



# 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

Hidekatsu Fukuta<sup>1</sup> · Toshihiko Goto<sup>2</sup> · Kazuaki Wakami<sup>2</sup> · Takeshi Kamiya<sup>3</sup> · Nobuyuki Ohte<sup>2</sup>

Published online: 28 April 2019

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## Abstract

Left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of heart failure with preserved ejection fraction (HFpEF) and contributes importantly to exercise intolerance that results in a reduced quality of life (QOL) in HFpEF patients. Although the effects of exercise training on LV diastolic function, exercise capacity, or QOL in HFpEF patients have been examined in randomized clinical trials (RCTs), results are inconsistent due partly to limited power with small sample sizes. We aimed to conduct a meta-analysis of RCTs examining the effects of exercise training on LV diastolic function and exercise capacity as well as QOL in HFpEF patients. The search of electronic databases identified 8 RCTs with 436 patients. The duration of exercise training ranged from 12 to 24 weeks. In the pooled analysis, exercise training improved peak exercise oxygen uptake (weighted mean difference [95% CI], 1.660 [0.973, 2.348] ml/min/kg), 6-min walk distance (33.883 [12.384 55.381] m), and Minnesota Living With Heart Failure Questionnaire total score (9.059 [3.083, 15.035] point) compared with control. In contrast, exercise training did not significantly change early diastolic mitral annular velocity (weighted mean difference [95% CI], 0.317 [−0.952, 1.587] cm/s), the ratio of early diastolic mitral inflow to annular velocities (−1.203 [−4.065, 1.658]), or LV ejection fraction (0.850 [−0.128, 1.828] %) compared with control. In conclusion, the present meta-analysis suggests that exercise training improves exercise capacity and QOL without significant change in LV systolic or diastolic function in HFpEF patients.

**Keywords** Exercise training · Heart failure with preserved ejection fraction · Diastolic function · Exercise capacity · Quality of life

## Introduction

Nearly half of patients with heart failure (HF) in the community have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF)

are high [1–3]. However, there is no established pharmacotherapy to improve survival in HFpEF [4–8]. Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance that results in a reduced quality of life (QOL) [9, 10]. Thus, improvement of exercise capacity and QOL presents another important clinical outcome in HFpEF patients.

There is much evidence that left ventricular (LV) diastolic dysfunction is associated with the pathophysiology of HFpEF [11–13] and studies have reported that LV diastolic dysfunction contributes importantly to exercise intolerance in HFpEF patients [14–17]. Although the effects of endurance exercise training on LV diastolic function, exercise capacity, or QOL in HFpEF patients have been examined in randomized clinical trials (RCTs) [18–25], results are inconsistent due partly to limited power with small sample sizes. Accordingly, we aimed to conduct a meta-analysis of RCTs examining the effects of exercise training on LV diastolic function and exercise capacity as well as QOL in HFpEF patients.

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s10741-019-09774-5>) contains supplementary material, which is available to authorized users.

✉ Hidekatsu Fukuta  
fukuta-h@med.nagoya-cu.ac.jp

<sup>1</sup> Core Laboratory, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467-8601, Japan

<sup>2</sup> Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

<sup>3</sup> Department of Medical Innovation, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

## Methods

This meta-analysis was performed and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [26].

Studies on the effect of exercise training on LV diastolic function, exercise capacity, or QOL in patients with HFpEF published until October 31, 2018 were identified using PubMed and EMBASE databases. For search of the eligible studies, the following keywords and Medical Subject Heading were used: *diastolic heart failure*, *heart failure with normal (preserved) ejection fraction*, *exercise*, and *training*. Our literature search was limited to studies involving human subjects and those published in English. Additionally, we manually searched the references that were cited in other relevant publications. Studies were considered eligible if they (1) included HF patients with preserved EF, (2) were RCT, (3) used cycling and/or walking as the primary training modality, (4) compared with standard medical care or placebo control group, and (5) assessed at least one of the following outcome measures: LV diastolic function, exercise capacity, and QOL.

Primary outcomes of interest were LV diastolic function, exercise capacity, and QOL. In the measures of LV diastolic function, the ratio of peak early to late diastolic mitral inflow velocities ( $E/A$ ), the E-wave deceleration time, the ratio of early diastolic mitral inflow to annular velocities ( $E/e'$ ), and the early diastolic mitral annular velocity ( $e'$ ) were extracted. In the measures of exercise capacity, peak exercise oxygen uptake ( $VO_2$ ) by expired gas analysis and 6-min walk distance (6MWD) were extracted. In the measures of QOL, scores of Minnesota Living With Heart Failure Questionnaire (MLHFQ) and the 36-item Short-Form Survey (SF-36) were extracted.

Secondary outcomes of interest were LV systolic function and LV structure. In the measures of LV systolic function and structure, LVEF, LV end-diastolic volume, and LV mass were extracted.

Other outcomes of interest were peak heart rate (HR) and peak systolic and diastolic blood pressure during exercise test and HR reserve which was defined as the difference between peak HR during exercise test and HR before exercise.

Information on the study and patient characteristics, methodological quality, intervention strategies, and clinical outcomes was systematically extracted separately by two reviewers (TG and KW). Disagreements were resolved by consensus.

For each outcome, the effect size for the intervention was calculated by the difference between the means of the intervention and control groups at the end of the intervention. If the outcome was measured on the same scale, the weighted mean difference (WMD) and 95% confidential interval (CI) were calculated. Otherwise, the standardized mean difference (SMD) and 95% CI were calculated. For each outcome,

heterogeneity was assessed using the Cochran's  $Q$  and  $I^2$  statistic; for the Cochran's  $Q$  and  $I^2$  statistic, a  $p$  value of  $<0.1$  and  $I^2 > 50\%$  were considered significant, respectively [27]. When there was significant heterogeneity, the data were pooled using a random-effects model; otherwise, a fixed-effects model was used. All analyses were based on intention-to-treat data. All the included studies did not report the standard deviation of the change or the correlation of the pre- and post-measurements and did only the pre- and post-measurements. Accordingly, the correlation was conservatively set at 0.5 as previously reported [28]. For all analyses, Comprehensive Meta-Analysis Software version 2 (Biostat, Englewood, NJ, USA) was used.

