Physical Exercise Modalities for the Management of Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis

Yuan Guo, MD, PhD,† Changhu Xiao, MD,‡ Kaixuan Zhao, MD,‡ Ziyu He, MD,† Sha Liu, MD,‡ Xuemei Wu, MD,‡ Shuting Shi, MD,‡ Zhu Chen, PhD,‡ and Ruizheng Shi, MD, PhD**

Abstract: Different physical exercise modalities have been widely studied in patients having heart failure with preserved ejection fraction (HFpEF) but with variably reported findings. We, therefore, conducted a systematic review and meta-analysis to evaluate whether the efficacy of physical activity in the management of HFpEF is related to exercise modalities. PubMed and Embase were searched up to July 2021. The eligible studies included randomized controlled trials that identified effects of physical exercise on patients with HFpEF. Sixteen studies were included to evaluate the efficiency of physical exercise in HFpEF. A pooled analysis showed that exercise training significantly improved peak oxygen uptake (VO_2), ventilatory anaerobic threshold, distance covered in the 6-minute walking test, the ratio of early diastolic mitral inflow to annular velocities, the Short Form 36 physical component score, and the Minnesota Living with Heart Failure Questionnaire total score. However, the changes in other echocardiographic parameters including the ratio of peak early to late diastolic mitral inflow velocities, early diastolic mitral annular velocity, and left atrial volume index were not significant. Both high-intensity and moderate-intensity training significantly improved exercise capacity (as defined by peak VO_2), with moderate-intensity exercise having a superior effect. Furthermore, exercise-induced improvement in peak VO_2 was partially correlated with exercise duration. Physical exercise could substantially improve exercise capacity, quality of life, and some indicators of cardiac diastolic function in patients with HFpEF. A protocol of moderate-intensity exercise training lasting a longer duration might be more beneficial compared with high-intensity training for patients with HFpEF.

Key Words: physical exercise, exercise modalities, heart failure with preserved ejection fraction, meta-analysis

(*J Cardiovasc Pharmacol*™ 2022;79:698–710)

Received for publication November 29, 2021; accepted February 1, 2022.

From the *Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China; †Department of Cardiovascular Medicine, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Zhuzhou, Hunan, China; and ‡Hunan Key Laboratory of Biomedical Nanomaterials and Devices, Hunan University of Technology, Zhuzhou, Hunan, China.

Supported by the National Natural Science Foundation of China (Grant No. 82002405). Supported by the China Postdoctoral Science Foundation (Grant No. 2021M693570). Supported by the Science and Technology Innovation Program of Hunan Province (Grant No. 2021RC2031). Supported by Hunan Health Committee Scientific Research Project of China (202103010009).

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jcvp.org).

Correspondence: Ruizheng Shi, MD, PhD, Department of Cardiovascular Medicine, Xiangya Hospital, Central South University, No. 87, Xiangya Road, Changsha 410008, Hunan, China (e-mail: xyshiruizheng@csu.edu.cn).

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome, the prevalence of which is increasing. It accounts for more than half of all cases of HF.[1] HFpEF has been identified as a heterogeneous disease leading to an intricate clinical phenotype because it is typically accompanied by multiple comorbidities such as hypertension, diabetes mellitus, obesity, and aging.[1,2] Comprehensive phenotyping evaluations of patients with HFpEF involve assessments for multisystem pathophysiological abnormalities that result in substantial morbidity and mortality. Very few effective treatments are available for HFpEF.[2,3] Fortunately, recent clinical trials exploring therapeutic strategies for HFpEF have reported some promising results.

Well-documented evidence has shown that aerobic exercise–based cardiac rehabilitation affords potent protection against cardiovascular diseases.[4–6] Exercise has been reported to confer multisystem benefits against cardiovascular diseases, such as exercise-induced inhibition of cardiomyocyte hypertrophy, inflammation, fibrosis, and microvascular dysfunction, and improvement in mitochondrial metabolism and endothelial function.[7–10] Exercise-induced systemic biological effects indicate that it could be a promising adjuvant therapy for the management of HFpEF.

Several clinical trials have been conducted to evaluate the effects of exercise in patients with HFpEF; however, variable findings have been reported thus far.[11–13] Most studies reported that exercise training not only markedly increased cardiorespiratory fitness, exercise capacity, and quality of life (QOL) score but also improved cardiac diastolic function in patients with HFpEF.[12,14,15] However, some controversy persists regarding the benefits of exercise for patients with HFpEF. Smart et al[16] investigated the effects of physical exercise and found no significant changes in diastolic function and QOL scores after a 16-week exercise program in patients with HFpEF. On the other hand, Palau et al[17] observed that 12-week inspiratory muscle training could significantly improve exercise capacity and QOL but without any change in diastolic function parameters. Thus, the differences in the findings pertaining to the effectiveness of physical exercise as a strategy for the management of HFpEF deserve more investigation.

Recently, it has been demonstrated that all intensities of physical activity are associated with a substantially reduced risk of death in a dose-response manner.[18] However, the differential effects of exercise modalities on HFpEF exist. Mueller et al[19] evaluated the effect of different exercise intensities in patients with HFpEF and found that both high-intensity interval training and moderate continuous training were not superior to guideline-based physical activity in improving peak oxygen uptake (VO_2). Donelli da Silveira et al[12] reported that compared with moderate continuous training, high-intensity interval training was far more effective in improving peak VO_2 and thus could be a potential exercise modality for patients with HFpEF. These findings indicate that exercise modalities might be an explanation for the outcome deviations noted, suggesting the importance of establishing an exercise protocol for patients with HFpEF. Hence, in this systematic review and meta-analysis, we evaluated current literature to investigate the efficacy of exercise training for the management of HFpEF. Furthermore, we analyzed the effects of different exercise modalities to elucidate exercise-induced protective effects against diseases so as to guide therapeutic strategies.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was followed to conduct this systematic review and meta-analyses.[20]

Literature Search Strategy

Electronic databases of PubMed and Embase of controlled trials were searched from inception of the database to 31 July 2021. Searches were limited to randomized controlled trial (RCT) and clinic trails in all languages. The MeSH terms of "diastolic heart failure" and "aerobic exercise" were mainly used. Besides, potentially eligible studies were also checked and reviewed from trials, textbooks, and abstracts of scientific meetings without language restriction.

Study Selection

Two authors (C.Z. and X.C.) independently reviewed and screened the titles and abstracts. After exclusions based on title and abstract review, the full text was reviewed by the 2 investigators to evaluate eligibility. Studies were eligible if (1) the RCT or clinical trial was performed in patients with HFpEF; (2) exercise training was conducted; (3) baseline information was available and a specific exercise protocol was implemented; and (4) at least one of the following outcome measures was assessed: exercise capacity, left ventricular (LV) diastolic function, and QOL. Any disagreement in the inclusion of an article was resolved by discussion with a third investigator.

