to MIP (Pm_{peak}/MIP, expressed in %). Pulmonary function was measured by a forced spirometry manoeuvre (forced vital capacity [FVC] and forced expiratory volume at the first second [FEV_1]).

Study design: Only RCTs were included. Articles published in English, Spanish or Portuguese were considered.

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Data Extraction and Quality Assessment

Initially, the title, abstract and keywords of the retrieved studies were screened by two independent reviewers (RFG and ILUV) following Cochrane guidelines[19]. Full-text copies of potentially eligible peer-reviewed studies were acquired to analyse compliance with the selection criteria. The reasons for excluding non-selected studies were described. Disagreements were resolved by consensus including a third reviewer (TdC). Relevant data were extracted from each included study (RFG and ILUV).

The PEDro scale was employed to assess the methodological quality of the included studies because it is a reliable method for assessing the quality of RCTs[24]. The maximum score is 10 points and a stratification of the total ratings of each study was performed: poor (< 4 points), fair (4–5 points), good (6–8 points) and excellent (9–10 points)[25]. The Cochrane risk of bias tool was employed to assess the risk of bias in each study. The "other biases" criterion was expanded to clarify specific items that have potentially biased the results. Following the guidelines, a descriptive justification for the judgment was recorded. The Cochrane risk of bias tool and the PEDro scale were used to determine risk of bias and methodological quality, as both tools measure related but not interchangeable constructs[26].

Two independent trained assessors (RFG and ILUV) evaluated the quality and risk of bias for each study following the same standards. The inter-rater reliability was determined using the Kappa coefficient: 1) > 0.81–1.00 indicated excellent agreement between the assessors; 2) 0.61–0.80 indicated good agreement; 3) 0.41–0.60 indicated moderate agreement; 4) 0.21–0.40 indicated poor agreement[27].

Data Synthesis and Analysis

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The qualitative analysis was conducted according to the Grading of Recommendations, Assessment, Development and Evaluation[28]. The GRADE assessments criteria are listed in **Appendix B**.

The statistical analysis was conducted with RStudio 3.0 software using the 'meta' and 'esc' packages. All significance tests were performed at a level of 5%. A meta-analysis was conducted only when data on the analysed outcomes were reported in at least 3 trials.

Given that, in some studies, there were partially considerable differences in standard deviations (SD) between pre- and post-intervention time points, we used the change between the pre- and post-intervention values. Thus, the difference in pre- and post-intervention mean and SD values were extracted for each outcome. In those studies where SD was not reported for the change between pre- and post-intervention, it was calculated according to Cochrane recommendations[19]. When necessary, the mean scores and SDs were estimated from graphs. When the trial reported only standard errors, they were converted to SD in accordance with the Cochrane recommendations[19]. When a study presented more than one valid comparison, they were combined to obtain a single estimator and to avoid the use of duplicate control group data, in accordance with Cochrane recommendations[19].

The presentation of the summary statistics for all analyses was performed using forest plots. The raw mean difference (MD) was used as overall effect size if studies used the same unit/tool of measurement. The standardised mean difference (SMD) was used as the overall effect size if studies used different units or tools of measurement. A random-effects model was used in all analyses to determine the overall effect size. The effect size of the statistical significance of the overall SMD was examined using Hedges' g: 1)

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trivial effect ($g < 0.20$); 2) small effect ($g = 0.20–0.49$); 3) moderate effect ($g = 0.50–0.79$); and 4) large effect ($g \geq 0.80$). The confidence interval of the pooled effect was calculated using the Knapp-Hartung adjustments[29].

The heterogeneity among the studies was estimated using Cochran's Q statistic test and the inconsistency index (I^2)[30]. Heterogeneity was considered when the Cochran's Q statistic test was significant ($p < 0.1$) and/or the I^2 was >50%[31]. To help with the clinical interpretation of the heterogeneity[32], the prediction interval (PI) based on the between-study variance tau-squared (τ^2) was reported. As recommended for continuous outcomes[33], the Restricted Maximum Likelihood Estimator was used to calculate the between-study variance τ^2.

The possible influence of the studies on the results obtained in the meta-analysis was assessed with an exclusion sensitivity analysis. The Luis Fury Kanamori (LFK) index was used as a quantitative measure to detect publication symmetry[34]: 1) no asymmetry (LFK within ±1); 2) minor asymmetry (LFK exceeding ±1 but within ±2); and 3) major asymmetry (LFK exceeding ±2). If there was significant asymmetry, a small-study effect method was applied to correct for publication bias using the Duval and Tweedie trim and fill method[35].

Role of the Funding Source

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

4. Results

Study selection

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The search strategy identified a total of 782 citations. After the exclusion of articles not meeting the selection criteria, a total of 13 studies were included. **Figure 1** displays the flowchart of the search strategy.

Characteristics of the included studies

A total of 849 individuals with IHD participated in the selected studies (mean age 63.2 years, 27.4% females; **Table 1**). The sex of the participants is not reported in two studies[36,37], and age is not reported in Valkenet et al.[37] study. Muammer et al.[38] and Labeix et al.[39] studies included patients with comorbidities (metabolic syndrome and obstructive sleep apnoea, respectively), which increases the clinical heterogeneity. Four studies[37,40–42] were developed in the context of a phase I cardiac rehabilitation programme, while the remaining studies were developed in the context of a phase II cardiac rehabilitation programme[36,38,39,43–48]. The modality of RMT employed for all studies was IMT, applied through threshold loading devices. Four studies compared the effects of IMT versus sham IMT (load ≤ 10 cmH_2O)[42–44,46]. The remaining 9 studies evaluated the additional effects of an IMT programme added to a physiotherapy cardiac intervention[36–41,45,47,48]. Arutyunov et al.[43] was the only study to perform two different and valid IMT interventions, which were combined to obtain a single estimator in the current meta-analysis. All studies except one[43] prescribed IMT loads based on a percentage of MIP. Loads increased progressively[36,37,40–44,47,48] or were kept stable[38,39,45,46] in a range between 15% and 80% of MIP, with the most commonly selected range between 30%–60% of MIP. Arutyunov et al.[43] study performed a 6-month intervention, but training loads were initially too low, so the training was considered effective from the 3rd month, at which time the loads exceeded the stimulus thresholds (30 cmH_2O). Similarly, Weiner et al.[42] study started at 15% of MIP, although in only half a week they achieved 30% of MIP, exceeding the stimulus thresholds. Training programmes were

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3 implemented between 2[40–42] to 12 weeks[36,43–45], 2[44,45] to 7 times per week[37,38,40,41,46] (**Table**
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5 **1**). Six studies reported no adverse events during the intervention[37,40,41,44–46], but
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8 Arutyunov et al.[43] reported 8 heart rhythm abnormalities among both IMT groups and 3
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10 blood circulation decompensations, and 2 pneumonias in the sham IMT group.
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13 **Methodological quality and risk of bias of included studies**
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15 The mean PEDro score was 5.6 for the included studies (range 4–8; **Appendix C**). The
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18 agreement between assessors was excellent (κ = 0.903).
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21 The risk of bias of the included studies is summarised in **Appendix D**. Overall, there
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23 was a high risk of bias in the trials included in this meta-analysis. The highest risk of
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25 bias was found in the blinding of outcome assessments and selective reporting items.
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28 The risk of bias in the blinding of participants and evaluators was considered low in all
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30 studies due to: 1) the effective implementation of IMT sham; and 2) the implementation
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32 of strict training protocols, a necessary condition in exercise interventions to reduce the
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35 risk of differential therapist behavior[49].
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38 **Functional exercise capacity**
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40 There was very low-quality evidence that RMT produces a statistically significant
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42 increase in peak VO_2 (9 studies[36,38,39,43–48] [n = 350]; MD = 2.18 $mL \cdot Kg^{-1} \cdot min^{-1}$ [0.54;
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45 3.83]), but not in 6MWD (3 studies[36,44,46] [n = 82]; MD = 37.57 m [−36.34; 111.48]),
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47 compared with the control groups (**Figure 2 and Table 2**). In both outcomes,
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49 heterogeneity was significant (I^2 = 82%) and PI crossed zero, so future studies might
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52 find contradictory results. No single study significantly affected the overall MD, and no
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54 evidence of publication bias was detected (symmetric funnel plot shape; no asymmetry
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56 [LFK index ≤ 0.17]; **Appendix E**).
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59 **Health-related quality of life**
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There was moderate-quality evidence from 6 studies[36,37,39,44–46] (n = 264) that RMT did not lead to statistically significant improvements in HRQoL compared with the control group (SMD = 0.22 [−0.16; 0.60]; **Figure 2 and Table 2**). Heterogeneity was not significant (I^2 = 20%). No single study significantly affected the overall SMD; however, evidence of publication bias was detected (asymmetric funnel plot shape; major asymmetry [LFK index = 2.78]; **Appendix E**). When the sensitivity analysis of these variables was adjusted for publication bias, the trim and fill method considered that one study should be added (**Appendix E**). However, there was no influence on the estimated effect because the initial results were maintained.

Respiratory muscle function

The meta-analysis results show that RMT produced a statistically significant increase in inspiratory muscle strength (high-quality evidence from 12 studies[36,38–48] [n = 736]; MD = 16.62 cmH_2O [12.48; 20.77]) and inspiratory muscle endurance (moderate-quality evidence from 3 studies[40,42,44] [n = 384]; SMD = 0.39 [0.19; 0.60]) compared with the control group (**Figure 3 and Table 2**). Heterogeneity was significant (I^2 = 66%) for inspiratory muscle strength, but not for endurance (I^2 = 0%). Future studies might have contradictory results for inspiratory muscle endurance, but not for strength, because PI crossed zero. No single study significantly affected the overall MD inspiratory muscle strength. For inspiratory muscle endurance, the removal of the study by Hulzebos et al.[40] would lead to an absence of significant differences between IMT and the control group (**Appendix F**). However, the elimination of any study assessing respiratory muscle endurance would preclude meta-analysis, given that a minimum of 3 studies was required for such analysis. Evidence of publication bias was only detected for inspiratory muscle endurance (asymmetric funnel plot shape; minor asymmetry [LFK index = −1.9]; **Appendix F**). When the sensitivity analysis was adjusted for publication

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3 bias, the initial results were maintained because the trim and fill method considered that
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5 no studies should be added. Therefore, the initial results were maintained.
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8 There was very low-quality evidence that RMT produced a statistically significant
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11 increase in expiratory muscle strength compared with the control group (6 studies[36,38,44–
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13 47] [n = 208], MD = 14.52 cmH_2O [5.51; 23.53]; **Figure 3 and Table 2**). Heterogeneity
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15 was significant ($I^2 = 75\%$) and PI crossed zero, so future studies might have
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18 contradictory results. No single study significantly affected the overall MD; however,
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20 evidence of publication bias was detected (asymmetric funnel plot shape; minor
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22 asymmetry [LFK index = −1.39]; **Appendix F**). When the sensitivity analysis was
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25 adjusted for publication bias, the initial results were maintained because the trim and fill
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27 method considered that no studies should be added.
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30 **Pulmonary function**
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33 There was moderate-quality evidence that RMT did not statistically significantly
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35 increase either FVC (4 studies[38,42,44,46] [n = 188]; MD = 2.07 % of predicted [−0.90;
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37 5.03]) or FEV_1 (6 studies[38,41,42,44,46,48] [n = 274]; MD = −0.75 % of predicted [−5.45;
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40 3.95]) compared with the control group (**Figure 4 and Table 2**). Heterogeneity was
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42 significant ($I^2 = 83\%$) for FEV_1, but not for FVC ($I^2 = 0\%$). For FVC, the study by
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44 Muammer et al.[38] likely had a strong influence on the meta-analysis results and could be
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47 considered an outlier. In fact, the removal of this study would show that IMT produced
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49 a statistically significant increase in FVC (**Appendix G**). In addition, evidence of
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51 publication bias was detected (asymmetric funnel plot shape; minor asymmetry [LFK
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54 index = 1.91]; **Appendix G**). When the sensitivity analysis of these variables was
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56 adjusted for publication bias, the trim and fill method considered that two studies should
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58 be added (**Appendix G**). However, there was no influence on the estimated effect
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60 because the initial results were maintained. For FEV_1, no single study significantly