## Results

The study identification and selection process is summarized in Fig. 1. A total of 8 trials including 436 HFpEF patients were included in the present meta-analysis.

Characteristics of the included trials are summarized in Table 1. Of the included trials, four trials were conducted in the USA, two in Asia, one in Europe, and one in Oceania. Follow-up duration ranged across trials from 12 to 24 weeks. As to the primary outcomes of interest in the present meta-analysis, five trials reported the effect of exercise training on  $E/A$ , three trials on E-wave deceleration time, four trials on  $E/e'$ , three trials on  $e'$ , five trials on peak  $VO_2$ , five trials on 6MWD, seven trials on MLHFQ, and five trials on SF-36. As to the secondary outcomes of interest, seven trials reported

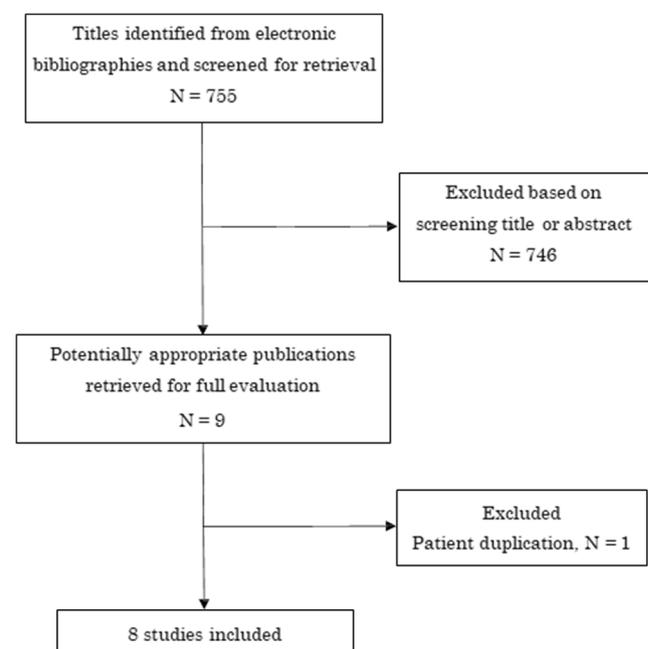


Fig. 1 Selection process for studies included in meta-analysis

**Table 1** Study characteristics

Study	Entry <i>N</i> , exercise/control	Loss to follow-up, <i>N</i> , exercise/control	Country	EF, NYHA class	Session time, frequency, intensity, duration	Training modality	Control	Primary outcome	Secondary outcome
Gary et al. [18]	16/16	1/3	USA	≥ 45% II–III	30–40 min, 3 times/week ~60% of target HR 12 weeks	Walking	Heart failure educational program	6MWD, MLHFQ	–
Kitzman et al. [19]	26/27	0/3	USA	≥ 50% II–III	1 h, 3 times/week ~70% of HR reserve 16 weeks	Walking/cycling	Attention control telephone call	<i>E/A</i> , DT, Peak $VO_2$ , 6MWD, MLHFQ, SF-36	EF, LVEDV, LV mass
Edelmann et al. [20]	46/21	2/1	Germany	≥ 50% II–III	20–40 min, 2–3 times/week ~60% of peak $VO_2$ 24 weeks	Cycling + resistance training	Usual care (maintenance of usual activity level)	<i>E/e'</i> , <i>e'</i> , Peak $VO_2$ , 6MWD, MLHFQ, SF-36	EF, LVEDV, LV mass
Smart et al. [21]	16/14	4/1	Australia	> 45% II–III	30 min, 3 times/week ~70% of peak $VO_2$ 16 weeks	Cycling	Usual care (maintenance of usual activity level)	<i>E/A</i> , DT, <i>E/e'</i> , <i>e'</i> , Peak $VO_2$ , MLHFQ	EF
Alves et al. [22]	20/11	0/0	Israel	> 55% NR	30 min, 3 times/week ~75% of maximal HR 24 weeks	Treadmill/cycling	Usual care	<i>E/A</i>	EF
Kitzman et al. [23]	32/31	8/1	USA	≥ 50% II–III	1 h, 3 times/week ~70% of HR reserve 16 weeks	Walking/cycling	Attention control telephone call	<i>E/A</i> , DT, Peak $VO_2$ , 6MWD, MLHFQ, SF-36	EF, LVEDV
Kitzman et al. [24]	51/49	5/3	USA	≥ 50% II–III	1 h, 3 times/week ~70% of HR reserve 20 weeks	Walking	Attention control telephone call or caloric restriction	<i>E/A</i> , <i>E/e'</i> , <i>e'</i> , Peak $VO_2$ , 6MWD, MLHFQ, SF-36	EF, LVEDV, LV mass
Fu et al. [25]	30/30	0/0	Taiwan	≥ 50% II–III	30 min, 3 times/week 80% of peak $VO_2$ 12 weeks	Cycling	Usual care	<i>E/e'</i> , MLHFQ, SF-36	EF

6MWD 6-min walk distance, DT E-wave deceleration time, *E/A* the ratio of peak early to late diastolic mitral inflow velocities, *E/e'* the ratio of early diastolic mitral inflow to annular velocities, *e'* early diastolic mitral annular velocity, EDV end-diastolic volume, EF ejection fraction, HR heart rate, LV left ventricular, NYHA New York Heart Association, MLHFQ Minnesota Living With Heart Failure Questionnaire, NR not reported, Peak  $VO_2$  peak exercise oxygen uptake, SF-36 36-item Short-Form Survey

the effect of exercise training on LVEF, four trials on LV end-diastolic volume, and three trials on LV mass.

Baseline patient characteristics of the included trials are summarized in Table 2. Many patients were taking HF and hypertension standard medications such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers ranging across trials from 23% to 92%, beta-blockers from 4% to 75%, and diuretics from 8% to 76%. Baseline measures of the primary, secondary, and other outcomes of interest in the present meta-analysis are shown in supplement Tables 1, 2, and 3.

