

# The Effect of Exercise Training, IMT and FES on Diastolic Function, Exercise Capacity and Quality of Life in Patients With Heart Failure With Preserved Ejection Fraction: a Systematic Review and Meta-analysis

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## Research

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## Abstract

**Background:** We aimed to better understand the effects of two exercise training interventions [endurance training and a combination of endurance and resistance training (combined exercise)] and two physiotherapies [functional electrical stimulation (FES) and inspiratory muscle training (IMT)] on diastolic function, exercise performance and quality of life (QoL) in heart failure with preserved ejection fraction (HFpEF) patients.

**Methods:** Cochrane Library, EMBASE and MEDLINE via PubMed for randomized controlled trials were searched from their inception to May 2020. The methodological quality was assessed using the Physiotherapy Evidence Database scale. All analyses were used by STATA.

**Results:** A total of 14 articles on 13 trials were included in this meta-analysis with 673 HFpEF patients. The pooling revealed that peak oxygen uptake was improved by endurance training [MD (95% CI): 1.89 ml.kg<sup>-1</sup>.min<sup>-1</sup> (1.32, 2.46), P < 0.001], FES [MD (95% CI): 2.28 ml.kg<sup>-1</sup>.min<sup>-1</sup> (0.92, 3.65), P = 0.001] and IMT [MD (95% CI): 2.72 ml.kg<sup>-1</sup>.min<sup>-1</sup> (1.44, 3.99), P < 0.001]. Similar results were observed for 6-minute walk test and QoL. Besides, endurance training increased arterial venous oxygen difference [MD (95% CI): 1.41 (0.09, 2.74), P = 0.036]. Combined exercise was beneficial to the ratio of peak early to late diastolic mitral inflow velocities [MD (95% CI): -2.90 (-4.97, -0.83), P = 0.006] and the early diastolic mitral annual velocity [MD (95% CI): 1.40 (0.68, 2.12), P = 0.006]. IMT improved ventilation/carbon dioxide ratio slope [MD (95% CI): -3.36 ml.kg<sup>-1</sup>.min<sup>-1</sup> (-6.17, -0.54), P = 0.019].

**Conclusions:** FES and IMT may be therapeutic options to improve functional capacity and QoL in HFpEF patients, and the outcomes are similar to endurance training. Combined exercise tends to improve diastolic function in HFpEF patients.

## Background

Heart failure with preserved ejection fraction (HFpEF) comes about nearly half of heart failure patients in the community, and the mortality and morbidity are high [1, 2]. Exercise intolerance is an important feature of HFpEF, measured objectively as peak oxygen uptake (peak VO<sub>2</sub>) and quality of life (QoL) [3]. Besides one of the mechanisms underlying exercise intolerance has been identified by left ventricular (LV) diastolic function [4]. However, the established neurohormonal-based therapies, used for treating heart failure with reduced ejection fraction (HFrEF), has failed to improve exercise intolerance, provide favorable clinical outcomes and reduce primary endpoints for HFpEF [5].

Exercise training appears to be a promising evidence-based strategy to improve exercise intolerance in HFpEF patients [6]. In current studies, exercise training has consistently been shown to produce clinically meaningful increase in exercise capacity and a reduction in symptoms [7, 8]. However, the previous meta-analyses hold inconsistent opinions on diastolic function in HFpEF patients experiencing exercise training [8-10] due partly to failed to assess the different modalities of exercise training. Thus, we tried to evaluate the effect of different types of exercise training [(endurance, resistance, and a combination of these (combined exercise))] on diastolic function, exercise performance and QoL in patients with HFpEF.

Clinicians should recommend a 30 minutes per day of exercise training tailored to the abilities and resources are particular to each patient and should monitor compliance and address barriers to exercise training in ongoing follow-up [11, 12]. Moreover, HFpEF is often elderly and has many chronic symptoms, their adherence of exercise training remains well below the recommended levels [13]. Therefore, other physical therapy should be carried out to relieve the symptoms of HFpEF.

At present, physiotherapies mainly included inspiratory muscle training (IMT) [14] and functional electrical stimulation (FES) [15], which have been found to improve exercise capacity and QoL in HFrEF [15, 16]. IMT involves exercising the diaphragm-based muscles with inspiratory function, which improves muscle endurance and strength, functional capacity, and ventilator response to exercise and promote the recovery of motor ability [17]. The previous studies have reported that the effect of IMT on patients with heart failure (HF), including improving inspiratory muscle strength, peak VO<sub>2</sub>, QoL and reduced dyspnea. The other physiotherapy involves the application of FES. FES, a neuromuscular stimulation, delivers in a specific recruitment pattern for performing a muscular movement necessary for exercise [15]. Electrically stimulated muscular contraction of lower limb muscles is safe and efficacious to improve the symptoms in chronic HF patients [18, 19]. Moreover, FES elicits benefits in endothelial function, emotional stress and QoL in patients with moderate to severe chronic HF [18, 20]. Notably, the potential benefits from IMT and FES implementation in HFpEF patients may not only be limited in patients unable to undergo exercise training, but also may be expanded in the general HFpEF population.

Despite the above promising data, there has so far been no published meta-analysis to evaluate the impact of IMT and FES modalities on exercise tolerance in patients with HFpEF. Therefore, the present meta-analysis is the first to investigate the effects of different modalities of exercise training (endurance training and combined exercise) and physiotherapies (FES and IMT) on diastolic function and exercise intolerance in HFpEF patients. It should be notable that no trials of separate resistance training meet the inclusion criteria in patients with HFpEF.

## Methods

The present study was approved by the Ethics Committee Board of Lanzhou University Second Hospital (D2019-098) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21].

### Patients and public involvement

This is a meta-analysis based on study-level data and no individual-level data were involved in the study or defining the research question or outcome measures.

### Search strategy

Studies on the effect of physical therapy in HFpEF patients published until May 31, 2020 were searched by Cochrane Library, EMBASE and MEDLINE via PubMed. We used a mix of medical subject heading (MeSH) and keywords including exercise training, aerobic exercise, endurance training, combined training, inspiratory muscle training, functional electrical stimulation, and heart failure with preserved ejection fraction. A manual search of the list of references of all identified studies and review articles was performed for additional relevant studies.

### Study selection

Inclusion criteria included the following: (1) published as randomized controlled trials (RCTs). (2) Patients (aged  $\geq 18$  years) with HFpEF were considered. (3) Patients (physical therapy group) undergoing endurance exercise, combined exercise, FES and IMT were considered. (4) Control group (non-intervention group) included those with a sedentary life style and those having some life-style education.