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3 affected the overall MD, and no evidence of publication bias was detected (symmetric
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5 funnel plot shape; no asymmetry [LFK index = −0.13]; **Appendix G**). However,
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8 elimination of the Piotrowska et al.[48] study would reveal an absence of heterogeneity
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10 (**Appendix G**).
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5. Discussion
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19 This is the first study to systematically assess the effects of an RMT intervention in
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21 individuals with IHD. Interestingly, only IMT programmes have been explored in this
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23 population, with no evidence concerning EMT or IMT+EMT modalities. The results
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25 suggest that IMT could improve inspiratory muscle strength and endurance with high-
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27 and moderate-quality evidence, respectively, while very low-quality evidence suggests
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30 that IMT could improve functional exercise capacity and expiratory muscle strength in
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32 individuals with IHD. The quality of the evidence indicates that these results should be
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34 interpreted with caution; therefore, to confirm these trends, further high quality RCTs
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36 are required.
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39 The current review indicates that an IMT intervention could improve functional exercise
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41 capacity in terms of peak VO_2 in individuals with IHD. This finding is concordant with
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44 the results of previous reviews in individuals with heart failure[15], COPD[17] and healthy
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46 individuals[18]. The current review also demonstrates that IMT appears to improve
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48 respiratory muscle strength and endurance, which is in line with current knowledge[15–18].
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51 Exercise intolerance might be due, in part, to an overactivation of the respiratory
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53 metaboreflex[7,9], caused by the respiratory muscle weakness observed in individuals with
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56 IHD[5]. Thus, these results could be explained by the fact that after an IMT programme,
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59 an increase occurs in the proportion of type I fibres and an increase in the size of type II
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3 fibres, as well as a better energetic economy of the respiratory muscles[50]. These muscle adaptations facilitate the elimination of waste metabolites generated during contraction, and higher exercise intensities would be necessary to activate metaboreceptors[9]. Therefore, the negative exercise consequences of metaboreflex such as the activation of IV afferent fibres, sympathetic activation, generalised vasoconstriction, reduction of peripheral blood flow and fatigue of peripheral musculature[9] would occur only during higher exercises intensities, enhancing the functional exercise capacity of the participant. In addition, the results of this review suggest association between MIP and peak VO_2 as established by Neves et al[51] in individuals with IHD.

It is noteworthy that no favourable results were found after an IMT programme in terms of 6MWD in individuals with IHD. The 6-minutes walking test (6MWT) is a submaximal proxy for maximal, graded exercise tests that measure peak aerobic capacity. Therefore, it is unlikely to generate respiratory fatigue, which appears at high intensities activities ($\geq$ 85% of peak VO_2)[52] or in prolonged moderate-intensity exercise[18]. The 6MWT is a voluntary effort during which the person's walking speed can vary, and the person might even stop and rest for a period of time, so two people with the same peak VO_2 might choose different walking strategies. In fact, in a group of individuals with heart failure, the VO_2 measured at the end of the 6MWT was on average 15% lower than peak VO_2[53]. Superior benefits have been detected for 6MWD in the included studies that employed a sham IMT group[44,46] compared to those employing a cardiac rehabilitation programme as a control group[36]. These findings suggest that the effects of IMT for 6MWD are blunted when the IMT is combined with a cardiac rehabilitation programme, which is a mainly aerobic intervention. A similar trend was found for individuals with heart failure after an IMT programme[15]. However, due to the few studies found, this issue needs further investigation. In addition, future

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3 research should consider assessing the anaerobic threshold, as it has been related to the
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5 onset of fatigue[54], and is an accurate biomarker of submaximal functionality.
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8 Interventions that have improved the cardiorespiratory capacity of individuals with IHD
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11 have shown no impact on the performance of activities of daily living, given that these
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13 activities are defined more by external sources and the patient's own concerns rather
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15 than by changes in symptoms[55]. In fact, daily activities are predominantly considered
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18 low to moderate intensity[56] and improvements after an IMT intervention only appear at
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20 high intensity activities. It is plausible that the lack of increase in 6MWD, —a test
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22 closely associated with ability to perform activities of daily living[57]—, might not impact
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24 the daily activities of individuals with IHD. In this regard, for those clinicians who have
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27 no access to maximal exercise testing involving high-cost equipment, the use of the
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29 Ruffier test, —a simple cardiorespiratory fitness test consisting of performing 30 squats
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31 in 45 seconds, following a metronome set at 80 bpm, and recording the heart rate
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34 before, immediately after, and one minute after completing the squats[58]—, might be
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36 more sensitive in detecting changes in functional exercise tolerance that occur in
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38 patients with IHD following an IMT programme. Indeed, we hypothesized that the
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41 increase in peak VO_2 found in this review could modulate heart rate through the
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43 autonomic nervous system and respiratory metaboreflex attenuation[9]. Therefore, IMT
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45 could be offered as complementary therapy along with other exercise modalities to
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48 increase peak VO_2 in individuals with IHD, allowing them to tolerate more challenging
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50 workouts that would generate more substantial clinical adaptations. However, further
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52 studies are needed to corroborate the clinical improvement in the performance of
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55 activities of daily living after an IMT programme in those individuals with IHD who
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57 have limitations in these activities.
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All these hypotheses justify the lack of positive results for HRQoL found in this review, because it is an outcome that largely depends on the social and functional perception of the individual[59]. However, these results are discordant with those found after an IMT programme in other populations that might have a more severe condition, such as heart failure[15] or COPD[17]. A marked functional limitation and a severe respiratory muscle weakness characterises both diseases[60], so IMT-induced conditioning might provide the benefit detected in these reviews for HRQoL. Notably, studies assessing HRQoL with cardiac-specific questionnaires[44,45] reported significant improvements, while those using generic instruments[36,37,39,46] did not. This could explain why, despite an improvement found in peak VO_2, no improvements were detected for HRQoL after the RMT programme. Future research should use specific cardiac questionnaires to obtain more consistent results.

All of the included studies performed an IMT-based intervention; therefore, the effects of combined IMT+EMT remain unexplored in individuals with IHD. Similarly, combined IMT+EMT interventions have not been investigated in patients with heart failure[15]. Interestingly, recent evidence suggests the superiority of IMT+RMT over IMT in isolation in healthy individuals[18] and in individuals with cardiovascular disease[16]. On one hand, several studies suggest that expiratory muscle fatigue develops before inspiratory fatigue in some respiratory diseases[61,62], further impairing functional exercise capacity through respiratory metaboreflex. On the other hand, Lee et al.[63] demonstrates that after 6 weeks of an IMT+EMT intervention, expiratory muscle strength improves and postural stability is enhanced, through improved core musculature functioning. In that sense, stability-enhancing interventions have been shown to increase walking speed in individuals with IHD[64]. Therefore, it is possible that IMT+EMT could provide an

additional benefit compared with IMT in isolation for the 6MWD and HRQoL in individuals with IHD.

Finally, previous research indicates that IMT does not appear to influence pulmonary function outcomes[15,16], in accordance with the results of the present review. Individuals with IHD who have no other concomitant respiratory disorders show no pulmonary function impairment[65]; therefore, to find improvements in those outcomes is even more difficult.

Several limitations can be ascribed to this review. The high risk of bias and the small sample sizes of the included studies limit the robustness of the results, which should therefore be interpreted with caution. In addition, there was variability in the medication taken by the different patients, as well as in whether or not they had undergone revascularization surgery, which could also affect the robustness of the results. The IMT protocols were diverse in terms of loads and periodisation, which could increase the heterogeneity of the analyses performed. However, the certainty of the evidence was reduced as a function of heterogeneity, as this aspect makes it difficult to determine the optimal training dose to obtain the desired effects. The low number of studies included prevented the performance sub-analyses. Some meta-analyses have been performed with only 3 studies —such as the 6MWD and the IME—, so the inclusion of new evidence could modify the obtained results. More high quality RCTs are needed to address these limitations.

The results of this review indicate that an IMT intervention could improve respiratory muscle strength and endurance as well as functional exercise capacity as measured by peak VO_2 in individual with IHD. Thus, IMT is postulated as an effective intervention in people with IHD, especially those with concomitant respiratory weakness (MIP<

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80% of predicted)[66]. Previous research confirms that IMT is a cost-effective and well-tolerated exercise option for individuals with cardiovascular diseases and can be performed from the patient's home via telerehabilitation[14]. Given that only 1 in 10 of the patients who could benefit from cardiac rehabilitation programmes actually end up participating[67], the IMT programme could overcome this barrier by increasing the therapeutic offer and optimising healthcare resources.

6. Conclusion

High and moderate-quality evidence suggests that IMT intervention could improve inspiratory muscle strength (high-quality evidence) and endurance (moderate-quality evidence), while very low-quality evidence indicates that IMT could improve peak VO_2 and expiratory muscle strength in individuals with IHD. No superior effects were found in the 6MWT, HRQoL or pulmonary function compared with the control group. The quality of evidence found in this study indicates that the results should be interpreted with caution until more high quality RCTs have been conducted.

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Disclosures

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Figure Legends

Figure 1. PRISMA flow diagram

Figure 2. Synthesis Forest plot for functional exercise capacity and health-related quality of life

Figure 3. Synthesis Forest plot for respiratory muscle function

Figure 4. Synthesis Forest plot for pulmonary function

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Table 1. Characteristics of included studies