The effect of exercise training on LV diastolic function is shown in Fig. 2. There was no significant difference in the changes of  $E/A$  (WMD [95% CI]=0.030 [−0.023, 0.082];  $P_{\text{random}}=0.266$ ), E-wave deceleration time (−2.040 [−26.534, 22.454] ms;  $P_{\text{random}}=0.870$ ),  $E/e'$  (−1.203 [−4.065, 1.658];  $P_{\text{random}}=0.41$ ), or  $e'$  (0.317 [−0.952, 1.587] cm/s;  $P_{\text{random}}=0.624$ ) between exercise training and control groups.

The effect of exercise training on exercise capacity is shown in Fig. 3. Exercise training significantly increased peak  $\text{VO}_2$  (WMD [95% CI]=1.660 [0.973, 2.348] ml/min/kg;  $P_{\text{random}}<0.001$ ) and 6MWD (33.883 [12.384 55.381] m;  $P_{\text{fix}}<0.01$ ) compared with the control group.

The effect of exercise training on MLHFQ score is shown in Fig. 4. Exercise training significantly improved total score (WMD [95% CI]=9.059 [3.083, 15.035] point;  $P_{\text{random}}<0.01$ ) and physical limitation scale (3.574 [0.590, 6.559] point;  $P_{\text{fix}}<0.05$ ) but not emotional limitation scale (−0.993 [−2.948, 0.962] point;  $P_{\text{random}}=0.320$ ) compared with control.

The effect of exercise training on SF-36 score is shown in Fig. 5. Exercise training significantly improved role limitations due to physical problems (WMD [95% CI]=11.989 [2.711, 21.267] point;  $P_{\text{fix}}<0.05$ ) and physical component score (4.450 [0.327, 8.572] point;  $P_{\text{random}}<0.05$ ) but not role

limitations due to emotional problems (10.196 [−3.999, 24.391] point;  $P_{\text{random}}=0.159$ ) or mental component score (2.187 [−3.171, 7.545] point;  $P_{\text{random}}=0.424$ ) compared with control.

The effects of exercise training on LV systolic function and LV structure are shown in Fig. 6. There was no significant difference in changes of LVEF (WMD [95% CI]=(0.850 [−0.128, 1.828] %;  $P_{\text{fix}}=0.088$ ), LV end-diastolic volume (SMD [95% CI]=−0.034 [−0.276, 0.208];  $P_{\text{fix}}=0.784$ ), or LV mass (SMD [95% CI]=0.072 [−0.205, 0.350];  $P_{\text{fix}}=0.609$ ) between exercise training and control groups.

The effects of exercise training on HR reserve and peak HR and systolic and diastolic blood pressure during exercise test are shown in Fig. 7. Exercise training significantly increased HR reserve compared with the control group (WMD [95% CI]=7.521 [1.797, 13.246];  $P_{\text{fix}}<0.05$ ). In contrast, there was no significant difference in changes of peak HR (WMD [95% CI]=7.25 [−0.868, 15.369];  $P_{\text{random}}=0.080$ ) or peak systolic (1.409 [−3.264, 6.082];  $P_{\text{random}}=0.555$ ) or diastolic blood pressure (−1.335 [−5.378, 2.709];  $P_{\text{random}}=0.518$ ) during exercise test between exercise and control groups.

When the pooled analysis was restricted to six trials that included HF patients with  $\text{EF} \geq 50\%$ , the results substantially remained unchanged. There was no significant difference in changes of  $E/A$  (WMD [95% CI]=0.029 [−0.037, 0.095];  $P_{\text{random}}=0.388$ ), E-wave deceleration time (−3.516 [−41.735, 34.703] ms;  $P_{\text{random}}=0.857$ ),  $e'$  (0.489 [−1.275, 2.253] cm/s;  $P_{\text{random}}=0.587$ ),  $E/e'$  (−1.520 [−4.523, 1.483];  $P_{\text{random}}=0.321$ ), or LVEF (0.842 [−0.144, 1.828] %;  $P_{\text{random}}=0.094$ ) between exercise training and control groups. In contrast, exercise training significantly improved peak  $\text{VO}_2$  (WMD [95% CI]=1.820 [0.939, 2.700] ml/min/kg;  $P_{\text{random}}<0.001$ ), 6MWD (29.222 [6.848, 51.596] m;  $P_{\text{fix}}<0.05$ ), and MLHFQ total score (11.024 [5.429, 16.618] point;  $P_{\text{random}}<0.001$ ) compared with control group.

**Table 2** Patient characteristics

Author, year	Mean age, year	Men, %	CAD, %	AF, %	Valvular disease, %	Hypertension, %	Diabetes, %	COPD, %	ACE-I/ARB, %	BBs, %	Diuretics, %
Gary et al. [18]	68	0	25	NR	NR	78	31	34	47 <sup>a</sup>	NR	NR
Kitzman et al. [19]	70	25	0	NR	0	68	17	0	23 <sup>a</sup>	23	51
Edelmann et al. [20]	65	44	0	NR	0	86	14	0	66	50	45
Smart et al. [21]	64	52	0	NR	0	16	16	0	76	4	8
Alves et al. [22]	63	71	32 <sup>b</sup>	3	NR	68	35	NR	51	74	16
Kitzman et al. [23]	70	23	0	NR	0	89	24	0	46	22	61
Kitzman et al. [24]	66	19	0	1	0	95	35	0	72	40	76
Fu et al. [25]	61	63	68	0	NR	63	42	0	92	75	72

ACE-I angiotensin converting enzyme inhibitor, AF atrial fibrillation, ARB angiotensin receptor blocker, BBs beta-blockers, NR not reported, CAD coronary artery disease, COPD chronic obstructive pulmonary disease

<sup>a</sup> The value is presented as a proportion of the use of ACE-I

<sup>b</sup> The value is presented as a proportion of previous history of myocardial infarction

Among the included trials, five trials reported adverse outcomes during exercise intervention. Although minor events including hypoglycemia [23, 24] palpitation, dyspnea, and mild musculoskeletal discomfort [20, 24] were reported, there were no serious adverse events judged related to exercise training.