Articles that failed to meet the inclusion criteria were removed, including reviews, animal studies, non-RCTs, non-English language, those investigations with only healthy participants, and intervention durations with less than 4 weeks. Exercise was defined to allow for inclusion of a broad range of structured physical activities and included endurance, resistance, combined training (endurance and resistance). Additionally, physiotherapies of FES and IMT were included in the definition of exercise for the purpose of this meta-analysis.

### Main outcomes

Primary outcomes of this study were exercise capacity measured by [peak  $VO_2$  and 6-minute walk test (6MWT)], QoL measured by [Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score]. Secondary outcomes were evaluated by diastolic function [measured by the ratio of peak early to late diastolic mitral inflow velocities (E/A), the ratio of early diastolic mitral inflow to annular velocities (E/e'), and the early diastolic mitral annular velocity (e')], ventilation/carbon dioxide ratio slope (VE/ $VCO_2$ ) slope and arterial-venous oxygen difference (A- $VO_2$  Diff).

### Data extraction

The following information was summarized: study characteristics (e.g. authors, year of publication and country), participant characteristics (e.g. age and sample size of different group), study methods/design, period of exercise intervention and outcomes. Full-text articles were retrieved for all title-abstracts that met the eligibility by two reviewers (Chenchen Zhuang and Xufei Luo), and a consensus reached by consulting a third reviewer (Qiongying Wang) if required.

### Risk of Bias

We evaluated the risk of bias for inclusion in this meta-analysis by the Physiotherapy Evidence Database (PEDro) scale [22]. The methodological quality of each article was independently assessed by the two reviewers using a total scale, including eligibility criteria, point estimates and variability, between-group comparisons, intention-to-treat analysis, adequate follow-up, blinded assessors, blinded subjects, blinded therapists, baseline comparability, concealed allocation and random allocation. When a disagreement occurred, a third reviewer was consulted.

### Data synthesis and analysis

For each outcome, the effect size in our study was assessed by the baseline to follow-up change. If the outcome was measured on the same scale, we used weighted mean difference (MD) and 95% confidence intervals (CI). When the  $I^2$  statistic was lower than 30% and  $P < 0.10$ , a fixed-effect model was used; otherwise, a random effects model was used. We assessed publication bias through Egger's regression test. Subgroup analysis was conducted to investigate the effect of different modalities of physical therapies on diastolic function, QoL and exercise performance. Furthermore, to account for differences in the functional capacity and QoL between intervention and control groups, we conducted meta-regression analysis for these outcomes (change in peak  $VO_2$  and change in MLWHF total score). All analyses were based on intention-to-treat data. All analyses were used by STATA version 14.0 (Stata Corporation, College Station, TX).

## Results

### Included studies

The flow chart is shown in Figure 1, screening identified 129 potential reports. After removal of duplicates, 152 records remained. After going through the titles and abstracts, 117 studies were excluded. Then 21 were excluded because they did not report HFpEF. 2 articles were identified as double publication, thus were rated as one study [23, 24]. Ultimately, 11 RCTs on conventional physical therapies [7, 23-32] and 3 RCTs on non-conventional physical therapies were included in this meta-analysis [18, 33, 34].

### Characteristics of studies

The basic characteristics of each study were summarized in Table 1. A total of 14 articles on 13 trials including 673 HFpEF patients were included in the present meta-analysis. One of all RCTs included not only FES intervention, but also IMT intervention [33]. Our original intention was to evaluate the effects of physiotherapy (FES and IMT) and exercise training (endurance training and combined exercise), respectively. The mean age of participants ranged from 60.5 to 75 years, and the proportion of women ranged from 35.6 to 100%. Primary outcomes of the study were exercise capacity (measured by peak  $VO_2$  and 6MWT), QoL (measured by MLHFQ total score). Secondary outcomes that were also evaluated in the study included diastolic function (measured by E/A, E/e' and e'), VE/ $VCO_2$  slope and A- $VO_2$  Diff.

### Quality assessment

The quality of included RCTs is presented in Table 2. In none of the studies was there objective evidence of imbalance in baseline characteristics between the intervention and control groups. The moderate risk of bias was due to inadequate blinding of participants and therapists, allocation concealment and intention-to-treat methodologies. Some may be contributed to insufficient reporting rather than inherent design weakness.

### Diastolic function

Eight trials with 416 patients reported on E/A (Fig. 2. A). The heterogeneity was small ( $I^2 = 0\%$ ,  $P = 0.606$ ), using a fixed-effect model. E/A was no change by endurance training [MD (95% CI): 0.03 (-0.03, 0.09),  $P = 0.307$ ], combined exercise [MD (95% CI): -0.03 (-0.17, 0.11),  $P = 0.678$ ], and FES [MD (95% CI): -0.12 (-0.29, 0.05),  $P = 0.162$ ].

Ten trials with 416 patients reported on E/e' (Fig. 2. B). There was a statistical heterogeneity ( $I^2 = 43.1\%$ ,  $P = 0.071$ ), using a random-effect model. E/e' was improved by combined exercise with one included study [MD (95% CI): -2.90 (-4.97, -0.83),  $P = 0.006$ ]. There was no change in E/e' by endurance training [MD (95% CI): -0.03 (-2.83, 2.78),  $P = 0.983$ ], FES [MD (95% CI): -2.16 (-4.41, 0.09),  $P = 0.060$ ] and IMT [MD (95% CI): -1.10 (-4.56, 2.36),  $P = 0.533$ ].

Four trials with 215 patients reported on e' (Fig. 2. C). There was a statistical heterogeneity ( $I^2 = 81.3\%$ ,  $P = 0.001$ ), using a random-effect model. e' was improved by combined exercise with one included study [MD (95% CI): 1.40 (0.68, 2.12),  $P = 0.001$ ]. There was no change in e' by endurance training [MD (95% CI): -2.90 (-4.97, -0.83),  $P = 0.140$ ] and IMT [MD (95% CI): 0.30 (-1.28, 1.88),  $P = 0.709$ ].

### Quality of life

Thirteen trials with 560 patients reported on the MLHFQ total score (Fig. 3). The heterogeneity was small ( $I^2 = 28.5\%$ ,  $P = 0.158$ ), using a fixed-effect model. The MLHFQ total score was improved by endurance training [MD (95% CI): -9.13 (-12.98, -5.28),  $P < 0.001$ ], FES [MD (95% CI): -14.74 (-22.44, -7.08),  $P < 0.001$ ] and IMT [MD (95% CI): -11.49 (-20.08, -2.91),  $P = 0.009$ ]. However, the MLHFQ total score was not significantly changed by combined exercise [MD (95% CI): -6.00 (-15.99, 3.99),  $P = 0.239$ ]. Meta-regression analysis showed no significant effect of exercise period, age and sex on the pooled MD (exercise period: meta-regression coefficient, 1.116;  $P = 0.574$ ; age: meta-regression coefficient, -0.689;  $P = 0.800$ ; sex: meta-regression coefficient, -0.523;  $P = 0.852$ ).