Author, year and design	Sample characteristics	Intervention groups	Training protocols	Outcomes	Results
Arutyunov et al. 2021 RCT	**N** = 37; 18 females (49%) **Age**: 66.3 ± 7.2 years **CR phase:** II	**IMT_1** (N = 13) **IMT_2** (N = 13) **Sham IMT** (N = 11)	**IMT_1**: 15–20 min per day; 3–5 days/week; 12 weeks. IMT_1: increased 2 cmH_2O every week **IMT_2**: Series with loads equal to the dynamic group and loads of 9 cmH_2O **Sham IMT**: Same protocol with unresisted breathing	**Functional exercise capacity:** CPET (Peak VO_2) **Respiratory muscle function:** MIP	**Functional exercise capacity:** Both IMT groups showed significant increase for peak VO_2 compared with sham IMT group at 12 weeks **Respiratory muscle function:** Both IMT groups showed significant increase for MIP compared with sham IMT group at 12 weeks
Dos Santos et al. 2019 RCT	**N** = 24; 7 females (29%) **Age**: 55.8 ± 6.2 years **CR phase:** II	**IMT+CR** (N = 12) **Sham IMT+CR** (N = 12)	**IMT**: 5 sets x 10 reps; 1 min rest interval. 2 days/week; 12 weeks. 50 to 80% of MIP **Sham IMT**: Same protocol with 9 cmH_2O **CR**: 30 min aerobic training at 1º ventilatory threshold. 30 min resistance training (3 sets x 10 reps; 30 sec rest intervals; 50% 1RM). 2 days/week; 12 weeks	**Functional exercise capacity:** CPET (Peak VO_2) and 6MWD **HRQoL:** MLHFQ **Respiratory muscle function:** MIP, MEP and IME **Pulmonary function:** FVC and FEV_1	**Functional exercise capacity:** The IMT+CR group showed significant increase for peak VO_2 and 6MWD compared with sham IMT+CR group at 12 weeks **HRQoL:** The IMT+CR group showed significant reduction for MLHFQ compared with sham IMT+CR group at 12 weeks **Respiratory muscle function:** The IMT+CR group showed significant increase for MIP, but not for MEP or IME compared with sham IMT+CR group at 12 weeks **Pulmonary function:** No differences were found for FVC or FEV_1 between groups at 12 weeks
Hermes et al. 2015 RCT	**N** = 24; 7 females (29%) **Age**: 57.3 ± 8.4 years **CR phase:** II	**IMT+CR** (N = 12) **CR** (N = 12)	**IMT**: 3 sets x 10 reps; respiratory rate between 15 and 20 cycles/minute; 2 days/week; 12 weeks. 30% of MIP **CR**: 30 min aerobic training at 55–65% of HRR. 20 min resistance training (3 sets x 10 reps; 50% 1RM). 2 days/week; 12 weeks	**Functional exercise capacity:** CPET (Peak VO_2) **HRQoL:** MLHFQ **Respiratory muscle function:** MIP and MEP	**Functional exercise capacity:** The IMT+CR group showed significant increase for peak VO_2 compared with CR group at 12 weeks **HRQoL**: The IMT+CR group showed significant reduction for MLHFQ compared with CR group at 12 weeks **Respiratory muscle function:** The IMT+CR group showed significant increase for MIP and MEP compared with CR group at 12 weeks
Hulzebos et al. 2006a RCT	**N** = 26; 13 females (50%) **Age**: 70.3 ± 9.8 years **CR phase:** I	**IMT+UC** (N = 14) **UC** (N = 12)	**IMT**: 20 min/day; 7 days/week; 2–4 weeks. 30% of MIP and adjusted based on RPE **UC**: Education about early mobilization and coughing the day before intervention	**Respiratory muscle function:** MIP **Pulmonary function:** FEV_1	**Respiratory muscle function:** No differences were found for MIP between groups at 2–4 weeks **Pulmonary function:** No differences were found for FEV_1 between groups at 2–4 weeks
Hulzebos et al. 2006b RCT	**N** = 276; 61 females (22%) **Age**: 66.9 ± 9.1 years **CR phase:** I	**IMT+UC** (N = 139) **UC** (N = 137)	**IMT**: 20 min/day; 7 days/week; at least 2 weeks 30% of MIP and adjusted based on RPE **UC**: Education about early mobilization, deep breathing manoeuvres and coughing the day before intervention	**Respiratory muscle function:** MIP and IME	**Respiratory muscle function:** The IMT+UC group showed significant increase for MIP and IME compared with UC group at 2–4 weeks

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Huzmeli et al. 2022 RCT	**N** = 40; 3 females (8%) **Age**: 57.9 ± 7.7 years **CR phase:** II	**IMT** (N = 20) **Sham IMT** (N = 20)	**IMT**: 30 min/day; 10–15 breaths with 5–10 secs rest intervals; 7 days/week; 8 weeks. 30% of MIP **Sham IMT**: Same protocol with 10 cmH_2O	**Functional exercise capacity:** CPET (MET) and 6MWD **HRQoL:** SF-36 **Respiratory muscle function:** MIP and MEP **Pulmonary function:** FVC and FEV_1	**Functional exercise capacity:** The IMT group showed significant increase for peak VO_2 and 6MWD compared with sham IMT group at 8 weeks **HRQoL:** No differences were found for SF-36 between groups at 8 weeks **Respiratory muscle function:** The IMT group showed significant increase for MIP and MEP compared with sham IMT group at 8 weeks **Pulmonary function:** The IMT group showed significant increase for FVC, but not for FEV_1 compared with sham IMT group at 8 weeks
Kurzaj et al. 2019 RCT	**N** = 62; 26 females (42%) **Age**: 62.3 ± 6.5 years **CR phase:** II	**IMT+CR** (N = 32) **CR** (N = 30)	**IMT**: 5 to 15 min; Twice a day; 5 days/week; 8 weeks. 30 to 60% of MIP **CR**: Aerobic training performed 45 min; 3 days/week; 8 weeks. Resistance training performed 2 days/week; 8 weeks	**Functional exercise capacity:** CPET (MET) **Respiratory muscle function:** MIP and MEP	**Functional exercise capacity:** Both groups showed a significant increase for MET at 8 weeks **Respiratory muscle function:** The IMT+CR group showed a significant increase for MIP and MEP, while CR group only showed a significant increase for MIP at 8 weeks
Labeix et al. 2022 RCT	**N** = 45; 5 females (11%) **Age**: 60.1 ± 9.4 years **CR phase:** II	**IMT+CR** (N = 22) **CR** (N = 23)	**IMT**: Twice a day; 30 reps each; 6 days/week; 6 weeks. 70% of MIP **CR**: 25 min aerobic interval training at 1° ventilatory threshold and progression based on RPE. 40 min resistance training based on RPE. 3 days/week; 6 weeks	**Functional exercise capacity:** CPET (Peak VO_2) **HRQoL:** SF-12 **Respiratory muscle function:** MIP	**Functional exercise capacity:** No differences were found for peak VO_2 between groups at 6 weeks **HRQoL:** The IMT+CR group showed significant increase for mental score of SF-12, but not for physical score of SF-12 compared with CR group at 6 weeks **Respiratory muscle function:** The IMT+CR group showed significant increase for MIP compared with CR group at 6 weeks
Miozzo et al. 2018 RCT	**N** = 18; sex not reported **Age** : 57.5 ± 8 years **CR phase:** II	**IMT+CR** (N = 9) **CR** (N = 9)	**IMT**: Progressive increase from 5 to 10 sets and from 10 to 12 reps; 12 weeks. 50–80% of MIP **CR**: 40 min aerobic training at 50–80% of HRR. 3 days/week; 12 weeks	**Functional exercise capacity:** CPET (Peak VO_2) and 6MWD **HRQoL:** SF-36 **Respiratory muscle function:** MIP and MEP	**Functional exercise capacity:** No differences were found for peak VO_2 or 6MWD between groups at 12 weeks **HRQoL:** No differences were found for SF-36 between groups at 12 weeks **Respiratory muscle function:** The IMT+CR group showed significant increase for MIP but not for MEP compared with CR group at 12 weeks
Muammer et al. 2020 RCT	**N** = 40; 7 females (18%) **Age**: 56.7 ± 6.6 years **CR phase:** II	**IMT+CR** (N = 20) **CR** (N = 20)	**IMT**: 15 min; twice a day; 5 breaths sets; 7 days/week; 6 weeks. 30% of MIP **CR**: Patient education, diaphragmatic breathing, stretching and proprioceptive neuromuscular facilitation. 3 days/week; 6 weeks	**Functional exercise capacity:** CPET (MET) **Respiratory muscle function:** MIP and MEP **Pulmonary function:** FVC and FEV_1	**Functional exercise capacity:** No differences were found for MET between groups at 6 weeks **Respiratory muscle function:** No differences were found for MIP or MEP between groups at 6 weeks **Pulmonary function:** No differences were found for FVC or FEV_1 between groups at 6 weeks
Piotrow-ska et al. 2021 RCT	**N** = 60; 24 females (40%) **Age**: 62.3 ± 6.5 years **CR phase:** II	**IMT+CR** (N = 30) **CR** (N = 30)	**IMT**: 5 to 15 min; twice a day; 5 days/week; 8 weeks. 30–60% of MIP **CR**: 45 min aerobic training at 40–70% of HRR; 3 days/week; 8 weeks. 45 min resistance training (8–10 different exercises). 2 days/week; 8 weeks	**Functional exercise capacity:** CPET (MET) **Respiratory muscle function:** MIP **Pulmonary function:** FEV_1	**Functional exercise capacity:** Both groups showed a significant increase for MET at 8 weeks **Respiratory muscle function:** Both groups showed a significant increase for MIP at 8 weeks **Pulmonary function:** Only the CR group showed a significant increase for FEV_1 at 8 weeks

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Valkenet et al. 2017 RCT	N = 113; Sex not reported **Age**: Not reported **CR phase:** I	**IMT+UC** (N = 119) **UC** (N = 116)	**IMT**: 20 min/day; 7 days/week; at least 2 weeks. 30% of MIP and adjusted based on RPE. **UC**: Education about early mobilization, deep breathing manoeuvres and coughing the day before intervention	**HRQoL**: EQ-5D-5L and SF-36	**HRQoL** No differences were found for EQ-5D-5L or SF-36 between groups at 2 weeks
Weiner et al. 1998 RCT	**N** = 84; 26 females (31%) **Age**: 61.5 ± 4.2 years **CR phase:** I	**IMT** (N = 42) **Sham IMT** (N = 42)	**IMT**: 30 min; 6 days/week; 2–4 weeks. 15–60% of MIP. **Sham IMT**: Same protocol with unresisted breathing	**Respiratory muscle function:** MIP and IME **Pulmonary function:** FVC and FEV_1	**Respiratory muscle function:** The IMT group showed significant increase for MIP and IME compared with sham IMT group at 2 - 4 weeks **Pulmonary function:** No differences were found for FVC or FEV_1 between groups at 2–4 weeks

6MWD: 6-minutes walk distance; CPET: Cardiopulmonary exercise testing; CR: Cardiac rehabilitation; EQ-5D-5L: EuroQol five dimensions questionnaire; FEV_1: Forced expiratory volume at 1 second; FVC: Forced vital capacity; HRQoL: Health-related quality of life; HRR: Heart rate reserve; IME: Inspiratory muscle endurance; IMT: Inspiratory muscle training; MEP: Maximal expiratory pressure; MET: metabolic equivalent of task; MIP: Maximal inspiratory pressure; MLHFQ: Minnesota Living with Heart Failure Questionnaire; VO_2: Oxygen consumption; RCT: randomized controlled trial; RPE: Rated of perceived exertion; RM: repetition maximum; SF-12: 12-Item Short Form Survey; SF-36: 36-Item Short Form Survey; UC: Usual care.