## Discussion

In the present study, we conducted a meta-analysis of RCTs examining the effects of exercise training on LV function and structure and exercise capacity as well as QOL in HFpEF patients. We observed that exercise training improved peak  $\text{VO}_2$ , 6MWD, and physical dimensions of QOL but not LV diastolic or systolic function, LV end-diastolic volume, or LV mass. Thus, we found that exercise training improved exercise capacity and QOL without significant change in LV function or structure in HFpEF patients.

Our observed improvement in exercise capacity and QOL after exercise training in HFpEF patients is in accordance with two previous meta-analyses [29, 30]. However, several important RCTs on the effect of exercise training on exercise capacity and QOL in HFpEF patients have been published since the meta-analysis was performed [24, 25]. Our meta-analysis confirms the reported favorable effect of exercise training on exercise capacity and QOL with a larger number of patients. Furthermore, our meta-analysis is the first to examine the effect on different aspects of QOL in HFpEF and to show that exercise training improved physical—but not mental or emotional—dimensions of QOL in these patients.

Inconsistent with our observations, a recent meta-analysis of Pearson et al. [31] reported that exercise training improved diastolic function assessed as  $E/e'$  in HFpEF patients. However, we believe that there are several limitations in the meta-analysis of Pearson et al. [31]. Specifically, the meta-analysis of Pearson et al. [31] included the trial on the effect of functional electrical stimulation [32], which is not classified as exercise training. Furthermore, the meta-analysis included the trial on the effect of respiratory muscle training by physical therapists [33], which is not commonly selected as a primarily training modality. The present meta-analysis is important in including only trials on which the primary training modality was cycling and/or walking, an easily available training modality.

Consistent with our meta-analysis, Pandey et al. [29] reported that exercise training did not improve LV diastolic function HFpEF patients. We believe that our meta-analysis is superior to the meta-analysis of Pandey et al. [29] in that we examined the effect of exercise training not only on measures of diastolic mitral inflow velocities but also on diastolic tissue Doppler measures. It is well known that measures of diastolic mitral inflow velocities such as  $E/A$  and E-wave deceleration

time have biphasic relationship with diastolic function grade, whereas diastolic tissue Doppler measures such as  $E/e'$  and  $e'$  correlate linearly with diastolic function grade [34]. Our meta-analysis confirms the reported neutral effect of exercise training on mitral inflow measures with a larger number of patients and further extends to diastolic tissue Doppler measures.

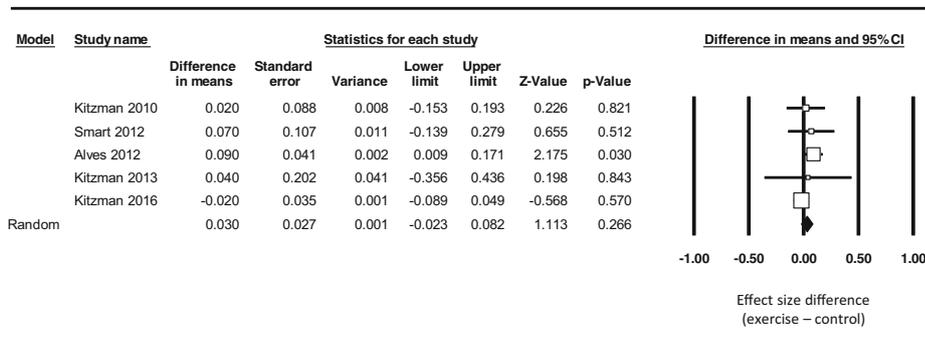
In the present meta-analysis, we observed that exercise training improved exercise capacity without improvement in LV function or structure in HFpEF patients. To consider the possible mechanisms for the observations, it may be useful to look over the pathophysiological background of exercise intolerance in HFpEF. During exercise, the oxygen consumption in the metabolizing tissues increases dramatically. Normally, this is accomplished by (1) an increase in cardiac output, a product of HR and stroke volume, and (2) increased utilization of oxygen by the metabolizing tissues [35]. Earlier studies have reported that, in HFpEF patients, stroke volume during exercise increases or maintains at the expense of increased LV end-diastolic pressure due to diastolic abnormalities, resulting in exertional dyspnea and thereby impaired QOL [14–17]. However, emerging data suggest that a limited increase in HR (chronotropic incompetence) as well as impaired oxygen utilization by active muscles during exercise may play a relatively greater role in limiting exercise performance in HFpEF patients [35].

From these aspects, the following mechanisms may underlie the improved exercise capacity with exercise training in HFpEF patients. In the present meta-analysis, we observed that exercise training improved HR reserve but not LV diastolic or systolic function. This finding suggests that improved chronotropic incompetence resulting from exercise training may contribute at least in part to improved exercise capacity in HFpEF patients. Furthermore, in an ancillary study of the included trial [19], exercise training increased utilization of oxygen by active muscles but not peak stroke volume during exercise [36]. Taken together, in HFpEF patients, the improved exercise capacity with exercise training appears to result from improved chronotropic incompetence and increased utilization of oxygen by active muscles.

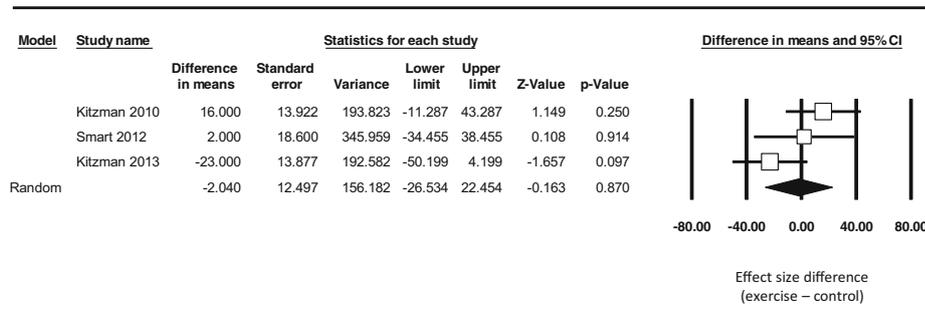
In the present meta-analysis, we observed that exercise training did not significantly improve mental or emotional dimensions of QOL in HFpEF patients. Consistent with this observation, there was no clear benefit of exercise training on depression in HFpEF patients in a meta-analysis of RCTs [37]. However, the meta-analysis included only 3 trials with 115 HFpEF patients [37]. Similarly, in our meta-analysis, subscales of QOL were not consistently reported in the included trials. Further large-scale RCTs are needed to determine the effect of exercise training on mental or emotional state in HFpEF patients.