Data Extraction

Detailed full-text articles were independently conducted by the 2 authors. Data were extracted based on study design, characteristics, and outcomes. Basic characteristics include year of publication, study design, sample number, sex, cardiac function, comorbidity, duration of follow-up, and exercise training protocol. Outcome indicators of exercise capacity, LV diastolic function, and QOL were, respectively, extracted for analysis. All analyzed data have been shown in **Supplemental Digital Content 1** (see **Table S1**, http://links.lww.com/JCVP/A793).

Risk of Bias Assessment

Two reviewers (Z.K. and H.Z.) independently assessed the risk of bias according to the Cochrane risk of bias tool. The quality of the included studies was, respectively, assigned as low, high, or unclear risk of bias, and the overall risk was visually displayed using RevMan 5.3 software. Agreement for the methodological quality assessment between both observers was tested, and disagreement was resolved by consensus.

Statistical Analysis

The effects of exercise training were calculated as differences between the means at baseline and the end of exercise training. Data pooled and analyzed with random-effects models, $P < 0.05$ was considered having significance after Z test. For continuous variables, the mean ± SD or median (interquartile range) values were analyzed and outcomes were presented as standardized mean differences (SMDs) and 95% confidential intervals (CIs). For each outcome, heterogeneity was assessed using Cochran's Q and I^2 statistic, and $P < 0.05$ with $I^2 > 50\%$ was considered significant. In case of significant heterogeneity, Galbraith plot analysis of the individual study was performed to quantitatively assess the source of bias. Subgroup analyses and metaregression models were conducted to identify the heterogeneity. All statistical analyses were performed using STATA 12.0 software (StataCorp, College Station, TX).

RESULTS

Eligible Studies and Characteristics

The search strategy yielded a total of 208 publications. After the screening of titles and abstracts, a full-text review was performed for 34 studies. Eighteen articles were excluded because exercise training was not used as an intervention in these studies or the results did not meet the screening criteria. In all, 16 studies were finally included in the qualitative analysis (Fig. 1).[11–17,19,21–28] The inclusion and exclusion criteria and main outcomes of these included studies have been shown in **Supplemental Digital Content 2** (see **Table S2**, http://links.lww.com/JCVP/A794). The characteristics of these studies are detailed in Table 1 and Table 2. Based on the pooled data, 597 individuals diagnosed with HFpEF were included in the exercise training group. The mean percentage of female patients was 70%, and the patients' age range was 60–75 years. The most prevalent

TABLE 1. Characteristics of Studies Included in the Meta-Analysis

Source	Design	Sample No.	Mean Age (Years), Mean ± SD	Race	Sex (% Female)	NYHA Class, LVEF (%), Mean ± SD	Body Mass Index (kg/m^2), Mean ± SD	Comorbidities (%)	Medication (%)	Follow-Up Period
Mueller et al[19]	RCT	176	69.5 ± 8.8	NR	67	II~III ≥50	29.8 ± 5.4	Hypertension (85.2); Hyperlipidemia (69.9); Diabetes (26.1); CAD (28.4); AF (27.8); SAS (18.8); PAD (5.1)	β-blockers (64.8); Thiazide/loop diuretics (56.8); ACEI/ARBs (73.3); Aldosterone antagonists (10.8)	12-month
Donelli da Silveira et al[12]	Single-blinded, parallel RCT	19	60 ± 9	NR	63.2	II~III 65 ± 5	33.5 ± 5.4	Hypertension (100); Dyslipidemia (57.9); Diabetes (57.9); CKD (15.8); AF (10.5); CAD (26.3)	ACEI/ARBs (100); β-blockers (89.5); Thiazide/loop diuretics (100); Statins (78.9); Aldosterone blockers (31.6); CCBs (68.4); antiplatelets (68.4)	12-week
Brubaker et al[13]	RCT	116	69.8 ± 6.5	White (58.2%)	81	II~III 60 ± 0.5	31.3 ± 6.3	Hypertension (84.5); Diabetes (20.7)	ACEI (35.3); Diuretic (56); β-blockers (21.6); CCBs (37.1); Digoxin (11.2); Nitrates (10.3)	16-week
Palau et al[23]	Open-label RCT	28	75 ± 9.4	NR	60.7	II~IV 68.1 ± 8.6	32.5 ± 5.2	Hypertension (96.4); Diabetes (35.7); Dyslipidemia (75); CAD (28.6); AF (53.6)	Furosemide and other diuretics (75); β-blockers (85.7); Statins (64.3); ACEI/ARBs (67.9)	12-week
Pandey et al[26]	RCT	24	70.0 ± 6.4	White (88%)	83.3	II~III 60 ± 5	29.9 ± 5.9	Hypertension (87); Diabetes (13)	Diuretics (41.7); ACEI (33.3); β-blockers (29.2); CCBs (45.8)	16-week
Maldonado-Martín et al[21]	Prospective, single-blinded RCT	47	65	NR	87.2	II~III ≥50	NR	NR	NR	16-week
Shaltout al[28]	Double-blind RCT	9	70.6 ± 7.6	White (67%)	89	II~III	31.5 ± 5.4	Hypertension (100); Diabetes (20)	ACEI/ARBs (55.6); Diuretics (55.6); β-blockers (22.2); CCBs (22.2)	4-week

TABLE 1. (*Continued*) Characteristics of Studies Included in the Meta-Analysis

Source	Design	Sample No.	Mean Age (Years), Mean ± SD	Race	Sex (% Female)	NYHA Class, LVEF (%), Mean ± SD	Body Mass Index (kg/m²), Mean ± SD	Comorbidities (%)	Medication (%)	Follow-Up Period
Kitzman et al[11]	Single-blind RCT	100	66.5 ± 5.2	White (55%)	81	II~III 61 ± 6	39.4 ± 6.1	Hypertension (95); Diabetes (35); AF (2)	ACEI/ARBs (72); Diuretics (76); Nitrates (9); β-blockers (40); CCBs (35)	20-week
Angadi et al[14]	RCT	15	64.6 ± 10.2	NR	20	II~III 65 ± 5	29.6 ± 4.2	Diabetes (26.7)	ACEI/ARB (53.3); Aspirin (60); β-blockers (66.7); Diuretics (53.3); Statins (5.3); Coumadin (33.3); CCBs (40)	4-week
Nolte et al[22]	Single-blind RCT	64	65 ± 7	NR	56	II~III 67 ± 7	31 ± 5	Overweight; Diabetes; Hypertension; Hyperlipidemia	ACEI/ARBs (66); β-blockers (50); Diuretics (45)	12-week
Palau et al[17]	RCT	26	73 ± 7.4	NR	50	II~IV 72.2 ± 11.1	32.4 ± 6.4	Hypertension (96.2); Dyslipidaemia (88.5); Diabetes (57.7); IHD (46.2); AF (34.6)	β-blockers (84.6); Diuretics (57.7); ACEI/ARB (69.2); Statins (84.6); Oral anticoagulants (46.2); Nitrates (7.7); Digoxin (3.8)	12-week
Yeh et al[27]	RCT	16	65.5 ± 10.9	White (81%)	50	I~III 63.5 ± 8.4	33 ± 11.8	CAD (37.5); Arrhythmia (31.3); Hypertension (75); Diabetes (18.8); Dyslipidaemia (50); Renal disease (37.5)	ACEI/ARBs (62.5); Diuretics (75); β-blockers (68.8); Nitrates (12.5); CCBs (43.8)	12-week