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Table 2. GRADE evidence profile for the effects of respiratory muscle training

Outcome Comparison; number of studies (trials); sample size	Risk of bias	Inconsistency	Indirectness of evidence	Imprecision	Publication bias	SMD (95% CI) or MD (95% CI)	Certainty of evidence
Functional exercise capacity							
Peak VO_2 ($mL \cdot Kg^{-1} \cdot min^{-1}$)							
IMT vs Control (overall effect); 9 studies; n=350	Not serious	Very serious[b]	Not serious	Serious[e]	Not serious	2.18 $mL \cdot Kg^{-1} \cdot min^{-1}$ (0.54 to 3.83)*	VERY LOW ⊕○○○
Six-minute walk distance (m)							
IMT vs Control (overall effect); 3 studies; n=82	Not serious	Very serious[b]	Not serious	Very serious[f]	Not serious	37.57 m (-36.34 to 111.48)	VERY LOW ⊕○○○
Health-related quality of life (SMD)							
IMT vs Control (overall effect); 6 studies; n=264	Not serious	Not serious	Not serious	Serious[e]	Not serious	0.22 (-0.16 to 0.60)	MODERATE ⊕⊕⊕○
Respiratory muscle function							
Inspiratory muscle strength (MIP in cmH_2O)							
IMT vs Control (overall effect); 12 studies; n=736	Not serious	Not serious	Not serious	Not serious	Not serious	16.62 cmH_2O (12.46 to 20.77)*	HIGH ⊕⊕⊕⊕
Expiratory muscle strength (MEP in cmH_2O)							
IMT vs Control (overall effect); 6 studies; n=208	Not serious	Very serious[b]	Not serious	Serious[e]	Not serious	14.52 cmH_2O (5.51 to 23.53)*	VERY LOW ⊕○○○
Inspiratory muscle endurance (SMD)							
IMT vs Control (overall effect); 3 studies; n=384	Not serious	Not serious	Not serious	Serious[e]	Not serious	0.39 (0.19 to 0.60)*	MODERATE ⊕⊕⊕○
Pulmonary function							
Forced Vital Capacity (% of predicted)							
IMT vs Control (overall effect); 4 studies; n=188	Not serious	Not serious	Not serious	Serious[e]	Not serious	2.07 % of predicted (-0.90 to 5.03)	MODERATE ⊕⊕⊕○
Forced Expiratory Volume at 1 sec (% of predicted)							
IMT vs Control (overall effect); 6 studies; n=274	Not serious	Not serious	Not serious	Serious[e]	Not serious	-0.75 % of predicted (-5.45 to 3.95)	MODERATE ⊕⊕⊕○

*Statistically significant differences.
[a] more than 50% of the studies presented high risk of bias and serious limitations in the effect estimated (lack of concealment and random allocation, attrition bias, PEDro scale score <6).
[b] Large Inconsistency: $I^2 \geq 75\%$ and Prediction Interval including results different from those stated in the meta-analysis together with > 30% of studies also favouring a different outcome.
[c] Substantial Inconsistency: $I^2 \geq 50\%$ and Prediction Interval including results different from those stated in the meta-analysis together with > 30% of studies also favouring a different outcome.
[d] different populations, interventions or comparator were included.
[e] sample size less than 400 patients.
[f] sample size less than 100 patients.
[g] asymmetry in the funnel plot shape and the LFK index, together with a change in the results when a sensitivity analysis adjusted for publication bias was performed.
IMT, inspiratory muscle training, MD, mean difference; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; VO_2, oxygen consumption; RMT, respiratory muscle training. SMD, standardised mean difference.

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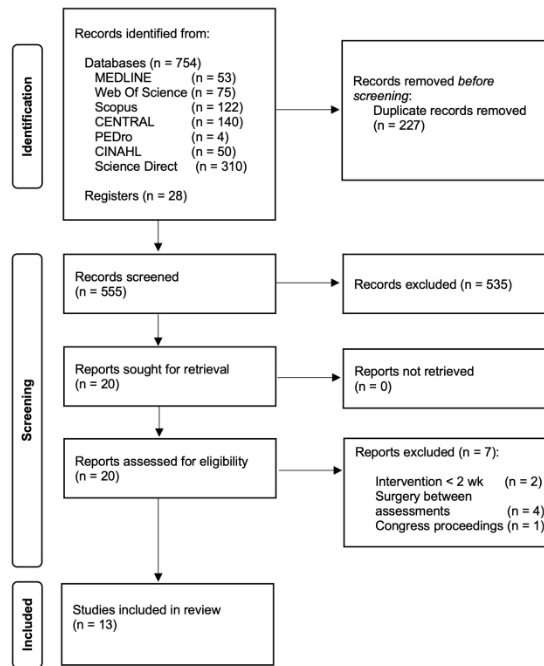

Figure 1. PRISMA flow diagram

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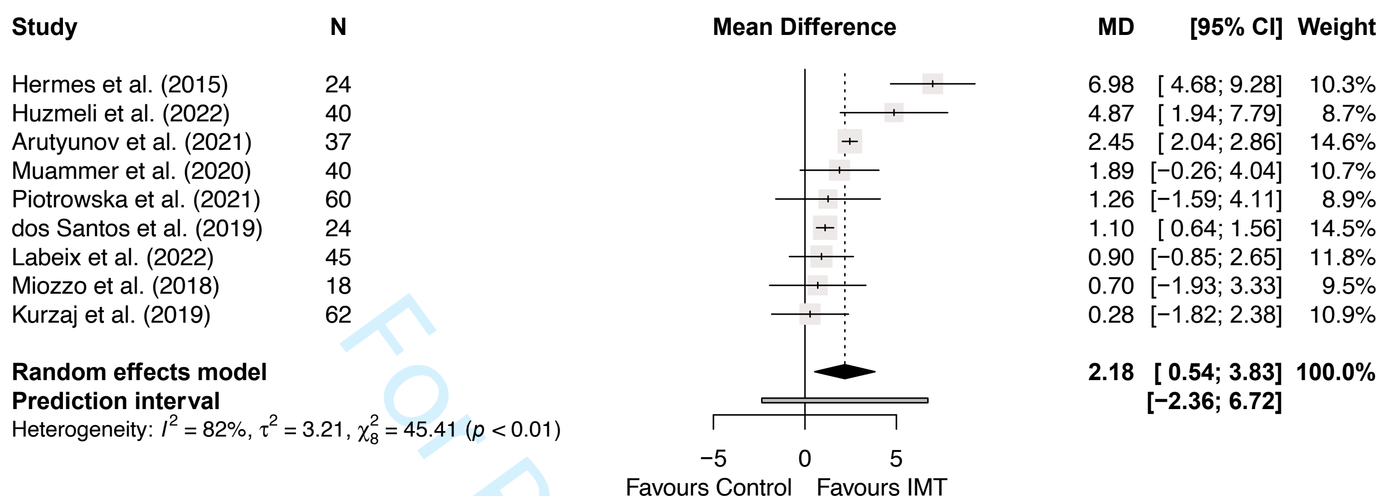
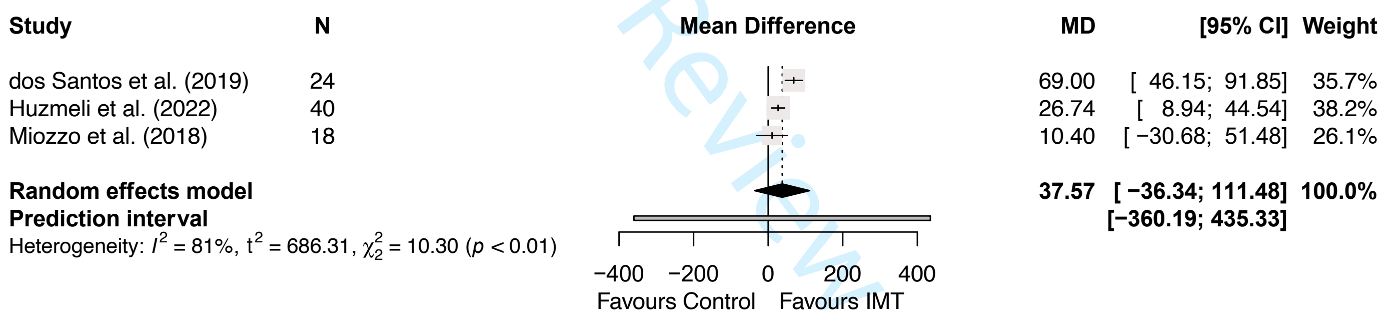
FUNCTIONAL EXERCISE CAPACITY





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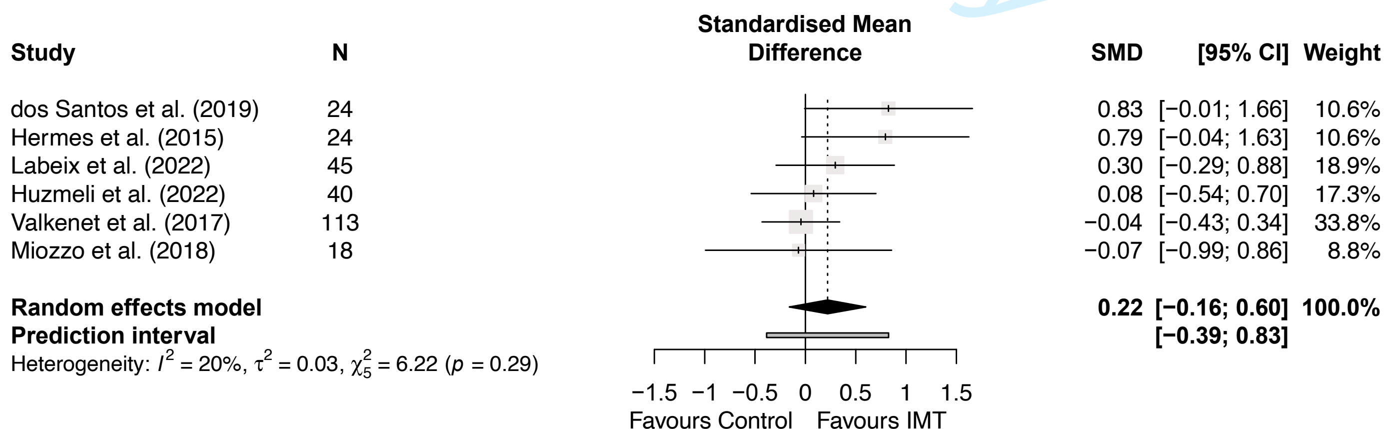

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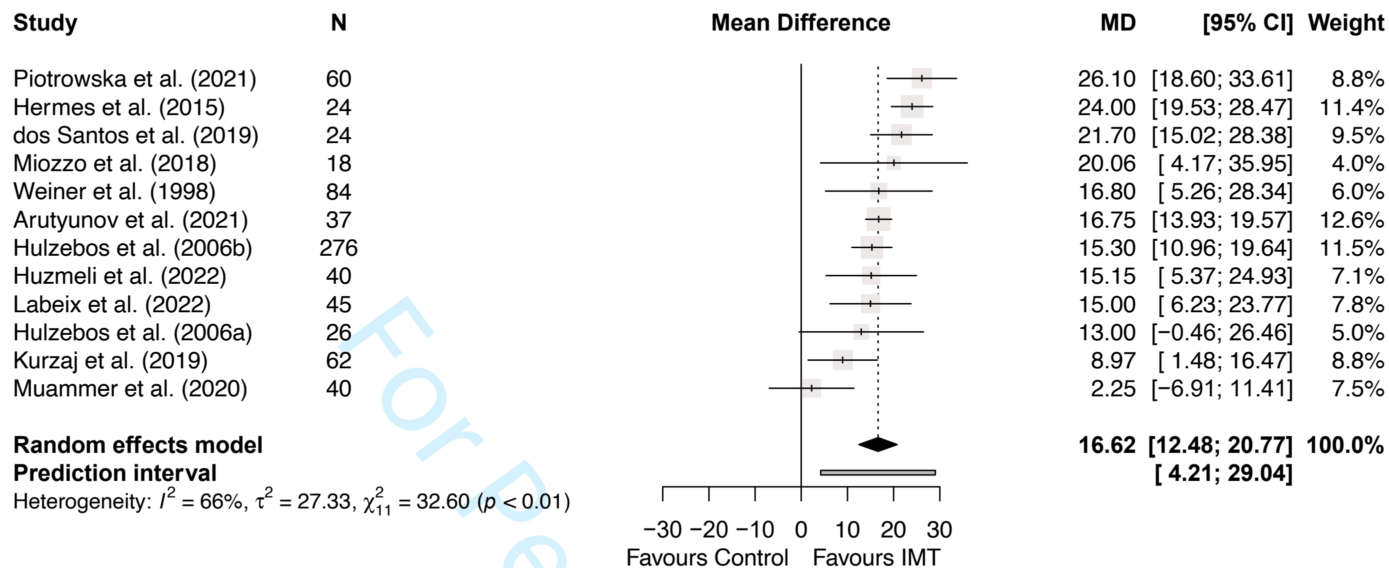