### Exercise performance

Our meta-analysis could be performed for two functional capacity indicators: 6MWT and peak  $VO_2$ ; one exercise physiology parameter: VE/VCO<sub>2</sub> slope.

Eight trials with 411 patients reported on 6MWT (Fig. 4. A). The heterogeneity was small ( $I^2 = 0.0\%$ ,  $P = 0.560$ ), using a fixed-effect model. 6MWT was increased by endurance training [MD (95% CI): 38.79 m (19.97, 57.61),  $P < 0.001$ ] and FES [MD (95% CI): 52.77 m (30.61, 74.93),  $P < 0.001$ ]. However, there was no change after IMT [MD (95% CI): 84.00 m (-31.73, 199.73),  $P = 0.155$ ] and combined exercise [MD (95% CI): 7.00 m (-37.61, 51.61),  $P = 0.758$ ].

Thirteen trials with 411 patients reported on peak  $VO_2$  (Fig. 4. B). The heterogeneity was small ( $I^2 = 0.0\%$ ,  $P = 0.739$ ), using a fixed-effect model. Peak  $VO_2$  was improved by endurance training [MD (95% CI): 1.89 ml.kg<sup>-1</sup>.min<sup>-1</sup> (1.32, 2.46),  $P < 0.001$ ], FES [MD (95% CI): 2.28 ml.kg<sup>-1</sup>.min<sup>-1</sup> (0.92, 3.65),  $P = 0.001$ ], IMT [MD (95% CI): 2.72 ml.kg<sup>-1</sup>.min<sup>-1</sup> (1.44, 3.99),  $P < 0.001$ ] and combined exercise [MD (95% CI): 3.30 ml.kg<sup>-1</sup>.min<sup>-1</sup> (0.44, 6.16),  $P = 0.024$ ]. Meta-regression analysis showed no significant effect of exercise period, age and sex on the pooled MD (age: meta-regression coefficient, 0.007;  $P = 0.989$ ; sex: meta-regression coefficient, 0.010;  $P = 0.826$ ). However, exercise period affected the change of peak  $VO_2$  (meta-regression coefficient, -0.736;  $P = 0.036$ ).

Eleven trials with 502 patients reported on VE/VCO<sub>2</sub> slope (Fig. 4. C). There was a statistical heterogeneity ( $I^2 = 39.9\%$ ,  $P = 0.083$ ), using a random-effect model. VE/VCO<sub>2</sub> slope was improved by IMT [MD (95% CI): -3.36 (-6.17, -0.54),  $P = 0.019$ ]. No significant difference was found after endurance training [MD (95% CI): -1.04 (-2.73, 0.64),  $P = 0.226$ ], FES [MD (95% CI): 0.35 (-2.67, 3.37),  $P = 0.819$ ], and combined exercise [MD (95% CI): -1.90 (-4.44, 0.64),  $P = 0.142$ ]. Smart et al. [26] may be the source of heterogeneity due to the small sample.

### A-VO<sub>2</sub> Diff

Two trials with 99 patients reported on A-VO<sub>2</sub> Diff (Fig. 5). The two trials were both belonged to endurance training. The heterogeneity was small ( $I^2 = 0.0\%$ ,  $P = 0.462$ ). A-VO<sub>2</sub> Diff was improved by endurance training [MD (95% CI): 1.41 (0.09, 2.74),  $P = 0.036$ ].

## Discussion

The present meta-analysis summarized data from 14 on 13 RCTs that examined the effects of two exercise training interventions and two physiotherapies on diastolic function, exercise performance and QoL in HFpEF patients. FES and IMT improved exercise performance and QoL, and the outcomes were similar to endurance training, but the change of diastolic function on FES, IMT and endurance training was not found. Notably, combined exercise has a potential to improve diastolic function on HFpEF patients.

The previous studies have focused primarily on overall exercise training rather than the different types of exercise training. The meta-analysis of Gomes-Neto et al. [35] only conducted endurance training and failed to represent other exercise modality. They showed that exercise training improved peak  $VO_2$  and QoL, but exercise training failed to improve diastolic function. The meta-analysis of Fukuta et al. [10] showed that exercise training improved exercise capacity in HFpEF patients. But a methodological limitation was the combination of results from Fukuta et al. that investigated endurance training and combined exercise. Besides, The previous meta-analyses held inconsistent opinions on diastolic function in HFpEF patients during exercise training [8-10]. Thus, the present meta-analysis compensated for the weakness of the previous studies.

The present meta-analysis observed that functional capacity indicators (peak  $\text{VO}_2$  and 6MWT) and QoL were improved by FES and IMT, as well as exercise training. The positive result of QoL in endurance training or combined exercise is in accordance with the previous meta-analyses [8-10]. In addition, the evaluation of A- $\text{VO}_2$  Diff is only reported by endurance training, showing a positive result. The peak  $\text{VO}_2$  may affect oxygen delivery and/or utilization via cardiac, vascular and skeletal muscle function [36-39]. Besides, the active skeletal muscle is the major reason to induce the augment of peak  $\text{VO}_2$  in HFpEF patients, including oxidative enzyme activity, capillary density and mitochondrial density [29].

Our findings showed that combined exercise improved  $E/e'$  and  $e'$ , failed to improve E/A, whereas, endurance training, FES and IMT failed to improve diastolic function. Smart et al. [26] suggested that 16-week endurance training may not be sufficient to elicit alteration in myocardial properties. Meanwhile, Fujimoto et al. [40] reported that 1-year endurance training had little effect on LV compliance and cardiovascular stiffness in HFpEF patients. Conversely, Edelmann et al. [23] reported that combined exercise improved diastolic function, as evidenced by a significant reduction in  $E/e'$  and  $e'$ . Diastolic function may be impacted by peripheral determinants (e.g. oxygen use by skeletal muscle, body mass index, etc), not by central determinants (e.g. E/A, E/E', etc) [41]. In response to exercise training, cardiac relaxation may be compounded by abnormalities in skeletal muscle oxygen use, which augments cardiac output, and flow into a small, stiff and slowly relaxing heart [42, 43]. Thus, the different results of diastolic function between combined exercise and endurance training may be induced by resistance training, which adds muscle bulk to peripheral muscles and increases bone mass.