(*continued on next page*)

TABLE 1. (*Continued*) Characteristics of Studies Included in the Meta-Analysis

Source	Design	Sample No.	Mean Age (Years), Mean ± SD	Race	Sex (% Female)	NYHA Class, LVEF (%), Mean ± SD	Body Mass Index (kg/m²), Mean ± SD	Comorbidities (%)	Medication (%)	Follow-Up Period
Kitzman et al[24]	Single-blind RCT	63	70 ± 7	White (76.2%)	76.2	II~III 56.9 ± 5.5	32.1 ± 6.6	Hypertension (88.9); Diabetes (23.8)	Diuretics (60.3); ACEI/ARBs (46); β-blockers (22.2); CCBs (31.7); Estrogen (34.9); Nitrates (11.1)	16-week
Smart et al[16]	RCT	25	64.3 ± 6.8	NR	48	II~III 57.8 ± 9.8	32.1 ± 6.4	Hypertension (16); Diabetes (16)	β-blockers (4); ACEI/ARBs (76); Diuretics (8)	16-week
Edelmann et al[15]	Single-blind RCT	64	65 ± 7	NR	56	II~III 67 ± 7	31 ± 5	Overweight (89); Diabetes (14); Hypertension (86); Hyperlipidemia (47)	ACEI/ARBs (65.6); β-blockers (50); Diuretics (45.3)	12-week
Kitzman et al[25]	RCT	46	70 ± 6	White (80%)	86.7	II~III 60.5 ± 8.6	30.5 ± 6.4	Diabetes (19.6); Hypertension (85.7)	ACEI (27.3); Digoxin (15.6); Diuretics (61.4); Nitrates (11.6); β-blockers (27.3); CCBs (42.2)	16-week

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CCBs, calcium channel blockers; CKD, chronic kidney disease; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; NR, not reported; PAD, peripheral artery disease; RCT, randomized clinical trial; SAS, sleep apnea syndrome.

comorbidities were hypertension, diabetes, and dyslipidemia. The exercise duration mainly ranged from 4 to 20 weeks and with a longest follow-up period reached to 12 months. Furthermore, 95% of the participants completed exercise training, and the exercise intensity was confirmed to range from moderate to high. The exercise modalities in these selected studies included walking, cycling, tai chi, and inspiratory muscle training. Most of the protocols were defined as regular exercise to high-intensity exercise with a weekly frequency of 2–3 sessions, with each session lasting for 20–60 minutes.

Quality Assessment

The Cochrane risk of bias assessment tool was used to perform quality assessment. Among these evaluated studies, 14 of them have been identified as good and 2 of them were considered as moderate (see **Fig. S1**, **Supplemental Digital Content 3**, http://links.lww.com/JCVP/A790).

Analyzed Outcomes

Exercise Capacity

The most typical indicators of cardiorespiratory fitness include VO_2 (mL/kg/min), ventilatory anaerobic threshold (VAT, mL/min), and ventilatory equivalent (VE)/carbon dioxide production (VCO_2) slope. Furthermore, the distance covered in the 6-minute walking test (6MWT, m) has been widely used to evaluate exercise capacity. After pooling data, 16 studies involving 567 participants showed a significant improvement in peak VO_2 after exercise training when compared with that at baseline [SMD (95% CI), 0.61 (0.43–0.80)]. Furthermore, the heterogeneity of peak VO_2 among the studies was identified as significant (I^2 = 50.5%, P = 0.011) (Fig. 2A). Galbraith plot analysis revealed the Mueller study[19] as the main cause of this heterogeneity (see **Fig. S2A**, **Supplemental Digital Content 3**, http://links.lww.com/JCVP/A791).

Seven studies including 228 individuals also showed substantially significant VAT after exercise training compared

TABLE 2. Physical Exercise Modalities in Included Studies

Source		Exercise Training Modalities
Mueller et al[19]	HIIT	3 times per week for 38 minutes per session, with maximum 80%–90% of heart rate reserve
	MCT	5 times per week for 40 minutes per session, with maximum 35%–50% of heart rate reserve
	Guideline exercise	1 time advice on physical activity according to guidelines
Donelli da Silveira et al[12]	HIIT	3 times per week for 12 consecutive weeks, with 80%–90% of peak VO_2 and 85%–95% of peak heart rate
	Moderate intensity	3 times per week for 12 consecutive weeks, with 50%–60% of peak VO_2 and 60%–70% of peak heart rate
Brubaker et al[13]		3 times per week for 16 weeks (48 sessions) of moderate-intensity endurance exercise, with maximum 60% heart rate reserve
Palau et al[23]		Inspiratory muscle training twice daily (20 minutes each session) for 12 weeks, resistance equal to 25%–30% of their maximal inspiratory pressure for 1 week and was modified each session to 25%–30% of their measured maximal inspiratory pressure
Pandey et al[26]		3 times a week for 16 weeks (48 sessions) of supervised exercise training, with maximum 60%–70% of heart rate reserve
Maldonado-Martín et al[21]		3 times a week for 16 weeks (48 sessions) of exercise training, with maximum 50%–70% of peak VO_2
Shaltout et al[28]		3 exercise sessions per week for 4 weeks of moderate-intensity exercise training, with maximum 70% of heart rate reserve
Kitzman et al[11]		3 times per week for 20 weeks consisting primarily of walking exercise, and intensity level was progressed as tolerated and based primarily on heart rate reserve
Angadi et al[14]	HIIT	3 times per week for 4 weeks (12 sessions) of treadmill training, with maximum 85%–90% peak heart rate
	MCT	3 times per week for 4 weeks (12 sessions) of treadmill training, with maximum 70% peak heart rate
Nolte et al		12 weeks (32 sessions) of supervised, facility-based training consisting of endurance and resistance training, with a maximum target heart rate of 70% of baseline peak VO_2
Palau et al[17]		Inspiratory muscle training twice a day (20 minutes per session) for 12 weeks, with breathing at a resistance equal to 25%–30% and modified each session according to the 25%–30% of inspiratory muscle training measured
Yeh et al 2013		Tai chi intervention consisted of 1-hour group classes held twice weekly for 12 weeks, included traditional warm-up exercises followed by 5 simplified tai chi movements; aerobic exercise included 1 hour twice a week with low-to-moderate training intensity
Kitzman et al[24]		3 times per week for 16 weeks (48 sessions) of endurance exercise training, with initially at 40%–50% of heart rate reserve and intensity increased gradually until 70% heart rate reserve
Smart et al[16]		16 weeks of supervised, outpatient, cycle ergometer exercise training, with initial intensity of 60%–70% peak oxygen consumption and uptitrated by 2–5 Watts per week
Edelmann et al[15]		12 weeks (32 sessions) of endurance and resistance training, with a target heart rate of 50%–60% of peak VO_2
Kitzman et al[25]		3 days per week for 16 weeks (48 sessions) of supervised aerobic exercise training, with exercise intensity increased to 60%–70% of heart rate reserve