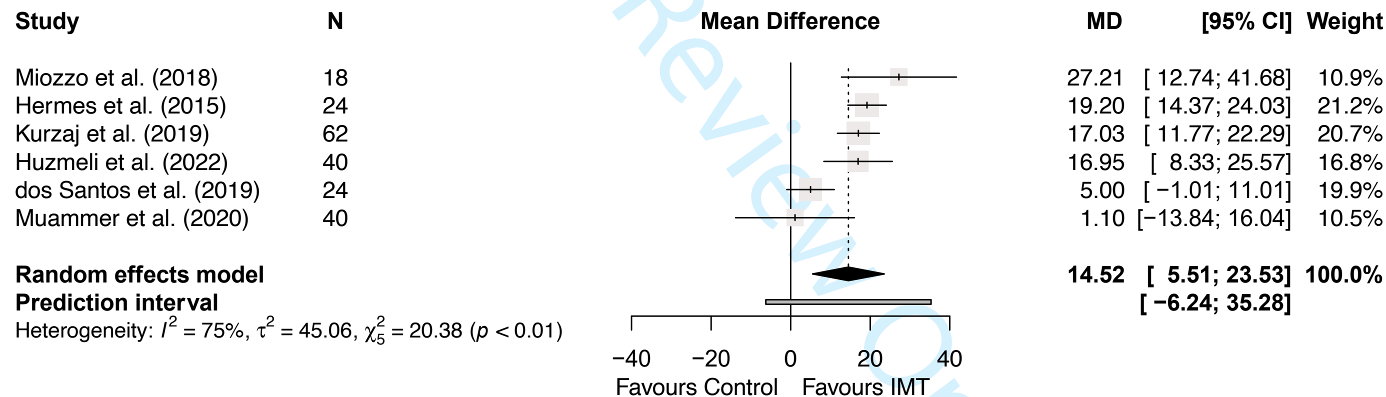

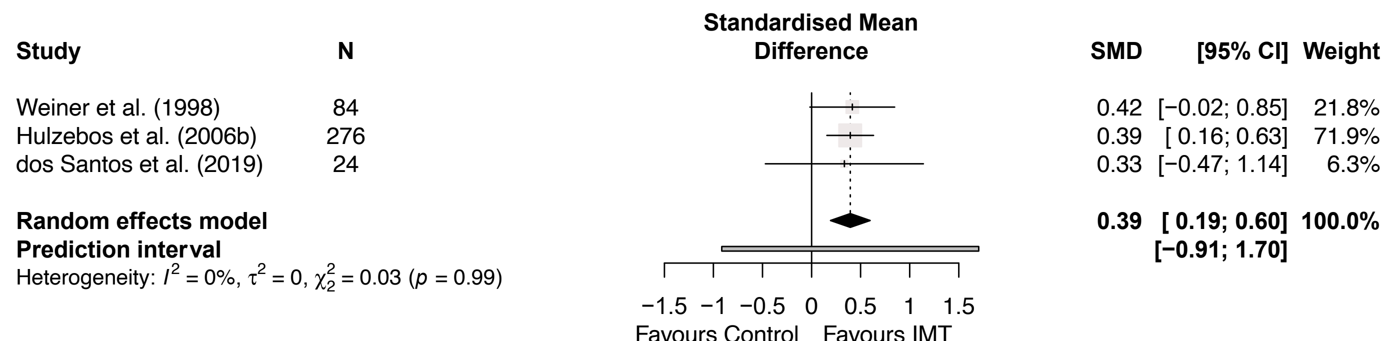

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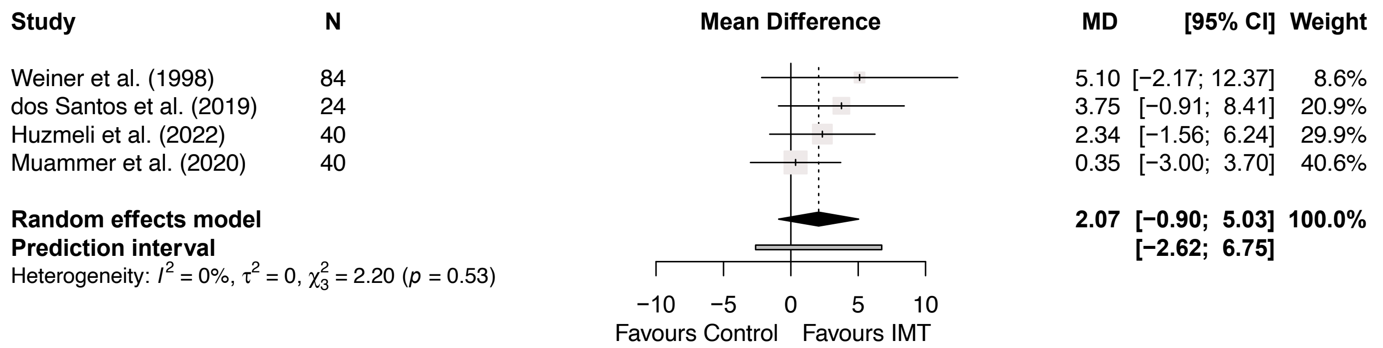

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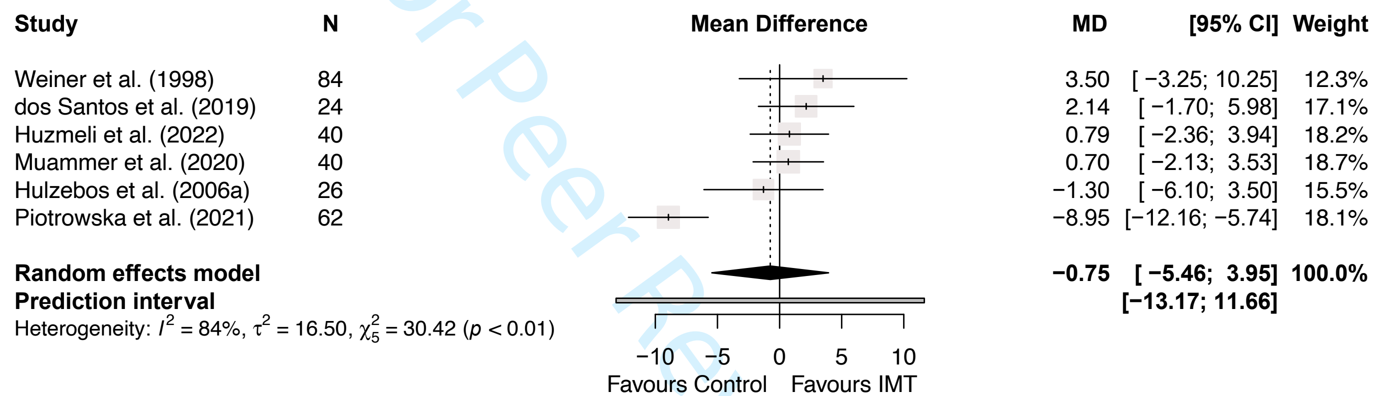

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Appendix B. GRADE assessment criteria.

The certainty of evidence analysis was based on classifying the results into levels of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, which is based on five domains: study limitations (risk of bias), imprecision, indirectness, inconsistency, and publication bias[1,2]. This classification categorizes the evidence as "high quality" (all five domains are also met; further research is very unlikely to change our confidence in the effect estimate), "moderate quality" (one of the five domains is not met; further research is likely to have an important impact on our confidence in the effect estimate and might change the effect estimate), "low quality" (two of the five domains are not met; further research is very likely to have a significant impact on our confidence in the effect estimate and is likely to change the estimate), and "very low quality" (three of the five domains are not met; any effect estimates highly uncertain)[1,2].

Reasons for downgrading

The GRADE approach rates evidence from randomized controlled trials that do not have serious limitations as high certainty. However, the certainty of evidence for the meta-analysis was downgraded according to the presence of the following criteria:

a) Study limitations (risk of bias): recommendations were downgraded one level in the event there was a high risk of bias and serious limitations in the effect estimated according to the Cochrane risk of bias tool and/or PEDro scale (more than 50% of the studies with poor or fair methodological quality: lack of allocation concealment, random allocation, bias of attrition, and/or PEDro scale score <6).

b) Inconsistency: recommendations were downgraded by one level when the inconsistency was substantial ($I^2 > 50\%$ and prediction interval including results different from those stated in the meta-analysis, together with more than 30% of

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studies also favouring a different outcome)[3,4]. Recommendations were downgraded by two levels when the inconsistency was large ($I^2 > 75\%$ and prediction interval including results different from those stated in the meta-analysis, together with more than 30% of studies also favouring a different outcome)[3,4].

c) Indirectness domain: recommendations were downgraded by one level if different populations, interventions, or comparators were found (the recommendations were downgraded in the absence of direct comparisons between the interventions of interest or when there are no key outcomes, and the recommendation is based only on intermediate outcomes or if more than 50% of the participants were outside the target group).

d) Imprecision domain: recommendations were downgraded by one level if fewer than 400 participants were included in the comparison and two levels when the samples sizes were fewer than 100 participants[5,6].

e) Publication bias domain: recommendations were downgraded by one level if there were likely to be unpublished studies that may impact on our confidence in the results obtained (evidence of publication bias due to asymmetry of the funnel plot shape and the Luis Fury Kanamori index, together with a change in the results when a sensitivity analysis adjusted for publication bias was performed).

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Appendix C. PEDro scores for included studies (n = 13).

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	TOTAL
Arutyunov et al. 2021[1]	Y	N	Y	N	N	N	N	N	Y	Y	**4**
dos Santos et al. 2019[2]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**8**
Hermes et al. 2015[3]	Y	N	Y	N	N	Y	Y	Y	Y	Y	**7**
Hulzebos et al 2006a[4]	Y	N	Y	N	N	Y	Y	Y	Y	Y	**7**
Hulzebos et al 2006b[5]	Y	Y	Y	N	N	N	Y	N	Y	Y	**6**
Huzmeli et al 2022[6]	Y	N	N	Y	N	N	N	Y	Y	Y	**5**
Kurzaj et al 2019[7]	Y	Y	Y	N	N	N	Y	Y	N	Y	**6**
Labeix et al. 2022[8]	Y	N	Y	N	N	N	Y	N	Y	Y	**5**
Miozzo et al. 2018[9]	Y	Y	Y	N	N	Y	N	N	Y	Y	**6**
Muammer et al. 2020[10]	Y	N	Y	N	N	Y	Y	N	Y	Y	**6**
Piotrowska et al. 2021[11]	Y	N	Y	N	N	N	Y	N	N	Y	**4**
Valkenet et al. 2017[12]	Y	Y	Y	N	N	N	N	N	Y	Y	**5**
Weiner et al. 1998[13]	Y	N	Y	N	N	N	N	N	Y	Y	**4**
N = No, Y = Yes									**Mean**		**5.6**

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Appendix D. Risk of bias summary and graph.