There are several limitations to our study. First, our meta-analysis included trials that were conducted before the definition of HFpEF was developed. Several of these trials defined

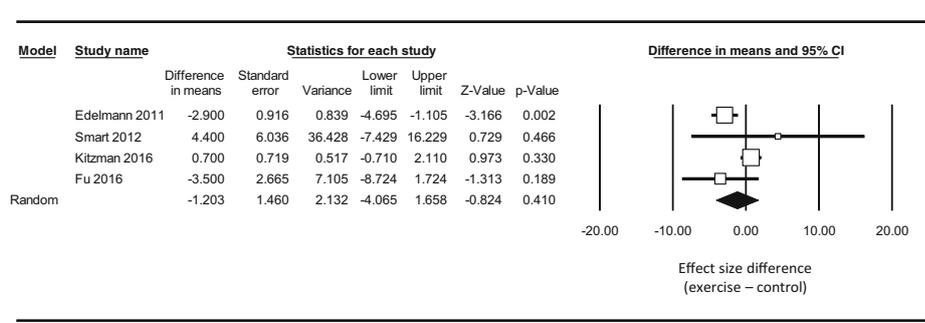
(a) E/A



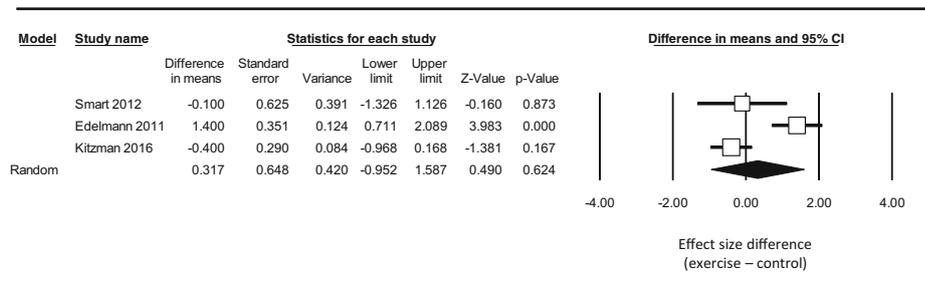
(b) E-wave deceleration time



(c) E/e'



(d) e'



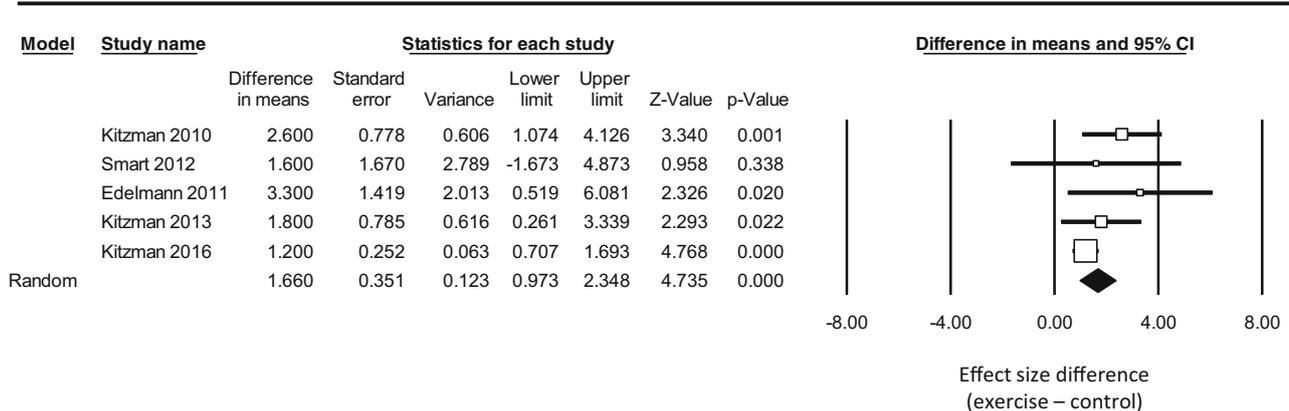
**Fig. 2** Forest plots showing the effects of exercise training on the ratio of peak early to late diastolic mitral inflow velocities ( $E/A$ ; **a**), E-wave deceleration time (ms; **b**), the ratio of early diastolic mitral inflow to annular velocities ( $E/e'$ ; **c**), and early diastolic mitral annular velocity ( $e'$ ; cm/s, **d**)

preserved EF as greater than or equal to 45% [18, 21], which is not consistent with a definition of HFpEF in recent guidelines [38, 39]. However, based on the reported mean EF of these trials (supplement Table 3), there appeared to be only a few patients with EF < 50% included in the present meta-analysis. Importantly, even when the pooled analysis was restricted to the trials of HF with EF  $\geq$  50%, the results remained substantially unchanged. Second, there is substantial variation in baseline clinical characteristics including gender, comorbidities, exercise capacity, QOL scores, echocardiographic variables, and drug treatment across the included trials, emphasizing the need for trials with homogeneous clinical characteristics. Third, most of the included trials excluded patients with