HIIT, high-intensity interval training; MCT, moderate continuous training; peak VO_2, peak oxygen uptake.

with that at baseline [SMD (95% CI), 0.59 (0.40–0.78)], which was identified to be without heterogeneity (Fig. 2B). Furthermore, 12 among the 16 RCTs determined the VE/VCO_2 slope after exercise training and found it to not be significant compared with that at baseline [SMD (95% CI), −0.18 (−0.37 to 0.01), $P = 0.06$]. In addition, the heterogeneity of the VE/VCO_2 slope did not reach significance (Fig. 2C). Regarding the 6MWT, 9 studies with 273 patients determined the distance covered. We found a significant increase in the distance covered in the 6MWT by patients with HFpEF after exercise training [SMD (95% CI), 0.59 (0.42–0.76)], suggesting that the distance covered in the 6MWT is a representative indicator of exercise capacity (Fig. 2D). Thus, the pooled data analysis revealed that physical exercise significantly improved cardiorespiratory fitness and exercise capacity in patients with HFpEF.

Cardiac Diastolic Function

Regarding the LV diastolic function, echocardiographic parameters such as 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′), the early diastolic mitral annular velocity (e′, cm/s), and left atrial volume index (LAVI, mL/m^2) were calculated.[29–31] The most widely used indicator for the evaluation of cardiac diastolic function is E/A. Nine of the 16 RCTs reported the impact of exercise training on E/A value, and pooling across analysis showed no significant change in the E/A of patients with HFpEF after exercise intervention [SMD (95% CI), 0.03 (−0.16 to 0.21)] (Fig. 3A). Regarding E/e′, another important indicator used for evaluating the diastolic function was evaluated in 12 trials with 425 patients. We found that it significantly reduced after exercise training compared with that at baseline [SMD (95% CI), −0.28 (−0.53 to −0.04)]. The heterogeneity of E/e′ among the studies was significant ($I^2 = 60.1\%$, $P = 0.004$) (Fig. 3B). Galbraith plot analysis further identified the Edelmann study[15] as the main reason for this heterogeneity (see **Fig. S2B**, **Supplemental Digital Content 3**, http://links.lww.com/JCVP/A791).

Eight studies with 286 patients having HFpEF evaluated e′, and pooled analysis showed that e′ after exercise

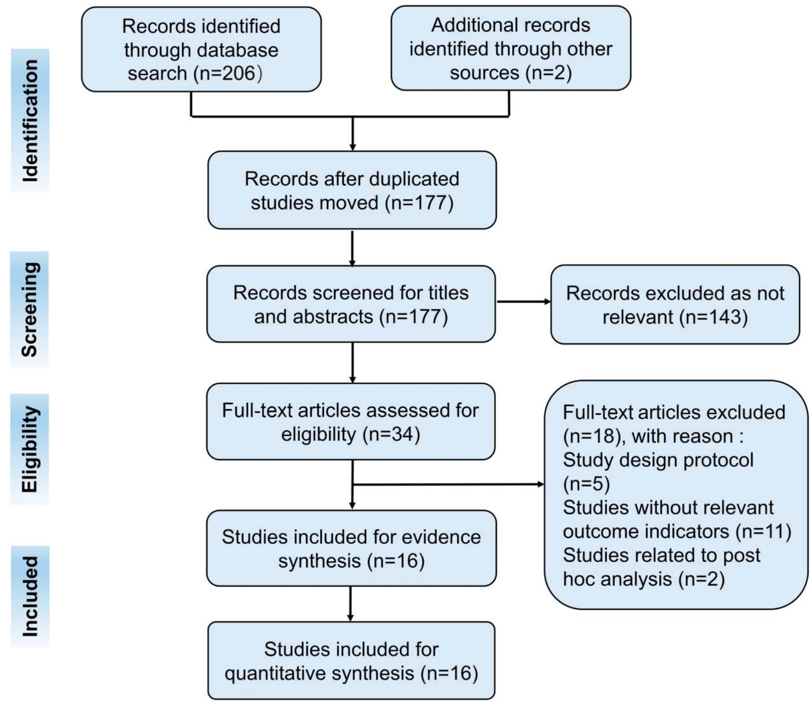

FIGURE 1. Flow diagram of the systematic review.

training was not significant (SMD [95% CI], 0.13 [-0.16, 0.43]). Nevertheless, substantial heterogeneity of e′ was found in these studies (I^2 = 60.2%, P = 0.014) (Fig. 3C). Galbraith plot analysis showed that this heterogeneity was mainly attributable to the Edelmann study[15] (see **Fig. S2C, Supplemental Digital Content 3**, http://links.lww.com/JCVP/A791). LVAI was evaluated in 6 studies with 207 individuals. Pooling analysis revealed that LAVI change after exercise training was not significant compared with that at baseline [SMD (95% CI), −0.18 (−0.36 to −0.01), P = 0.065]. Thus, although most echocardiographic parameters showed changes without significance, the pooled data showed that E/e′ significantly improved after exercise training, indicating it may be the most sensitive indicator of diastolic function.

QOL

General QOL was assessed with the 36-item Short Form Health Survey (SF-36) physical component score, and a high score indicated a better QOL. HF-specific QOL was generally assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and Minnesota Living with Heart Failure (MLWHF) scores. A high KCCQ score or a low MLWHF score indicated a better QOL.

A pooled analysis of data from 6 RCTs involving 215 patients showed significant improvement in SF-36 scores after exercise training compared with that in the control group [SMD (95% CI), 0.65 (0.45–0.84)] (Fig. 4A). Regarding QOL, 11 studies with 291 individuals evaluated it based on MLWHF scores. It has been shown that exercise training could significantly reduce MLWHF scores compared with baseline [SMD (95% CI), −0.60 (−0.76 to −0.43)]. Both scores were found to have heterogeneity without significance (Fig. 4B). This finding indicated that physical exercise could significantly improve QOL in patients with HFpEF.

Only 2 studies evaluated QOL based on the KCCQ score. Pooling analysis showed that exercise training slightly improved the KCCQ score in patients with HFpEF [SMD (95% CI), 0.66 (−0.10 to 1.43), P = 0.088]. Furthermore, there was significant heterogeneity (I^2 = 89.8%, P = 0.002) (Fig. 4C). However, the reason for this heterogeneity could not be determined because of the limited number of studies. Thus, the sensitivity of the KCCQ score for the evaluation of QOL among patients with HFpEF should be confirmed with more trials.