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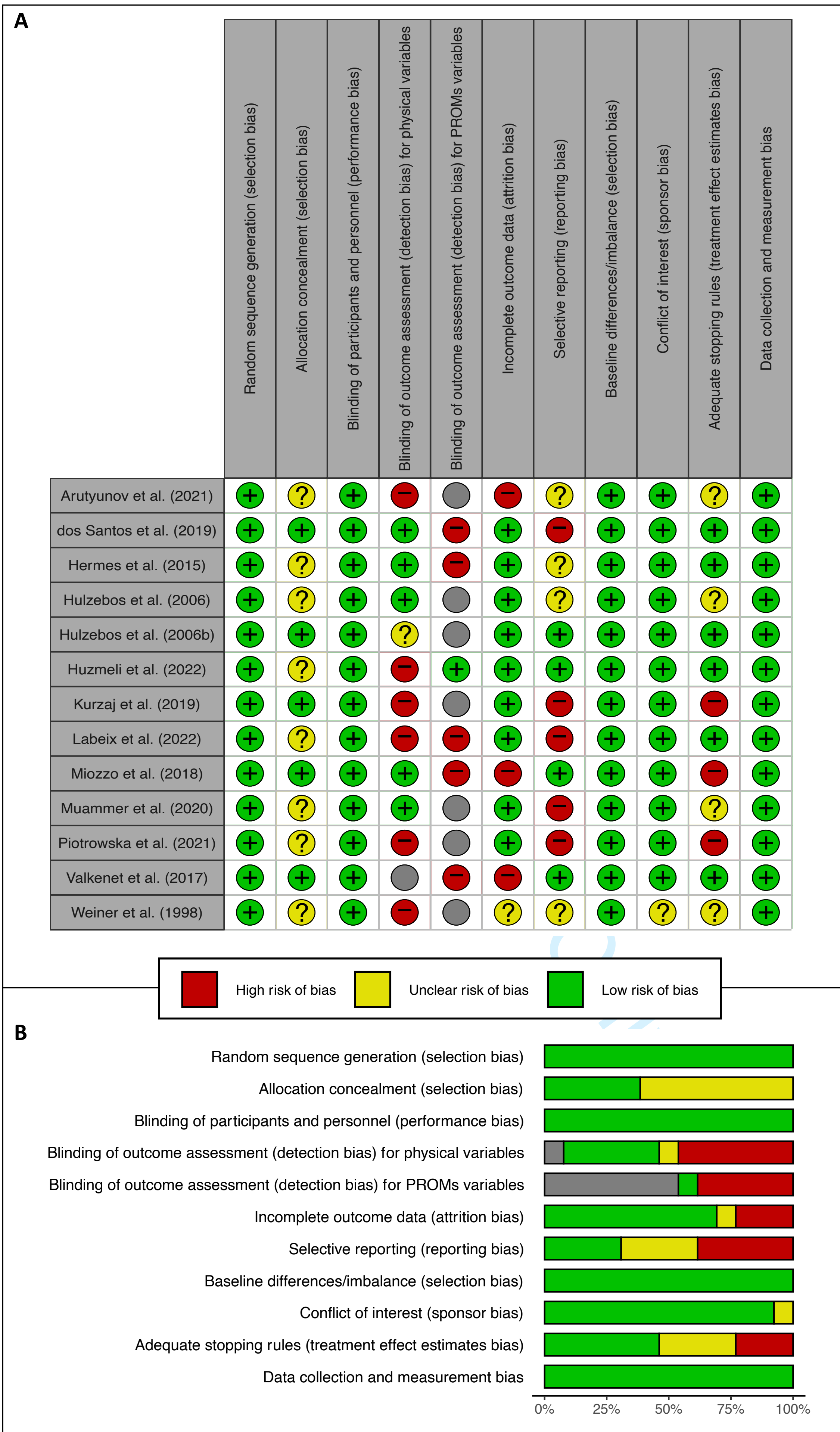


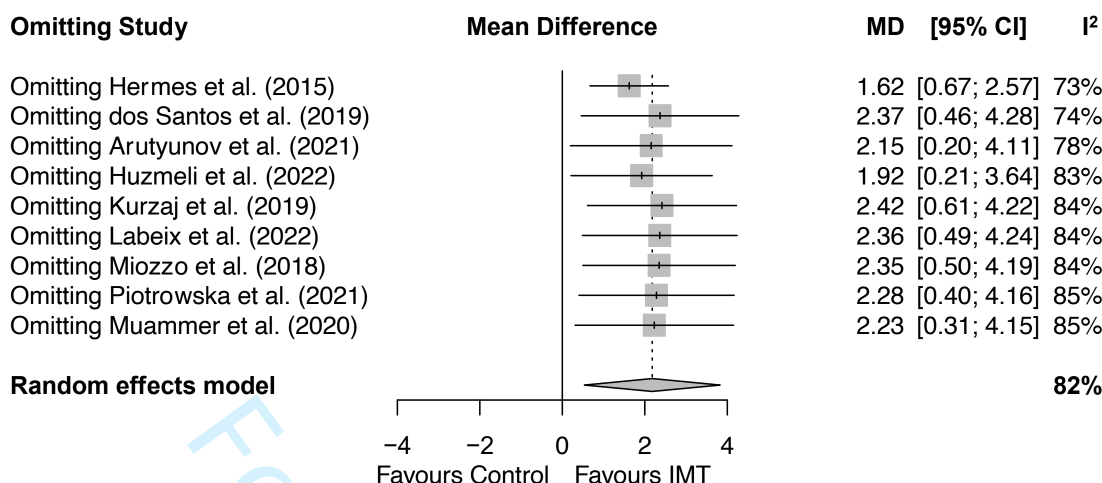
A. Risk of bias summary: review authors' judgements about each Risk of bias item for each included study.

B. Risk of bias graph: review authors' judgements about each Risk of bias item presented as percentages across all included studies.

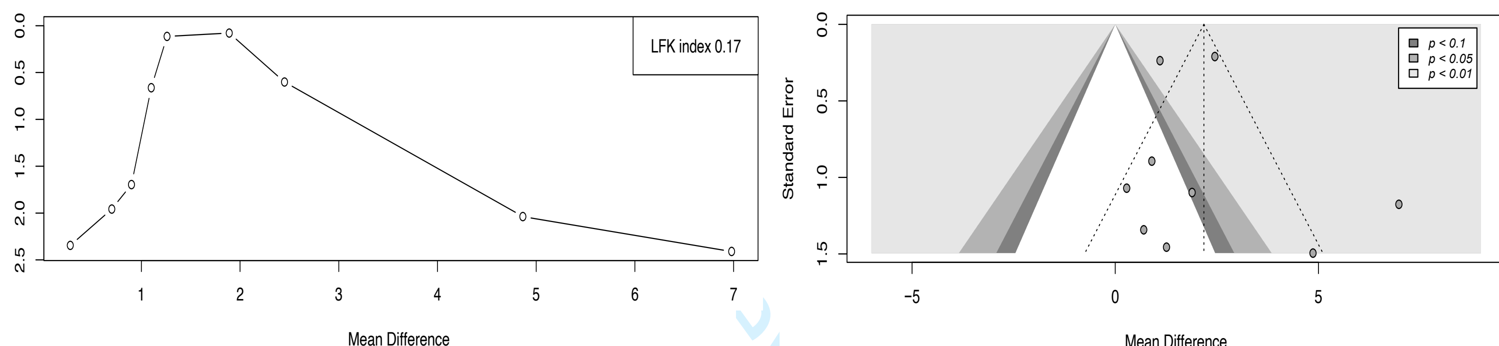
Appendix E. Sensitivity and publication bias funnel plots for functional exercise capacity and health-related quality of life.

FUNCTIONAL EXERCISE CAPACITY (Peak VO2 [mL·Kg^{-1}·min^{-1}])

A. Leave-one-out sensitivity analysis

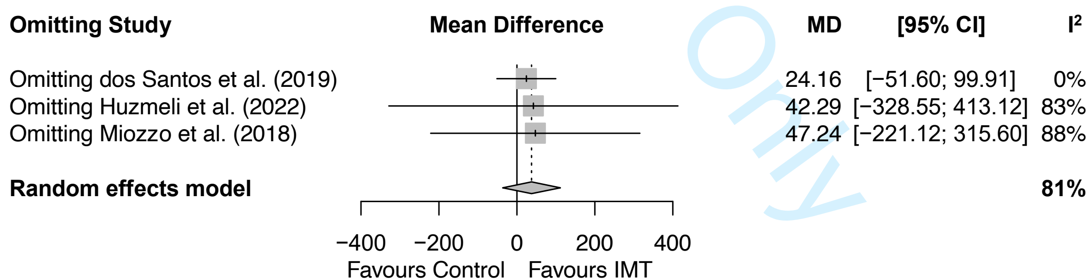


B. Publication bias

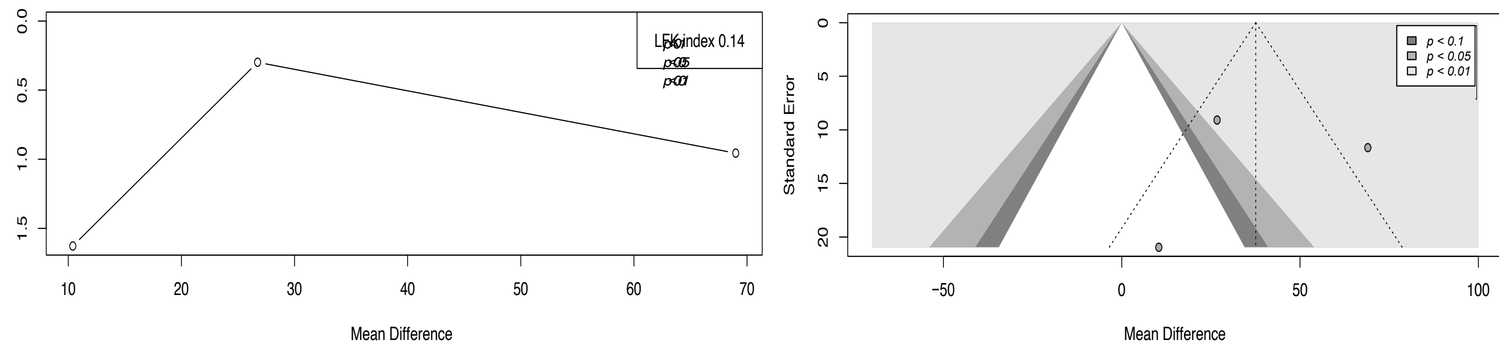


FUNCTIONAL EXERCISE CAPACITY (Six-minute walk distance [m])