FES improves selected muscle in a coordinated manner and the aerobic oxidative capacity, which results in a functional pattern such as walking, cycling, or rowing [44-48]. FES seems to act primarily on peripheral vascular system, whereas its effects may be indirect on central diastolic function. Moreover, IMT improve pathophysiologic manifestations of HF via breathing against an external inspiratory load. Prior literature has reported improvement in exercise capacity, functional autonomy, diaphragmatic thickness and mobility, and cardiac autonomic control.

Our result showed that IMT significantly improved  $\text{VE}/\text{VCO}_2$  slope, but no positive effect was found in other types of physical therapy. Various studies of HF patients have shown that selective respiratory muscle training improved submaximal and maximal exercise capacity and/or perceived dyspnea during daily living activities in HFpEF patients [17, 49-54]. Interestingly, the magnitude of outcome in HFpEF patients following IMT intervention was similar [17, 54] or even stronger [49, 51, 52] compared to other important trials aiming to evaluate the effect of IMT in HFpEF patients. The development of diaphragmatic fatigue is a delay, leading to a reduction in the recruitment of accessory respiratory muscles, and an improved ventilatory efficiency [53, 55].

### **Strengths and limitation**

Although this study shows that FES and IMT may be effective for HFpEF, which may be an compensate rehabilitation to patients unable to experience exercise training. Moreover, combined exercise exhibits a positive effect on diastolic function

All included studies were RCTs, and none were rated as poor in methodological quality according to the PEDro score, which suggests that the data presented are reliable. However, some included RCTs have small sample sizes, and according to the subgroup analysis of the different modalities of physical therapy on cardiac function, QoL and exercise performance. Second, there are only two studies reported combined exercise, however, they share one set of date using different results [23, 24].

Further research is needed to pay more attention to the mechanism of hemodynamics and muscle function on HFpEF patients experiencing physical therapy. Besides, larger scale, good quality RCTs are needed for further investigating the effect of combined exercise, FES and IMT on patients with HFpEF.

## **Conclusions**

In conclusion, our meta-analysis suggests that FES and IMT tend to a positive effect to HFpEF patients, the positive outcomes may be superior to exercise training. Besides, IMT tends to improve  $\text{VE}/\text{VCO}_2$  slope. FES and IMT are surrogate rehabilitation for patients unable of exercise training.

## **Declarations**

### **Consent for publication**

The present study was approved by the Ethics Committee Board of Lanzhou University Second Hospital (D2019-098).

### **Competing interests**

No potential conflict of interest was reported by the authors.

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### **Author Contributions**

1. Conception and design: Chenchen Zhuang and Jing Yu
2. Administrative support: Lanzhou University Second Hospital
3. Provision of study: Xufei Luo
4. Collection and assembly of data: Chenchen Zhuang and Xufei Luo

5. Data analysis and interpretation: Chenchen Zhuang and Xufei Luo
6. Manuscript writing: All authors
7. Final approval of manuscript: All authors

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## Tables

Table 1

## Characteristics of the included studies

| Article, year           | Country | Study sample                    | Participants include in the analysis                                                                                                                 | Intervention/comparison groups                                           | Duration of trial period                                                                                                                                  | Outcomes                                                                                 |
|-------------------------|---------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Palau (2019)            | Spain   | NYHA class I-III<br>LVEF > 50%  | Total patients: n = 28<br>G1: n = 15, 6 males/9 females, mean age (SD): 72 (9)<br>G2: n = 13, 4 males/9 females, mean age (SD): 75 (9)               | G1: FES<br>G2: Usual care                                                | Twice per week for 12 weeks                                                                                                                               | E/e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                              |
| Palau (2019)            | Spain   | NYHA class I-III<br>LVEF > 50%  | Total patients: n = 28<br>G1: n = 15, 7 males/8 females, mean age (SD): 75 (10)<br>G2: n = 13, 4 males/9 females, mean age (SD): 75 (9)              | G1: IMT<br>G2: Usual care                                                | Twice per week for 12 weeks                                                                                                                               | E/e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                              |
| Palau (2019)            | Spain   | NYHA class I-III<br>LVEF > 50%  | Total patients: n = 28<br>G1: n = 15, 6 males/9 females, mean age (SD): 72 (9)<br>G2: n = 13, 4 males/9 females, mean age (SD): 75 (9)               | G1: FES<br>G2: Usual care                                                | Twice per week for 24 weeks                                                                                                                               | E/e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                              |
| Palau (2019)            | Spain   | NYHA class I-III<br>LVEF > 50%  | Total patients: n = 28<br>G1: n = 15, 7 males/8 females, mean age (SD): 75 (10)<br>G2: n = 13, 4 males/9 females, mean age (SD): 75 (9)              | G1: IMT<br>G2: Usual care                                                | Twice per week for 24 weeks                                                                                                                               | E/e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                              |
| Maldonado-Martín (2017) | Spain   | NYHA class II-III<br>LVEF > 50% | Total patients: n = 47, 6 males/41 females<br>G1: n = 23, mean age (SD): 67.5 (5.9)<br>G2: n = 24, mean age (SD): 65.6 (4.8)                         | G1: Endurance training<br>G2: Attention control group                    | Three times per week for 16 weeks                                                                                                                         | 6MWT, peak VO <sub>2</sub>                                                               |
| Kitzman (2016)          | USA     | NYHA class II-III<br>LVEF > 50% | Total patients: n = 100<br>G1: n = 51, 10 males/41 females, mean age (SD): 66.9 (5.5)<br>G2: n = 49, 9 males/40 females, mean age (SD): 66.0 (4.8)   | G1: Endurance training<br>G2: No intervention                            | Three times per week for 20 weeks                                                                                                                         | E/A, E/e', e', 6MWT, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                    |
| Fu (2016)               | China   | NYHA class II-III<br>LVEF > 50% | Total patients: n = 59<br>G1: n = 30, 20 males/10 females, mean age (SD): 60.5 (14.8)<br>G2: n = 29, 18 males/11 females, mean age (SD): 62.4 (12.9) | G1: Endurance training<br>G2: General health care                        | Three sessions per week for 12 weeks                                                                                                                      | E/A, E/e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope, A-VO <sub>2</sub> Diff |
| Nolte (2015)            | Germany | NYHA class II-III<br>LVEF > 50% | Total patients: n = 64<br>G1: n = 44, 20 males/24 females, mean age (SD): 64 (8)<br>G2: n = 20, 8 males/12 females, mean age (SD): 65 (6)            | G1: A combination of endurance and resistance training<br>G2: Usual care | Weeks 1-4: endurance training two times per week<br>From week 5 onward: endurance training three times per week<br>Resistance training two times per week | E/A, VE/VCO <sub>2</sub> slope                                                           |
| Karavidas (2013)        | Greece  | NYHA class II-III<br>LVEF > 50% | Total patients: n = 30<br>G1: n = 15, 6 males/9 females, mean age (SD): 69.4 (8.6)<br>G2: n = 15, 6 males/9 females, mean age (SD): 68.5 (7.9)       | G1: FES<br>G2: A placebo training                                        | Five times per week for 6 weeks                                                                                                                           | E/A, E/e', QoL, 6MWT                                                                     |
| Kitzman (2013)          | USA     | NYHA class II-III               | Total patients: n = 63                                                                                                                               | G1: Endurance training<br>G2: Attention control                          | Three times per week for 16 weeks                                                                                                                         | E/A, QoL, 6MWT, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope                         |