Differential Effects Across Subgroups

Significant heterogeneity existed in the effects of exercise on peak VO_2, E/e′, and e′, and these differential effects may result from exercise intensity and duration in patients with HFpEF. Three studies reported the use of moderate-intensity and high-intensity exercise for patients with HFpEF. Pooled analysis of 3 studies with 150 participants showed a significant difference in peak VO_2 between the exercise training and control groups [SMD (95% CI), 0.30 (0.05–0.54), P = 0.018]. However, subgroup analysis showed that E/e′ and e′ were not markedly significant. Furthermore, compared with high-intensity training, moderate-intensity exercise increased peak VO_2 more effectively (Fig. 5).

A regression analysis was conducted to identify whether exercise duration was related to the differential effects of exercise in patients with HFpEF. Pooling data analysis revealed that peak VO_2 was positively but not significantly correlated with exercise duration (P = 0.07, see

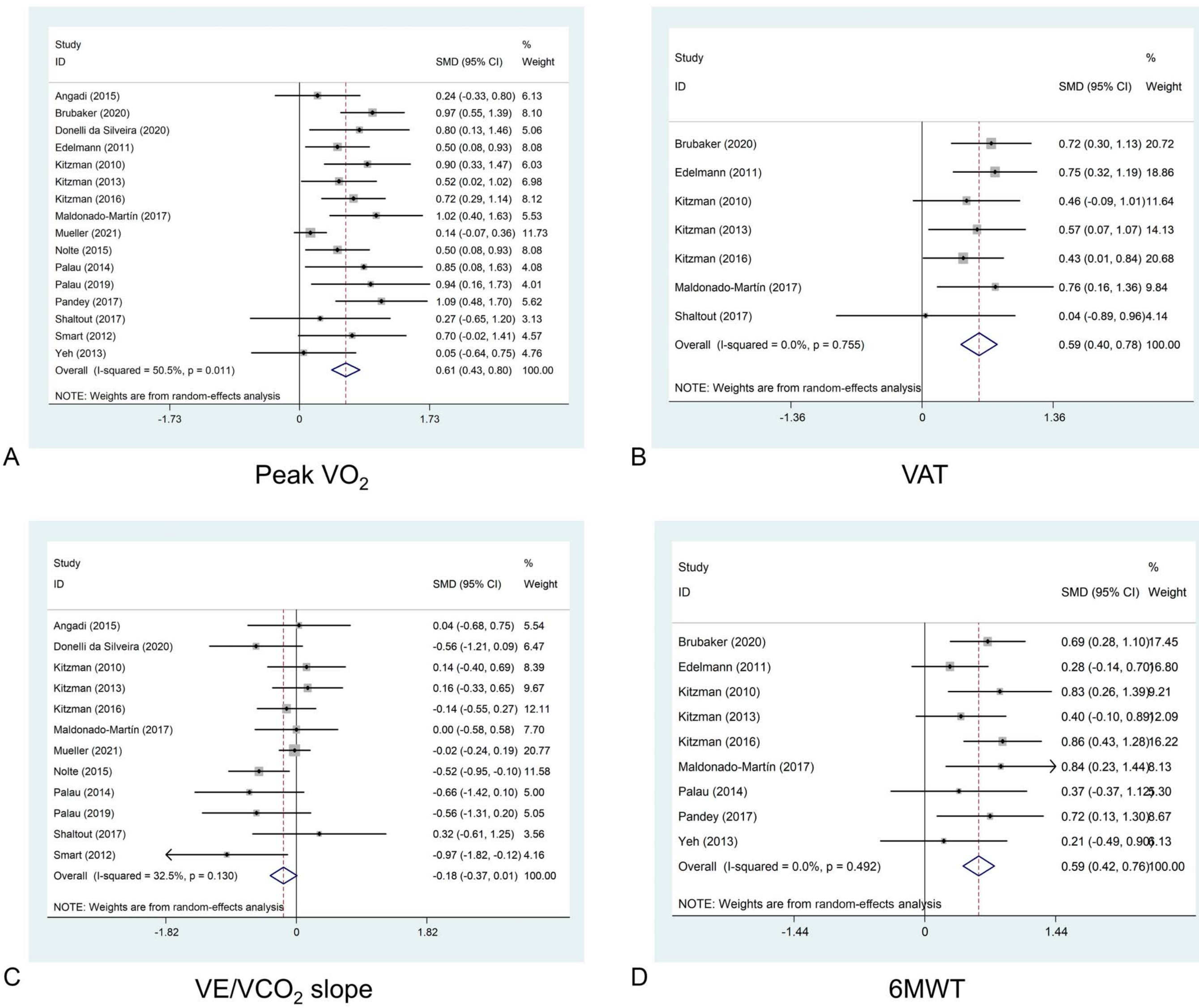

FIGURE 2. Forest plot showing effects of physical exercise on exercise capacity. The indicators of exercise capacity were calculated as differences between the means at baseline and the end of exercise training. After data pooled as continuous variables and analyzed with random-effects models, the difference was considered significant when $P < 0.05$. Heterogeneity was assessed using Cochran's Q and I^2 statistic, and $P < 0.05$ with $I^2 > 50\%$ was considered significant. All results are reported as an SMD (baseline after exercise) with a 95% CI. A, Peak VO_2 ($P < 0.001$). B, VAT ($P < 0.001$). C, VE/VCO_2 slope ($P = 0.06$). D, 6MWT distance ($P < 0.001$).

Fig. S3A, **Supplemental Digital Content 4**, http://links.lww.com/JCVP/A792). Similarly, the regression analysis showed that E/e′ and e′ were also related to exercise duration but without significance (see Fig. S3B-C, **Supplemental Digital Content 4**, http://links.lww.com/JCVP/A792). Thus, the differential effects of exercise training in patients with HFpEF were at least in part related to exercise intensity and duration.

DISCUSSION

The principal findings of this meta-analysis showed that exercise training could significantly improve exercise capacity, LV diastolic function (as defined by E/e′), and QOL score in patients with HFpEF. The subgroup analysis further suggested that compared with high-intensity training, moderate-intensity exercise might improve peak VO_2 more significantly. The regression analysis indicated that peak VO_2 was positively correlated with exercise duration in patients with HFpEF. Exercise training intensity and duration could at least partly be the source of heterogeneity in the analyzed studies.