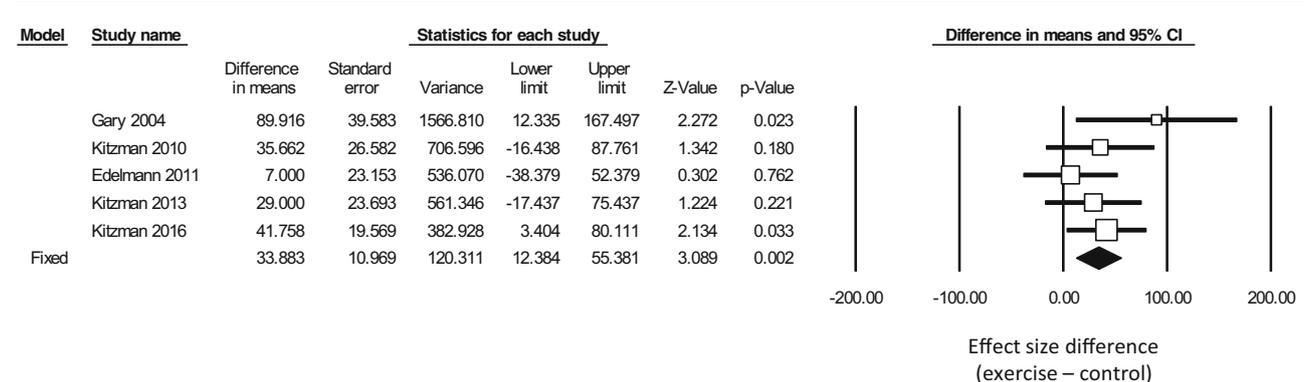
comorbidities such as atrial fibrillation, coronary artery disease, and chronic obstructive pulmonary diseases, which are common in HFpEF patients [40]. Our observed beneficial effect of exercise training cannot be extended into HFpEF patients with these comorbidities. Finally, the number of patients included in our meta-analysis was relatively small and measures of LV function or structure were not consistently reported in the included trials. Furthermore, exercise training periods in the included trials were relatively short (12–24 weeks). Our observed neutral effects of exercise training on LV function and structure may be due in part to limited power and/or the relatively short period of exercise training. Further trials with larger sample size and longer intervention period are necessary.

In conclusion, our meta-analysis showed that aerobic exercise training improved exercise capacity and QOL without significant change in LV function or structure in HFpEF patients. Given the limited number of patients, the short intervention period, and the substantial variation in baseline

### (a) Peak $VO_2$



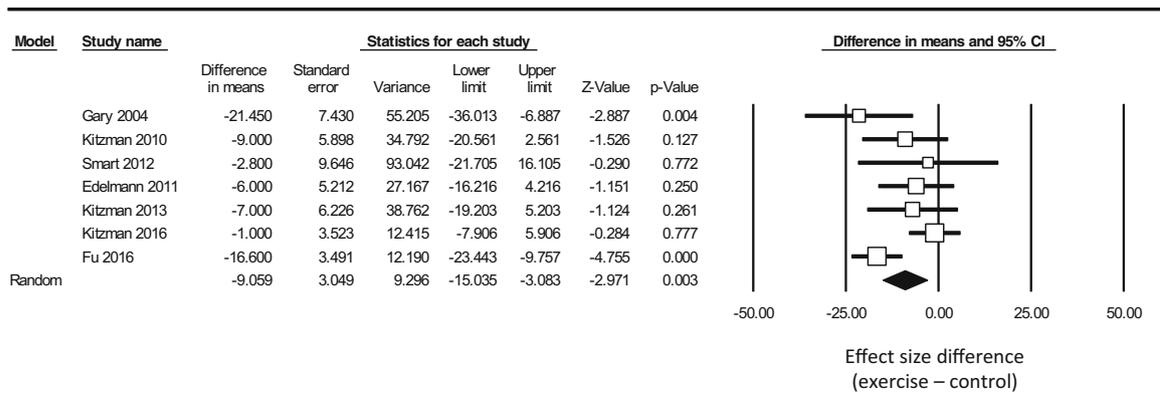
### (b) 6MWD



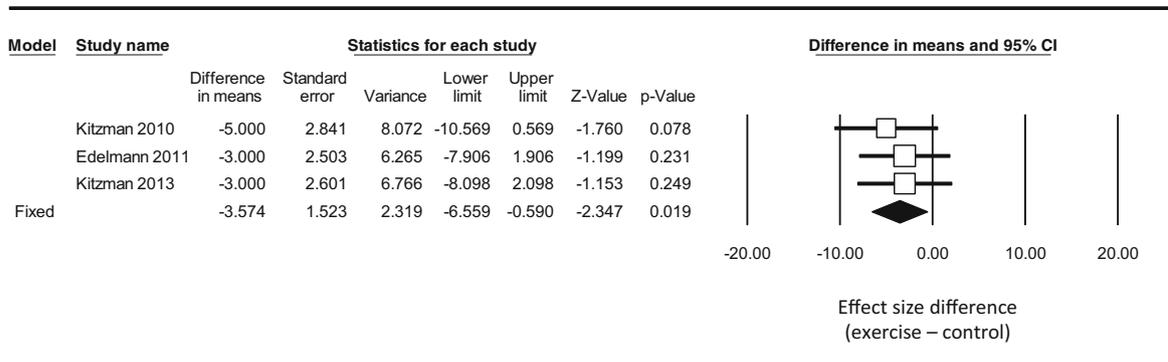
**Fig. 3** Forest plots showing the effects of exercise training on peak exercise oxygen uptake ( $VO_2$ ; ml/min/kg, **a**) and 6-min walking distance (6MWD; m, **b**)

# MLHFQ

## (a) Total score



## (b) Physical limitation scale



## (c) Emotional limitation scale

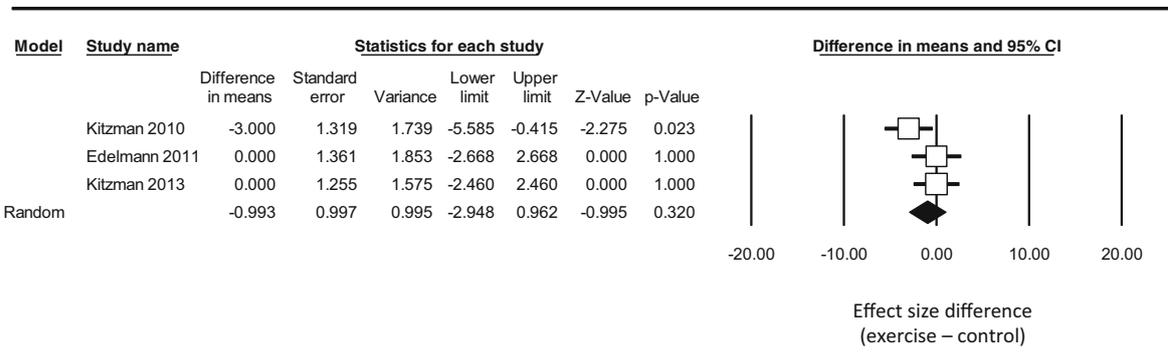
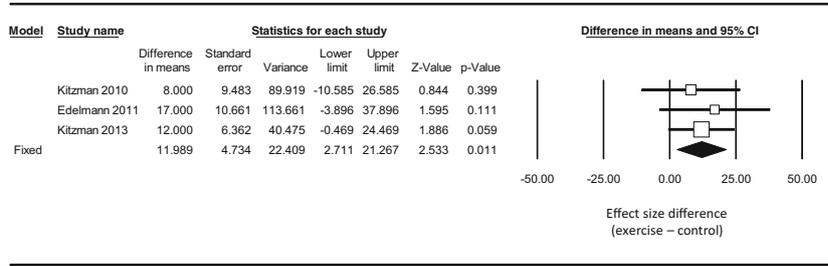