|                  |           |                                 |                                                                                                                                           |                                                                          |                                                                                                                                                           |                                                                      |
|------------------|-----------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
|                  |           | LVEF > 50%                      | G1: n = 32, 72% females, mean age (SD): 70 (7)<br>G2: n = 31, 80% females, mean age (SD): 70 (7)                                          |                                                                          |                                                                                                                                                           |                                                                      |
| Palau (2013)     | Spain     | NYHA class I-IV<br>LVEF > 50%   | Total patients: n = 26<br>G1: n = 14, 7 males/7 females, mean age (SD): 68 (13)<br>G2: n = 12, 6 males/6 females, mean age (SD): 74 (3)   | G1: IMT<br>G2: No intervention                                           | Two sessions per week for 12 weeks                                                                                                                        | E/e', e', QoL, 6MWT                                                  |
| Smart (2012)     | Australia | NYHA class I-II<br>LVEF > 50%   | Total patients: n = 25<br>G1: n = 12, 7 males/5 females, mean age (SD): 68 (11)<br>G2: n = 13, 6 males/7 females, mean age (SD): 65 (6)   | G1: Endurance training<br>G2: Sedentary control group                    | Three times per week for 16 weeks                                                                                                                         | E/A, E/e', e', QoL, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope |
| Haykowsky (2012) | USA       | NYHA class II-III               | Total patients: n = 40<br>G1: n = 22, 4 males/18 females, mean age (SD): 70 (6)<br>G2: n = 18, 1 males/17 females, mean age (SD): 68 (5)  | G1: Endurance training<br>G2: Attention control group                    | Three times per week for 16 weeks                                                                                                                         | Peak VO <sub>2</sub> , A-VO <sub>2</sub> Diff                        |
| Alves (2012)     | Portugal  | NYHA class I-III<br>LVEF > 50%  | Total patients: n = 31, 22 males/9 females, mean age (SD): 62.9 (10.2).<br>G1: n = 20<br>G2: n = 11                                       | G1: Endurance training<br>G2: No intervention                            | Three times per week for 24 weeks                                                                                                                         | E/A                                                                  |
| Edelmann (2011)  | Germany   | NYHA class II-III<br>LVEF > 50% | Total patients: n = 64<br>G1: n = 44, 20 males/24 females, mean age (SD): 64 (8)<br>G2: n = 20, 8 males/12 females, mean age (SD): 65 (6) | G1: A combination of endurance and resistance training<br>G2: Usual care | Weeks 1-4: endurance training two times per week<br>From week 5 onward: endurance training three times per week<br>Resistance training two times per week | E/e', e', QoL, 6MWT, peak VO <sub>2</sub>                            |
| Kitzman (2010)   | USA       | NYHA class II-III<br>LVEF > 50% | Total patients: n = 53<br>G1: n = 26, 6 males/20 females, mean age (SD): 70 (6)<br>G2: n = 27, 7 males/20 females, mean age (SD): 69 (5)  | G1: Endurance training<br>G2: Attention control group                    | Three times per week for 16 weeks                                                                                                                         | E/A, QoL, 6MWT, peak VO <sub>2</sub> , VE/VCO <sub>2</sub> slope     |
| Gary (2004)      | USA       | NYHA class II-III<br>LVEF > 50% | Total patients: n = 28<br>G1: n = 15, 15 females, mean age (SD): 67 (11)<br>G2: n = 13, 13 females, mean age (SD): 69 (11)                | G1: Endurance training<br>G2: Control group                              | Three sessions per week for 12 weeks                                                                                                                      | QoL, 6MWT                                                            |

NYHA: New York Heart Association

Table 2

## Risks of bias among the included studies

| Article, year           | Eligibility criteria | Random allocation | Concealed allocation | Baseline comparability | Blind subjects | Blind therapists | Blind assessors | Adequate follow-up | Intention to treat analysis | Between-group comparisons | Poi esti and vari |
|-------------------------|----------------------|-------------------|----------------------|------------------------|----------------|------------------|-----------------|--------------------|-----------------------------|---------------------------|-------------------|
| Palau (2019)            | YES                  | YES               | NO                   | YES                    | NO             | YES              | YES             | YES                | NO                          | YES                       | YES               |
| Maldonado-Martín (2017) | YES                  | YES               | NO                   | YES                    | NO             | YES              | NO              | YES                | NO                          | YES                       | YES               |
| Kitzman (2016)          | YES                  | YES               | NO                   | YES                    | NO             | YES              | NO              | YES                | YES                         | YES                       | YES               |
| Fu (2016)               | YES                  | NO                | NO                   | YES                    | NO             | NO               | NO              | YES                | NO                          | YES                       | YES               |
| Nolte (2015)            | YES                  | YES               | NO                   | YES                    | NO             | NO               | NO              | YES                | NO                          | YES                       | YES               |
| Karavidas (2013)        | YES                  | YES               | NO                   | YES                    | NO             | NO               | YES             | YES                | NO                          | YES                       | YES               |
| Kitzman (2013)          | YES                  | YES               | NO                   | YES                    | NO             | NO               | YES             | YES                | YES                         | YES                       | YES               |
| Palau (2013)            | YES                  | YES               | NO                   | YES                    | NO             | NO               | NO              | YES                | YES                         | YES                       | YES               |
| Haykowsky (2012)        | YES                  | YES               | NO                   | YES                    | NO             | YES              | NO              | YES                | YES                         | YES                       | YES               |
| Alves (2012)            | YES                  | YES               | NO                   | YES                    | NO             | YES              | NO              | YES                | YES                         | YES                       | YES               |
| Smart (2012)            | YES                  | YES               | NO                   | YES                    | NO             | NO               | NO              | YES                | YES                         | YES                       | YES               |
| Edelmann (2011)         | YES                  | YES               | NO                   | YES                    | NO             | NO               | NO              | YES                | NO                          | YES                       | YES               |
| Kitzman (2010)          | YES                  | YES               | NO                   | YES                    | NO             | NO               | YES             | YES                | YES                         | YES                       | YES               |
| Gary (2004)             | YES                  | YES               | NO                   | YES                    | NO             | NO               | NO              | YES                | NO                          | YES                       | YES               |