The 16 RCTs included in this meta-analysis reported that exercise training could significantly improve exercise capacity in patients with HFpEF, which was assessed based on peak VO_2, VAT, and distance covered in the 6MWT. This result has been confirmed by previous studies. Leggio et al[32] analyzed 9 studies and found that exercise training

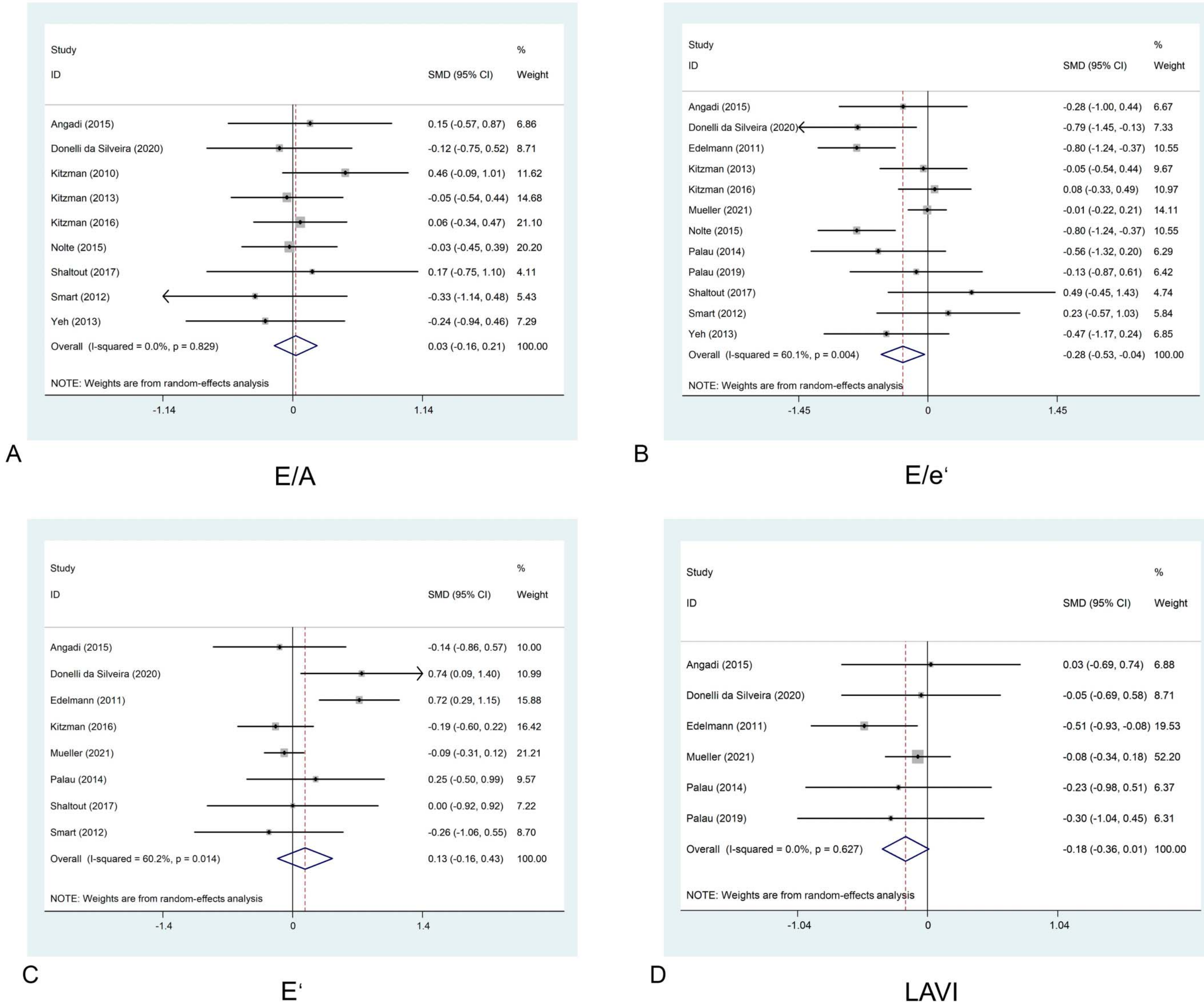

FIGURE 3. Forest plot showing effects of exercise training on cardiac diastolic function. The indicators of cardiac diastolic function were calculated as differences between the means at baseline and the end of exercise training. After data pooled as continuous variables and analyzed with random-effects models, the difference was considered significant when $P < 0.05$. Heterogeneity was assessed using Cochran's Q and I^2 statistic, and $P < 0.05$ with $I^2 > 50\%$ was considered significant. All results are reported as an SMD (baseline—after exercise) with a 95% CI. A, E/A (P = 0.79). B, E/e′ (P = 0.023). C, e′ (P = 0.381). D, LAVI (P = 0.065).

significantly improved peak VO_2, distance covered in the 6MWT, and ventilatory threshold in patients with HFpEF. Fukuta et al[33] demonstrated the effects of aerobic exercise on patients with HFpEF by analyzing 8 studies and reported a significant improvement in exercise capacity. Unlike that in previous studies, in this study, we performed a subgroup analysis to determine the potential differences among the included studies and found that compared with high-intensity training, moderate-intensity exercise may be more beneficial in increasing exercise capacity. Besides, a larger study sample size was included in this meta-analysis than in previous works, which increases result accuracy.

In this meta-analysis, we also tested whether exercise training could significantly improve E/e′ and found that other echocardiographic parameters including E/A, e′, and LAVI did not have a significant impact. This finding is largely consistent with that of a previous report, and the most recent meta-analysis reported that cardiac diastolic function changed after exercise training in patients with HFpEF, although the difference was not significant.[32–34] However, the finding that E/e′ significantly improved after exercise training may be a result of more RCTs being included in this meta-analysis. This also suggests that E/e′ may be the most important indicator for evaluating cardiac diastolic function.

We found that exercise training could significantly improve QOL. Most studies evaluated QOL in patients with HFpEF by using the SF-36 and MLWHF scores. Although our analysis showed that both indicators improved after