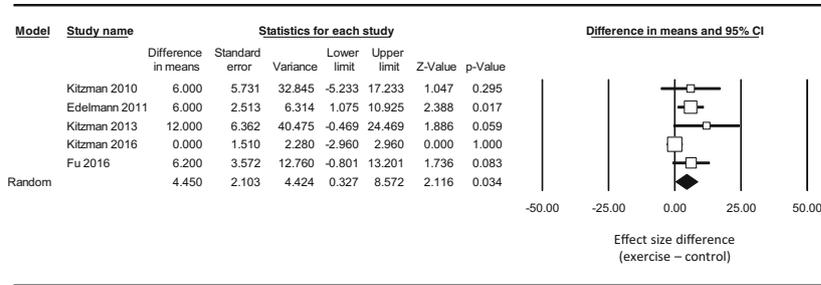
Fig. 4 Forest plots showing the effect of exercise training on Minnesota Living With Heart Failure Questionnaire (MLHFQ) scores

## SF-36

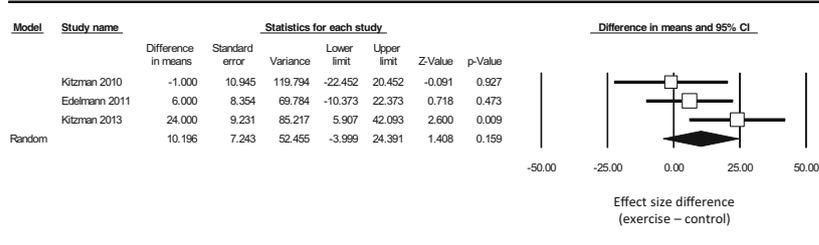
### (a) Role limitations due to physical problems



### (b) Physical component score



### (c) Role limitations due to emotional problems



### (d) Mental component score

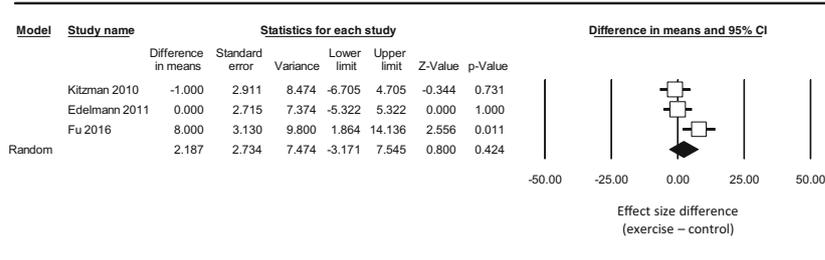
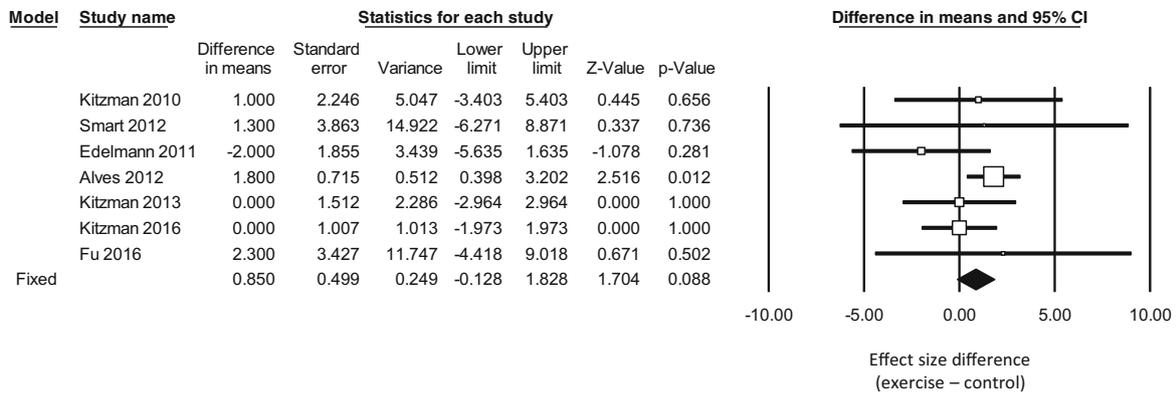
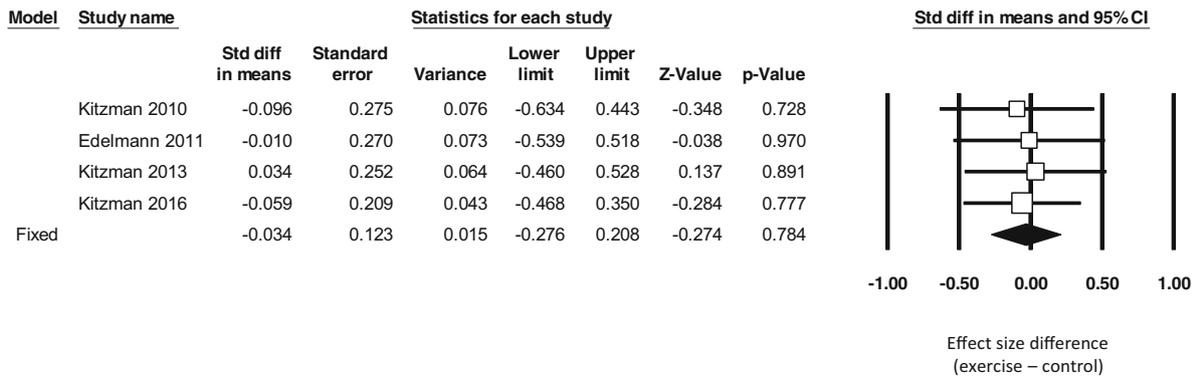