## Figures

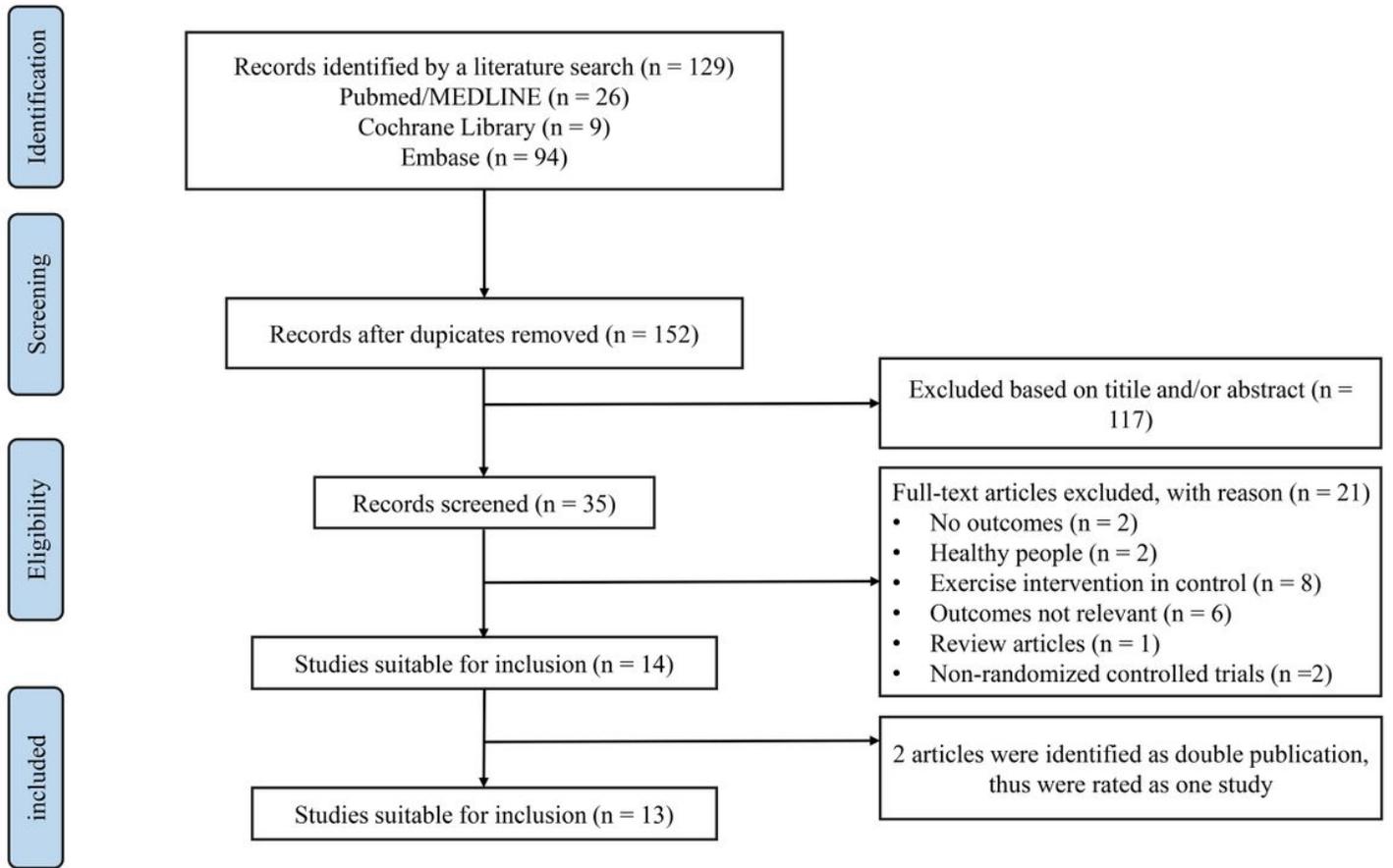
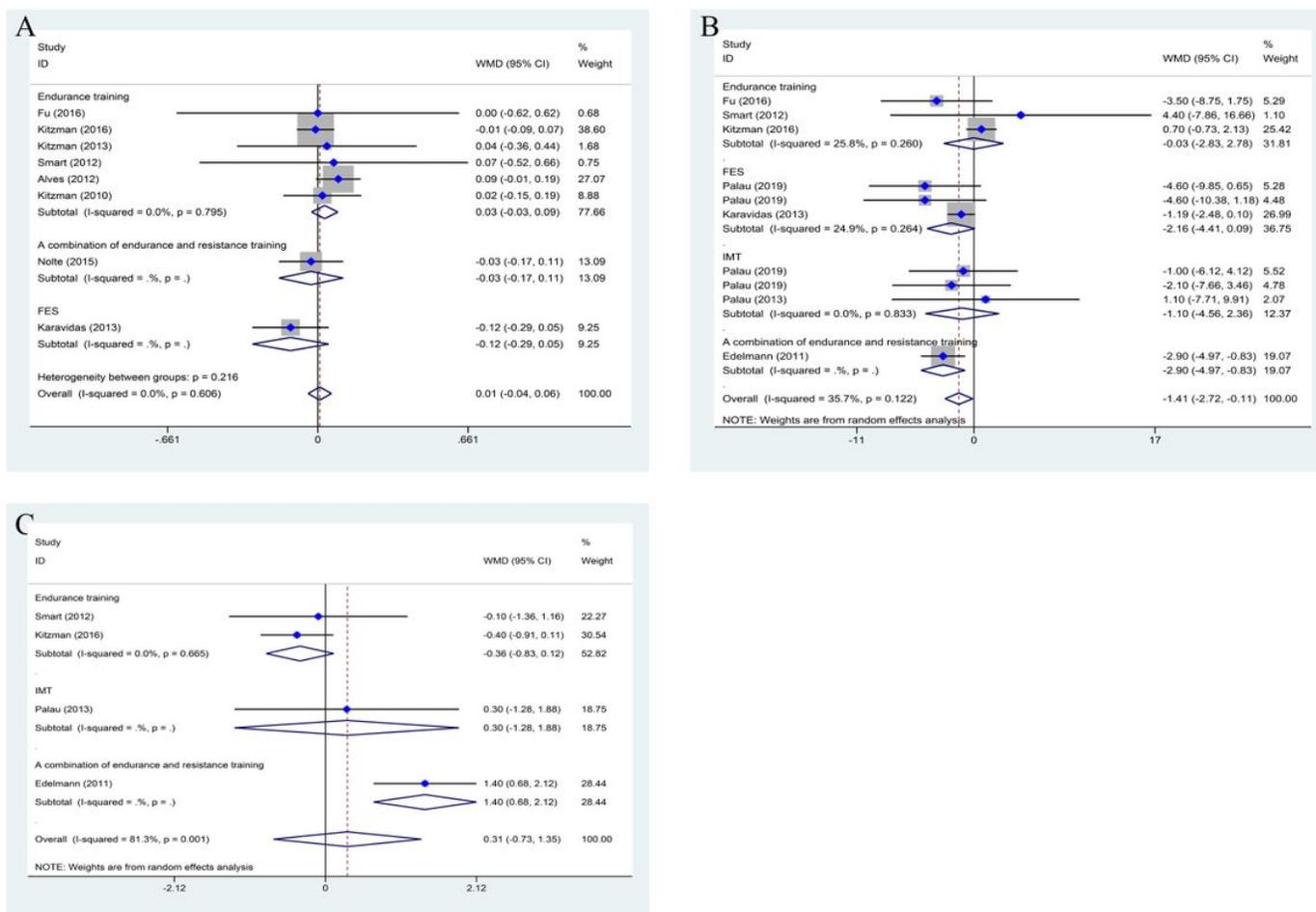