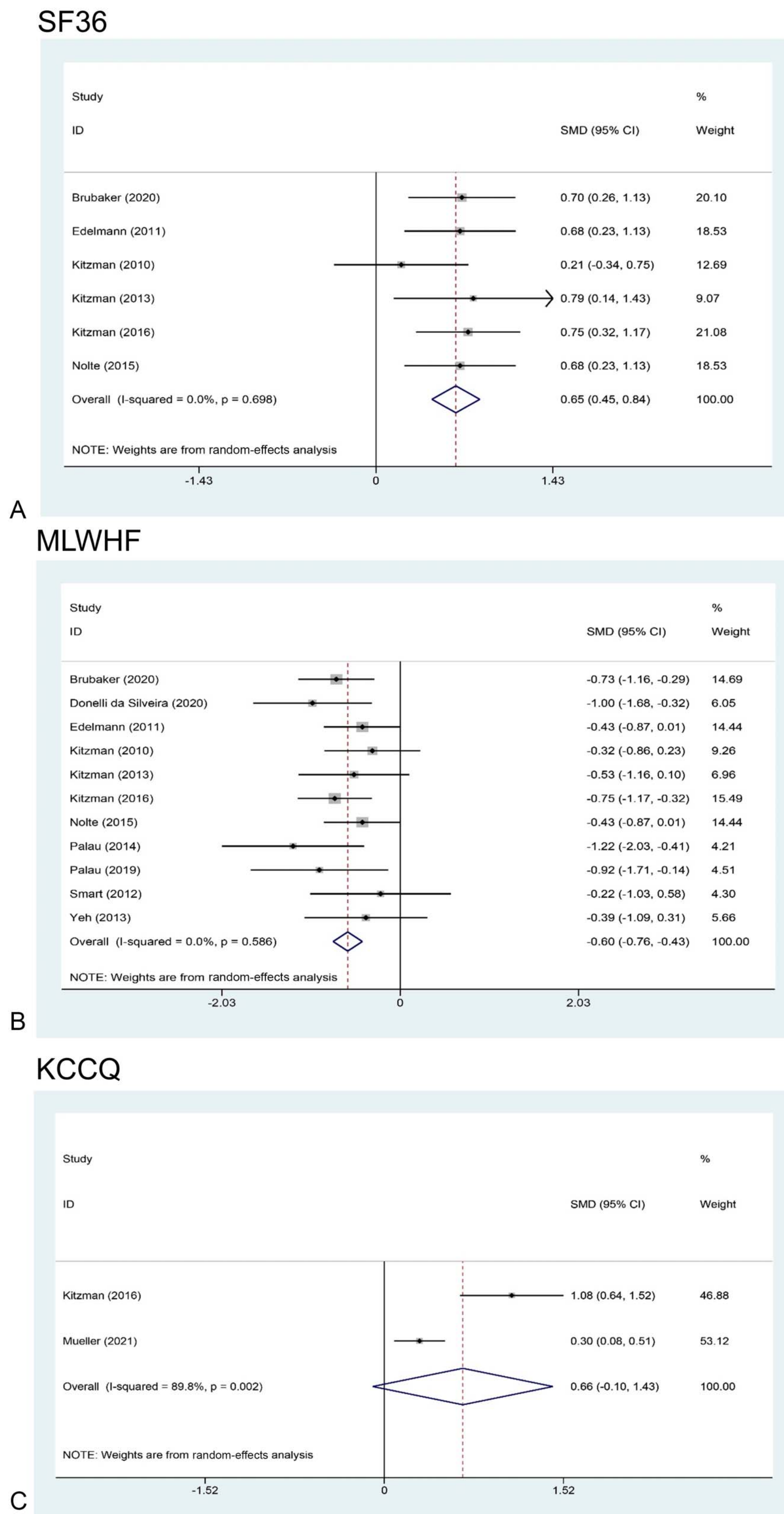

FIGURE 4. Forest plot for the effect of exercise training on quality of life. The indicators of quality of life were calculated as differences between the means at baseline and the end of exercise training. After data pooled as continuous variables and analyzed with random-effects models, the difference was considered significant when $P < 0.05$. Heterogeneity was assessed using Cochran's Q and I^2 statistic, and $P < 0.05$ with $I^2 > 50\%$ was considered significant. All results are reported as an SMD (baseline—after exercise) with a 95% CI. A, SF-36 score ($P < 0.001$). B, MLWHF score ($P < 0.001$). C, KCCQ score ($P = 0.088$).

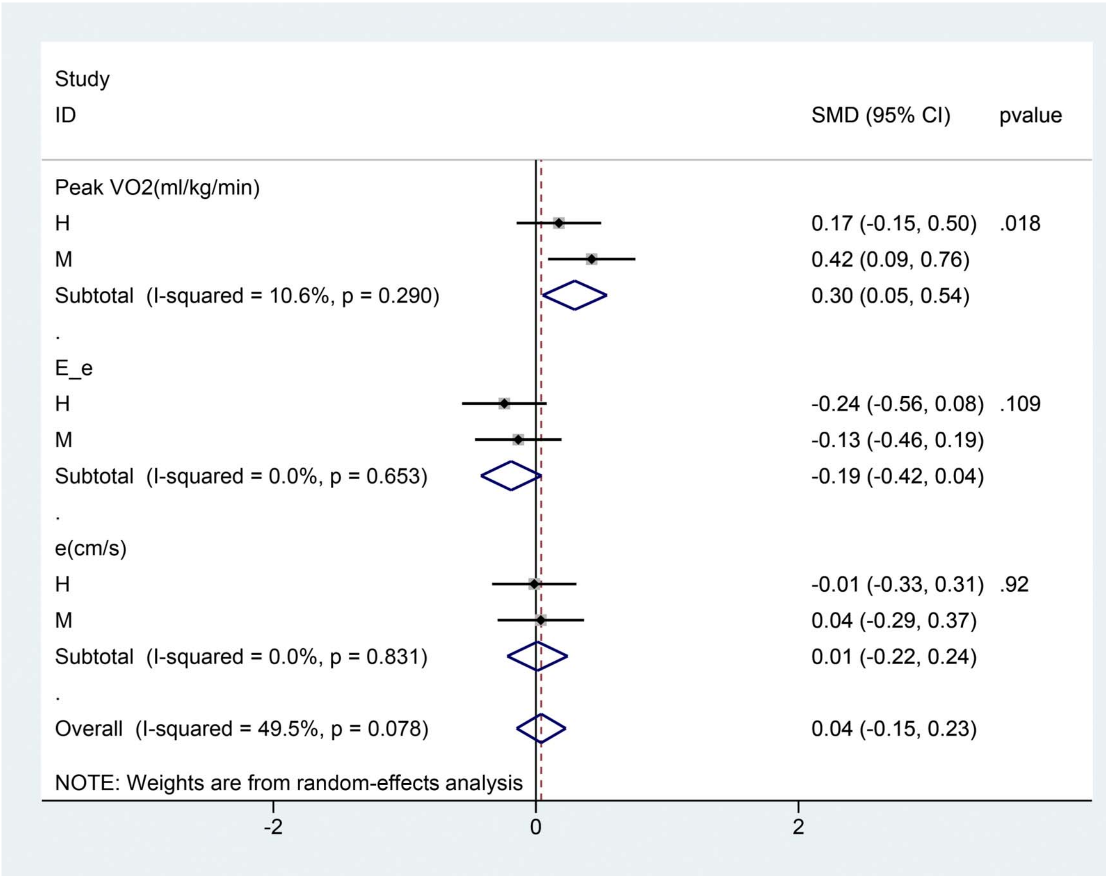

FIGURE 5. Effects of exercise intensity on exercise capacity and cardiac diastolic function across subgroups. High-intensity and moderate-intensity exercise training on peak VO2, E/e′, and e′ were, respectively, compared. All results are reported as an SMD (baseline after exercise) with a 95% CI. Peak VO_2 reflects exercise capacity. E/e′ means the ratio of early diastolic mitral inflow to annular velocities, and e′ means early diastolic mitral annular velocity, which indicates left ventricular diastolic function.

exercise training, the finding remains controversial.[25,32] Recently, the KCCQ score was used to evaluate QOL in patients with HFpEF. It was found that exercise training could also increase the KCCQ score but not significantly. This finding may be largely attributable to the inclusion of only 2 RCTs for analysis and exhibits substantial significance heterogeneity between the trials. Besides, this bias could also be explained by differences in the comorbidities of the patients.