A. Leave-one-out sensitivity analysis



B. Publication bias



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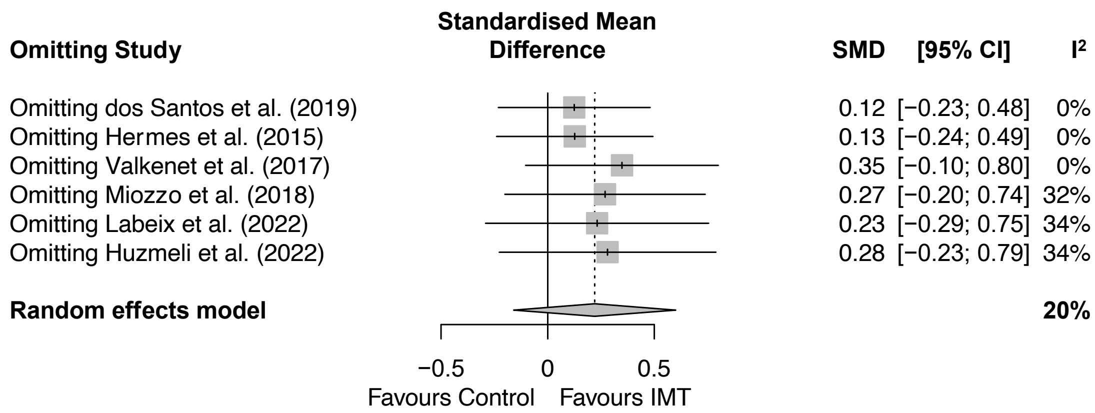
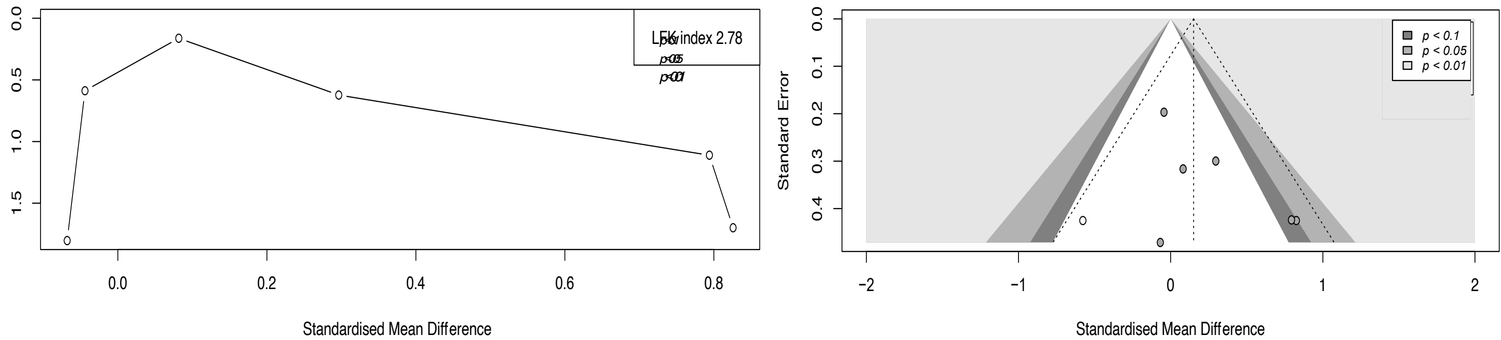
HEALTH-RELATED QUALITY OF LIFE

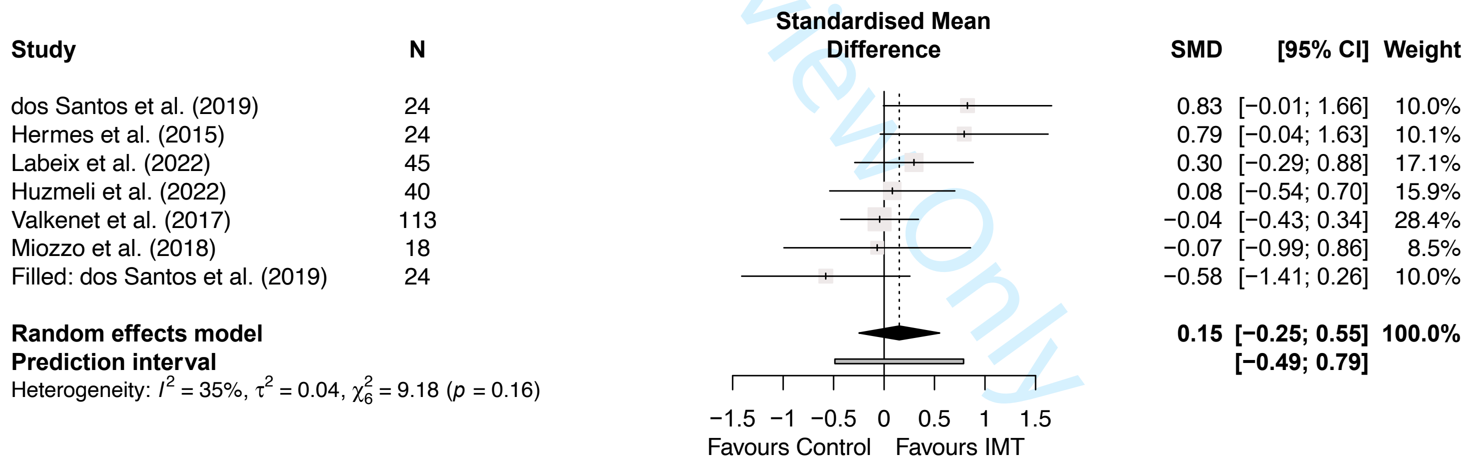
A. **Leave-one-out sensitivity analysis**



B. **Publication bias**



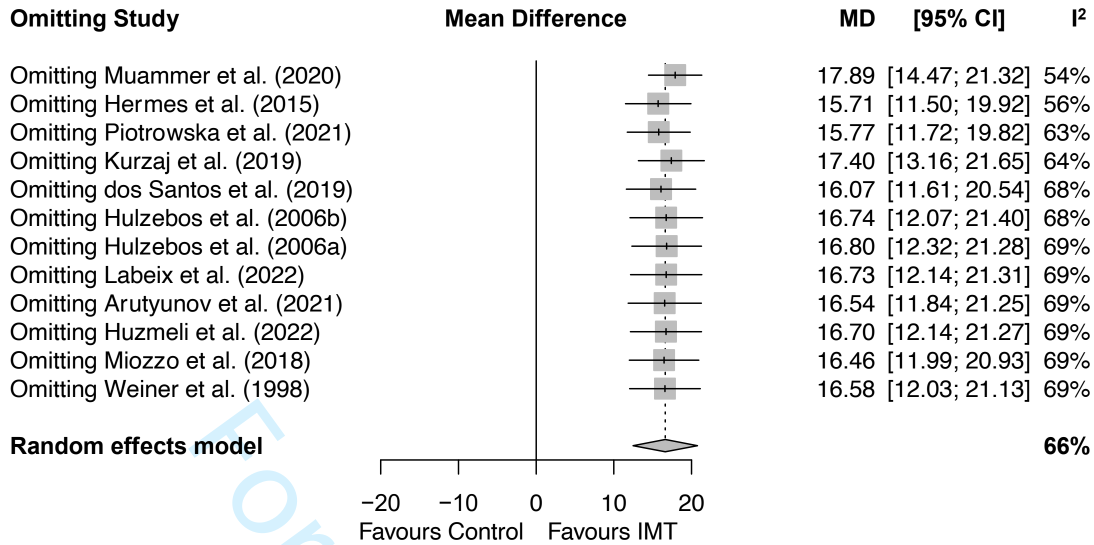
C. **Funnel plot of the studies included in the analysis and the studies filled to adjust for publication bias**



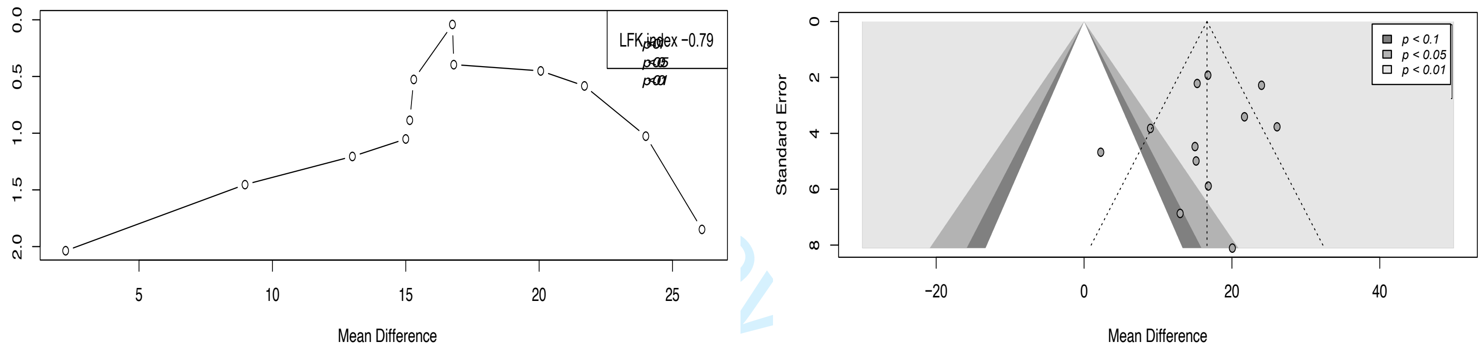
Appendix F. Sensitivity and publication bias funnel plots for respiratory muscle function.

INSPIRATORY MUSCLE STRENGTH (MIP in cmH_2O)

A. Leave-one-out sensitivity analysis

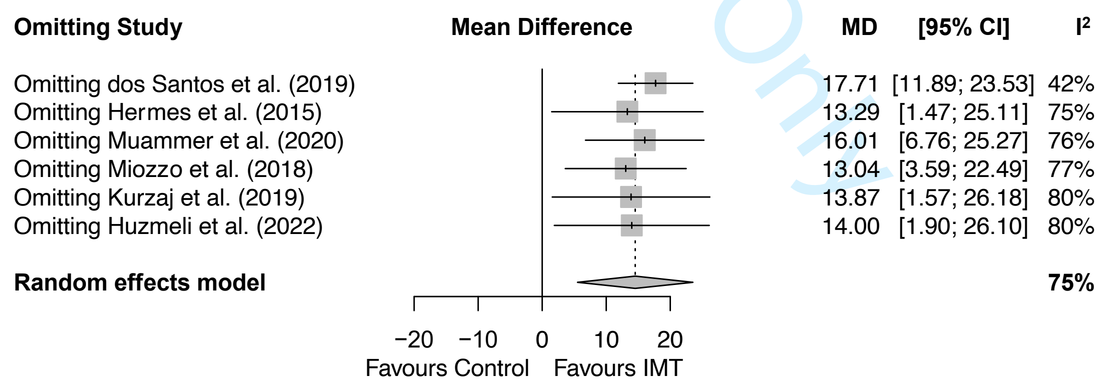


B. Publication bias

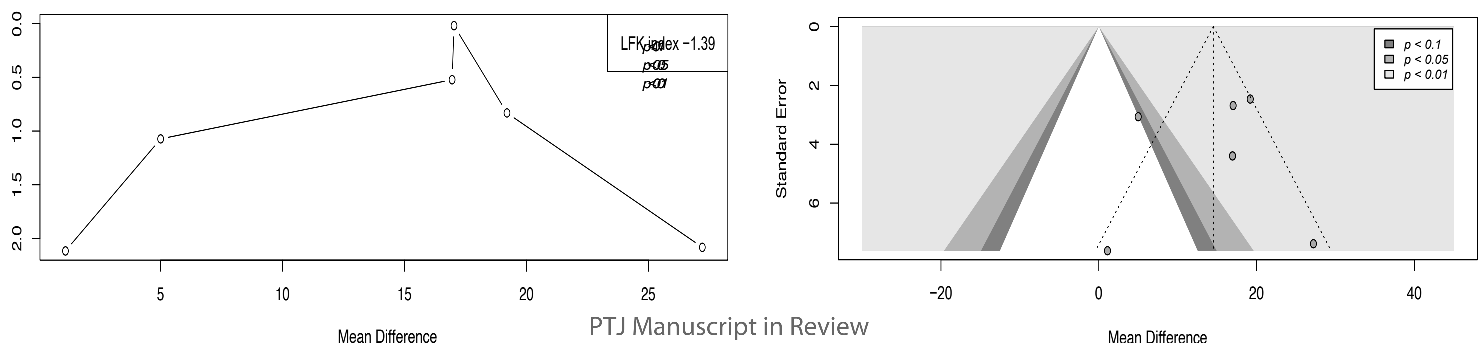


EXPIRATORY MUSCLE STRENGTH (MEP in cmH_2O)