Figure 1

Flow chart of the study selection procedure.



**Figure 2**  
 Forest plot showing the effects of exercise and physiotherapy on diastolic function: the ratio of peak early to late diastolic mitral inflow velocities (E/A; A), change in the ratio of early diastolic mitral inflow to annular velocities (E/E'; B), the early diastolic mitral annular velocity (e'; C).

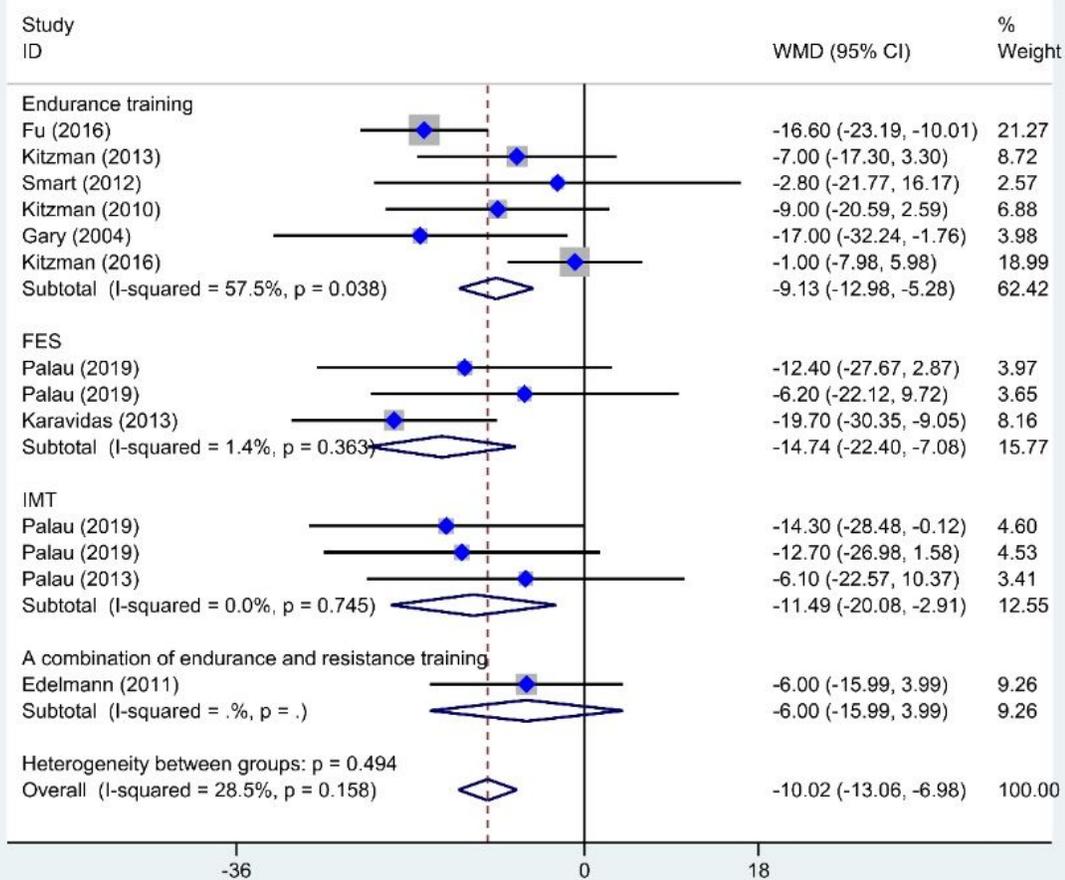
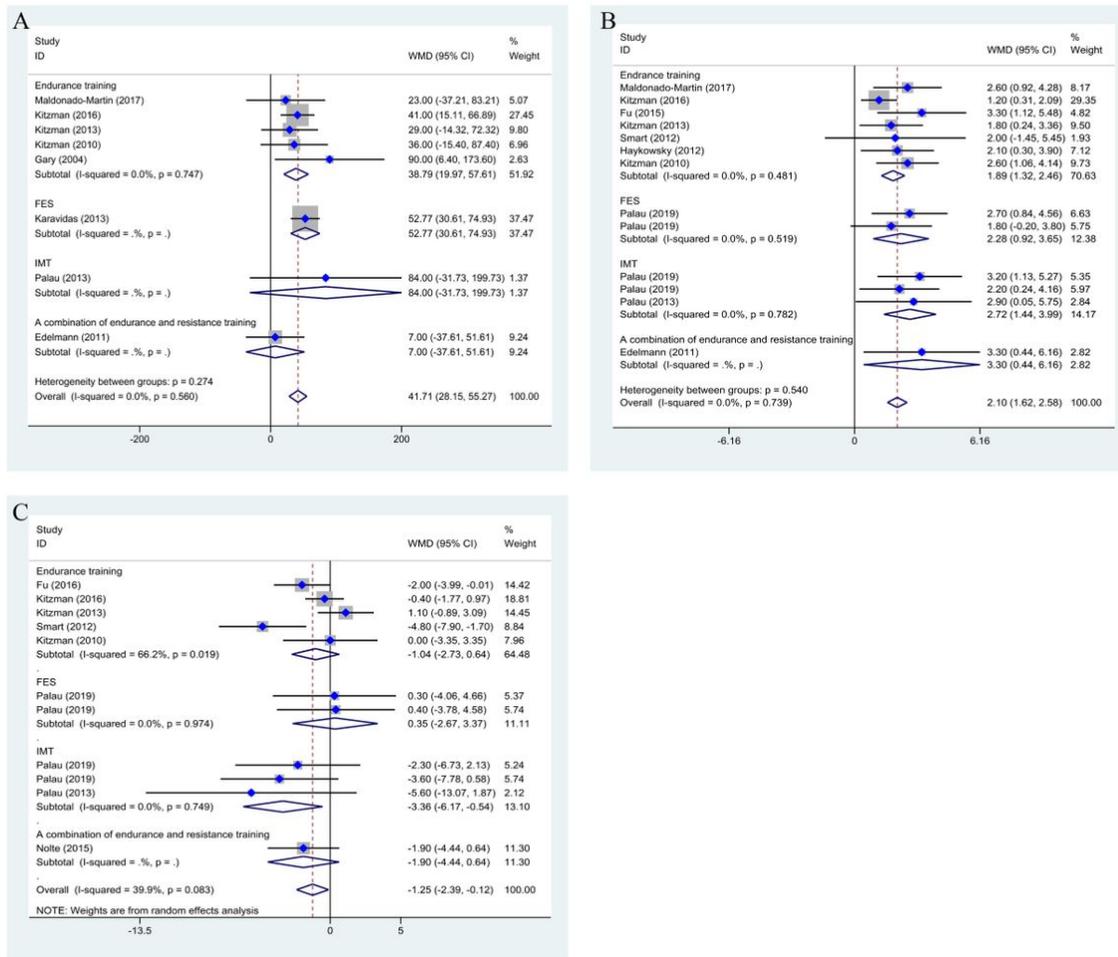
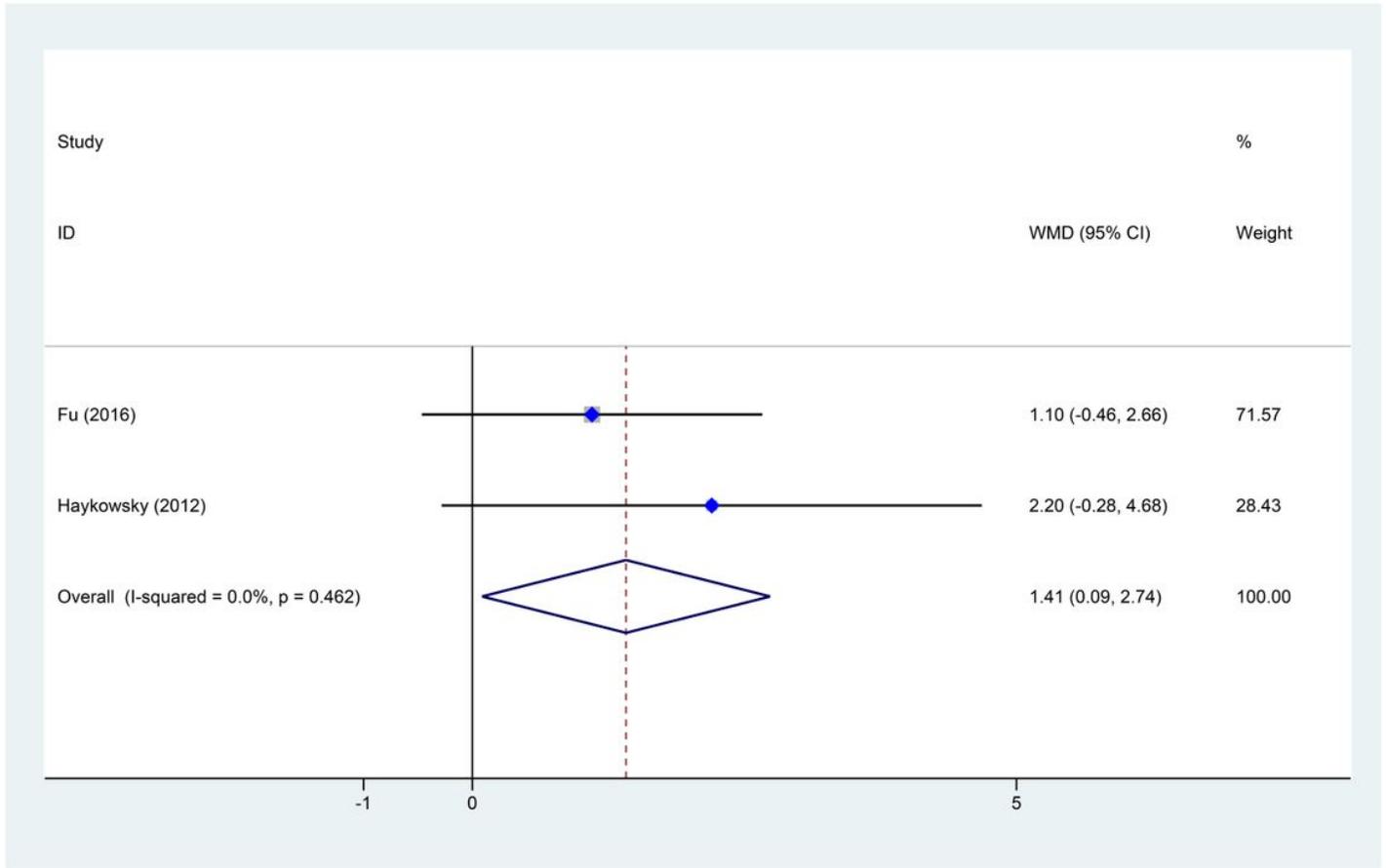


Figure 3

Forest plot showing the effects of exercise and physiotherapy on Minnesota Living With Heart Failure Questionnaire (MLHFQ) total score.



**Figure 4**  
 Forest plot showing the effects of exercise and physiotherapy on exercise performance: 6-minute walk test (6MWT; A), change in peak oxygen consumption (peak VO<sub>2</sub>; B), ventilation/carbon dioxide ratio slope (VE/VCO<sub>2</sub> slope; C)



**Figure 5**

Forest plot showing the effects of endurance training on arterial-venous oxygen difference (A-VO<sub>2</sub> Diff)