The heterogeneity of these studies has been analyzed, and Galbraith plot analysis was used to identify specific studies. Numerous factors might cause these heterogeneities, including studied criteria and outcomes and patient' characteristics of age, race, comorbidities, and different training interventions. The subgroup analysis helped determine potential reasons for the observed magnitude of heterogeneity. The most distinctive difference of the design in the Mueller's study is that different exercise intensity and duration were included.[19] The subgroup analysis in this study showed that both moderate-intensity and high-intensity exercise could benefit patients with HFpEF, while compared with high-intensity training, moderate-intensity exercise could result in a greater improvement in peak VO_2. This finding is inconsistent with that reported by Angadi et al,[14] who found that high-intensity exercise training could be more potent compared with moderate-intensity exercise for early exercise training adaptations in patients with HFpEF. Besides, a recent study reported that low-volume high-intensity exercise is inefficient for the modulation of total body fat mass or total body fat percentage compared with nonexercise control and moderate exercise training.[35] This also suggests that different exercise modalities affect patients differently.

It has been found that moderate-intensity exercise could more effectively attenuate LV remodeling, with the greatest benefits afforded by long-term training compared with high-intensity exercise training performed for 2–3 months. Nevertheless, the latter remains superior to nonexercise control.[36] We also found that exercise capacity increased with longer exercise duration. This suggests that long-term exercise training could afford sustainable benefits for patients with HFpEF.

LIMITATIONS

This meta-analysis has the following limitations. First, the sample sizes of the studies included in this systematic review were relatively small. The pooling analysis of the differential effects of exercise intensity only included 3 studies, which may cause deviation in results across subgroups. Second, typical indicators were chosen for this meta-analysis. However, not all indicators of cardiorespiratory fitness and diastolic function reported in these studies were included, which might also lead to a bias. Moreover, the subgroup analysis to identify the significant heterogeneity between studies mainly included exercise intensity and duration, although sex differences, aging, and comorbidities might also be the reasons for the variability.

CONCLUSIONS

To the best of our knowledge, this meta-analysis is the first to highlight the beneficial effects of different physical exercise modalities for patients with HFpEF. It provides evidence that indicators of exercise capacity, LV diastolic function (as determined E/e′), and QOL significantly improved after physical exercise in patients with HFpEF, although partial indicators of cardiac diastolic function changed without having a significant impact. Moreover, both moderate-intensity and high-intensity exercise could benefit patients with HFpEF, and moderate exercise training may increase peak VO_2 more as compared with high-intensity exercise. Improvement in exercise capacity is positively related to exercise duration to some extent in patients with HFpEF. These results deserve further investigation.

REFERENCES

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591–602.
2. Cuijpers I, Simmonds SJ, van Bilsen M, et al. Microvascular and lymphatic dysfunction in HFpEF and its associated comorbidities. *Basic Res Cardiol*. 2020;115:39.
3. Mishra S, Kass DA. Cellular and molecular pathobiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2021;18:400–423.
4. Bozkurt B, Fonarow GC, Goldberg LR, et al. Cardiac rehabilitation for patients with heart failure: JACC Expert Panel. *J Am Coll Cardiol*. 2021;77:1454–1469.
5. Thomas RJ, Beatty AL, Beckie TM, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol*. 2019;74:133–153.
6. Ehlken N, Lichtblau M, Klose H, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J*. 2016;37:35–44.
7. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15:731–743.
8. McGee SL, Hargreaves M. Exercise adaptations: molecular mechanisms and potential targets for therapeutic benefit. *Nat Rev Endocrinol*. 2020;16:495–505.
9. Nayor M, Shah RV, Miller PE, et al. Metabolic architecture of acute exercise response in middle-aged adults in the community. *Circulation*. 2020;142:1905–1924.
10. Guo Y, Chen J, Qiu H. Novel mechanisms of exercise-induced cardioprotective factors in myocardial infarction. *Front Physiol*. 2020;11:199.
11. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2016;315:36–46.
12. Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, et al. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *Eur J Prev Cardiol*. 2020;27:1733–1743.
13. Brubaker PH, Avis T, Rejeski WJ, et al. Exercise training effects on the relationship of physical function and health-related quality of life among older heart failure patients with preserved ejection fraction. *J Cardiopulm Rehabil Prev*. 2020;40:427–433.
14. Angadi SS, Mookadam F, Lee CD, et al. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985)*. 2015;119:753–758.
15. Edelmann F, Gelbrich G, Düngen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780–1791.
16. Smart NA, Haluska B, Jeffriess L, et al. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. *Congest Heart Fail*. 2012;18:295–301.
17. Palau P, Domínguez E, Núñez E, et al. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. *Eur J Prev Cardiol*. 2014;21:1465–1473.
18. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ*. 2019;366:l4570.
19. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2021;325:542–551.
20. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
21. Maldonado-Martín S, Brubaker PH, Eggebeen J, et al. Association between 6-minute walk test distance and objective variables of functional capacity after exercise training in elderly heart failure patients with preserved ejection fraction: a randomized exercise trial. *Arch Phys Med Rehabil*. 2017;98:600–603.
22. Nolte K, Herrmann-Lingen C, Wachter R, et al. Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial. *Eur J Prev Cardiol*. 2015;22:582–593.
23. Palau P, Domínguez E, López L, et al. Inspiratory muscle training and functional electrical stimulation for treatment of heart failure with preserved ejection fraction: the TRAINING-HF Trial. *Rev Esp Cardiol (Engl Ed)*. 2019;72:288–297.
24. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62:584–592.
25. Kitzman DW, Brubaker PH, Morgan TM, et al. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail*. 2010;3:659–667.
26. Pandey A, Kitzman DW, Brubaker P, et al. Response to endurance exercise training in older adults with heart failure with preserved or reduced ejection fraction. *J Am Geriatr Soc*. 2017;65:1698–1704.
27. Yeh GY, Wood MJ, Wayne PM, et al. Tai chi in patients with heart failure with preserved ejection fraction. *Congest Heart Fail*. 2013;19:77–84.
28. Shaltout HA, Eggebeen J, Marsh AP, et al. Effects of supervised exercise and dietary nitrate in older adults with controlled hypertension and/or heart failure with preserved ejection fraction. *Nitric Oxide*. 2017;69:78–90.
29. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–3317.

30. Shah AM, Cikes M, Prasad N, et al. Echocardiographic features of patients with heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2019;74:2858–2873.
31. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms by using noninvasive methods. *JACC Cardiovasc Imaging*. 2020;13:245–257.
32. Leggio M, Fusco A, Loreti C, et al. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev*. 2020;25:703–711.
33. Fukuta H, Goto T, Wakami K, et al. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2019;24:535–547.
34. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8:33–40.
35. Sultana RN, Sabag A, Keating SE, et al. The effect of low-volume high-intensity interval training on body composition and cardiorespiratory fitness: a systematic review and meta-analysis. *Sports Med*. 2019;49:1687–1721.
36. Tucker WJ, Beaudry RI, Liang Y, et al. Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. *Prog Cardiovasc Dis*. 2019;62:163–171.