A. Leave-one-out sensitivity analysis



B. Publication bias



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INSPIRATORY MUSCLE ENDURANCE

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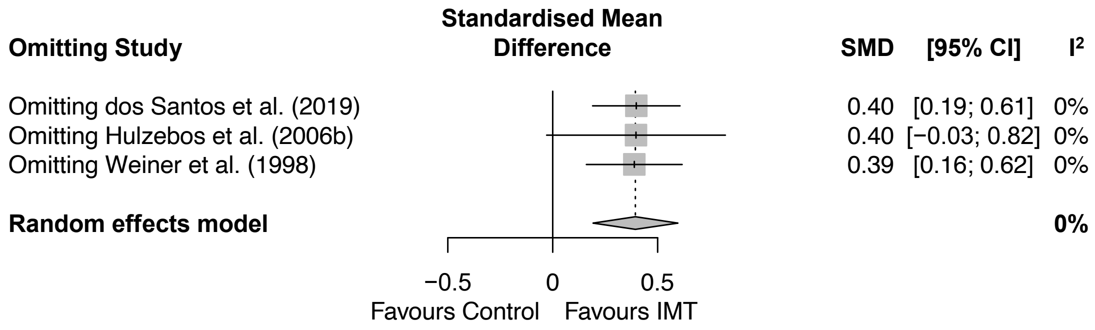
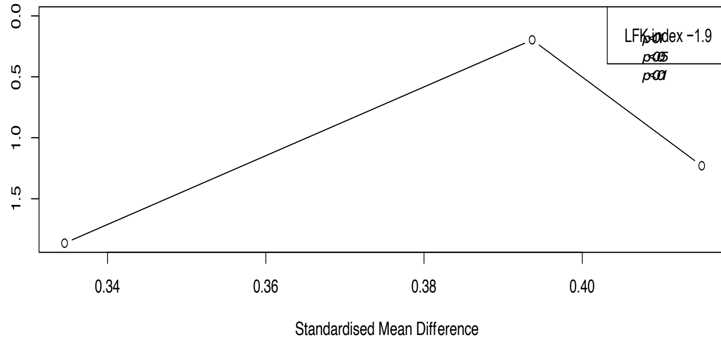
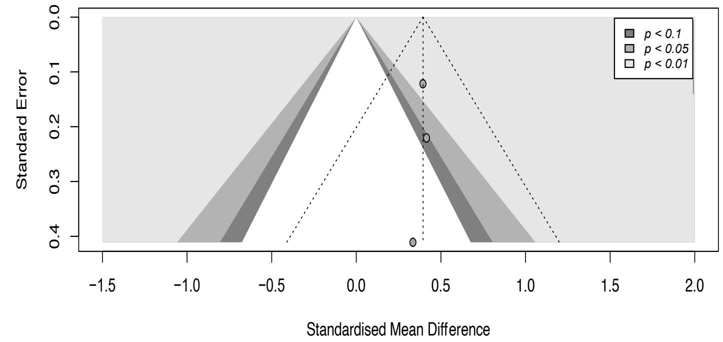
A. **Leave-one-out sensitivity analysis**



B. **Publication bias**





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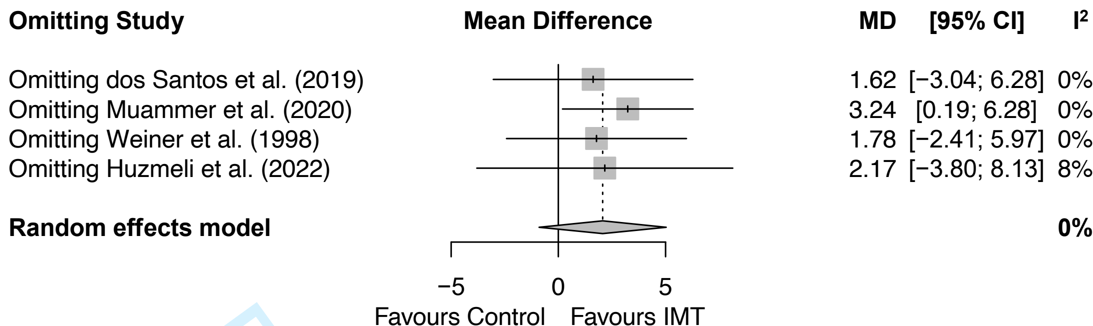
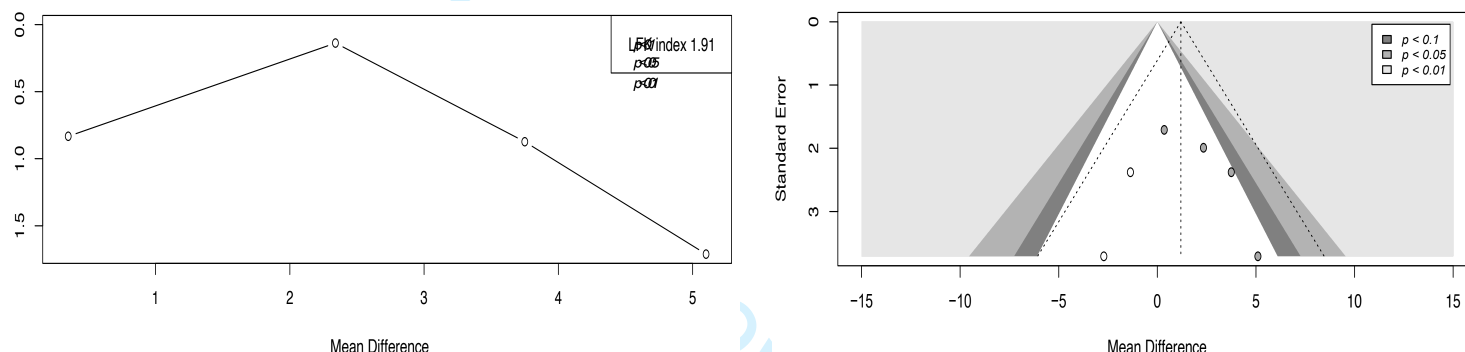
Appendix G. Sensitivity and publication bias funnel plots for pulmonary function.

FORCED VITAL CAPACITY (FVC in % of predicted)

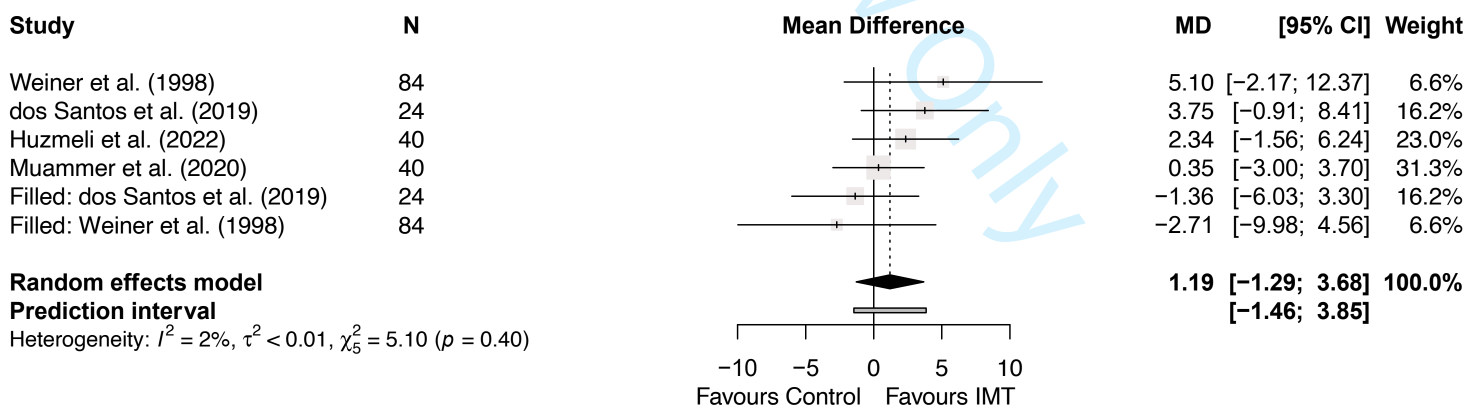
A. Leave-one-out sensitivity analysis



B. Publication bias



C. Funnel plot of the studies included in the analysis and the studies filled to adjust for publication bias



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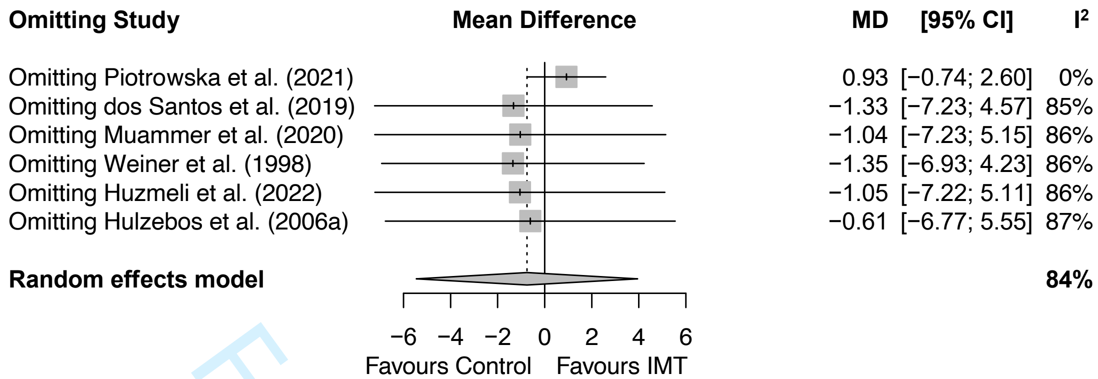
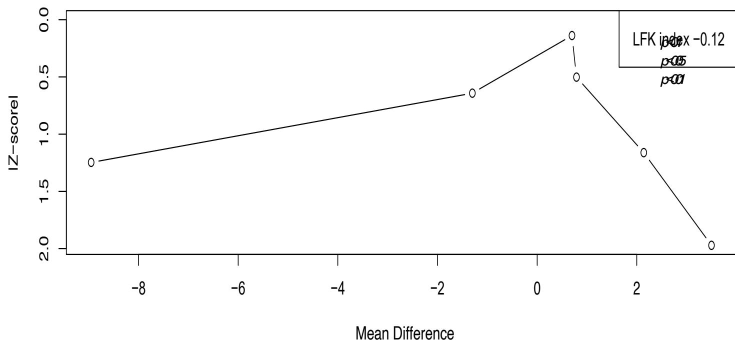
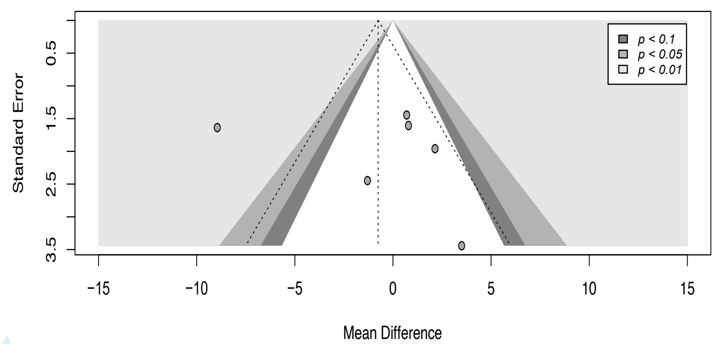
FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV_1 in % of predicted)

A. Leave-one-out sensitivity analysis



B. Publication bias





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