Fig. 5 Forest plots showing the effect of exercise training on the 36-item Short-Form Survey (SF-36) scores

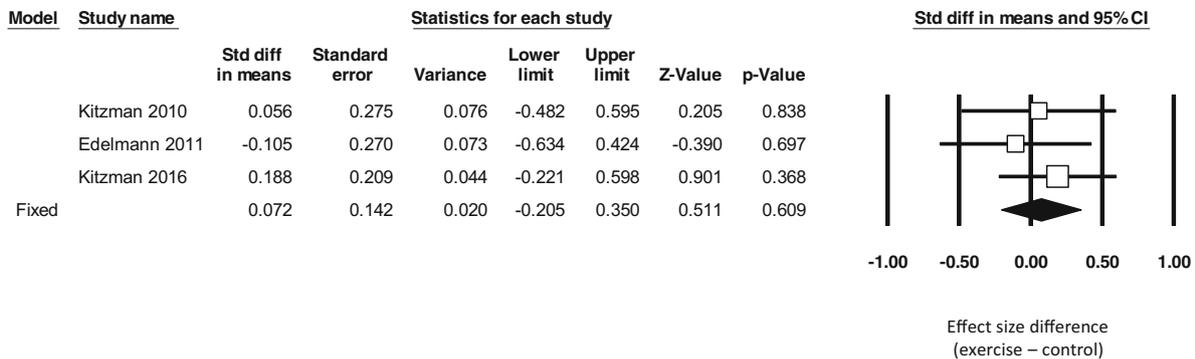
### (a) EF



### (b) LV end-diastolic volume

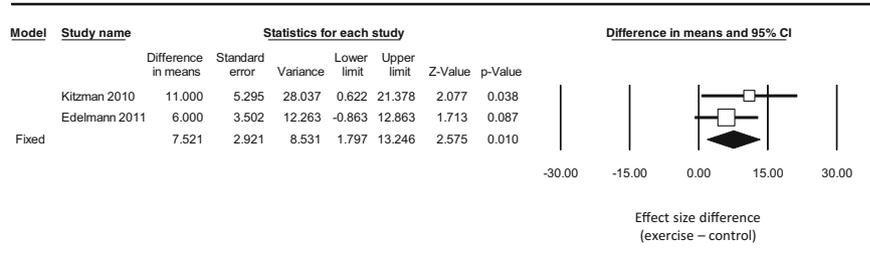


### (c) LV mass

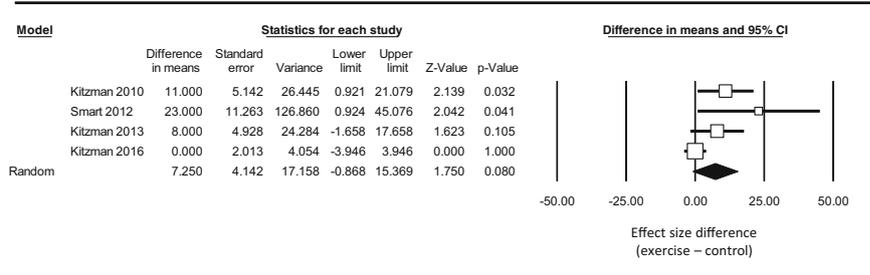


**Fig. 6** Forest plots showing the effects of exercise training on left ventricular (LV) ejection fraction (EF; %, **a**), LV end-diastolic volume (**b**), and LV mass (**c**)

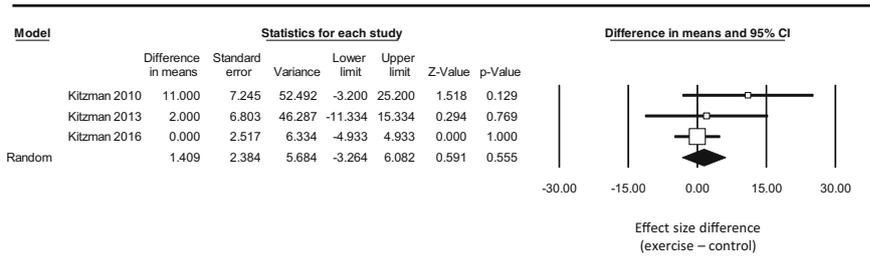
**(a) HR reserve**



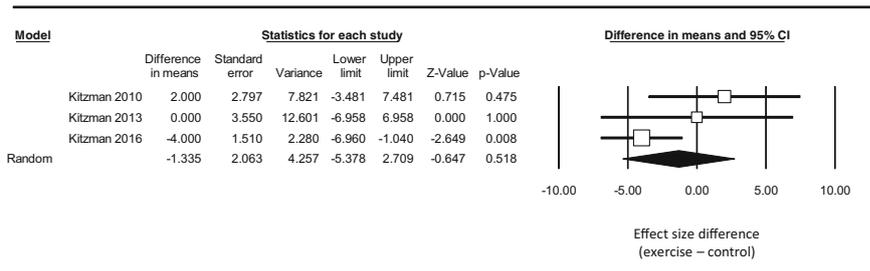
**(b) Peak HR**



**(c) Peak systolic blood pressure**



**(d) Peak diastolic blood pressure**



**Fig. 7** Forest plots showing the effects of exercise training on heart rate (HR) reserve (bpm; **a**) and peak HR (bpm; **b**) and systolic and diastolic blood pressure (mmHg; **c** and **d**) during exercise test

clinical characteristics in the included trials, further large multicenter and long-term trials for HFpEF patients with homogeneous clinical characteristics are necessary to confirm our observed effects of exercise training.

### Compliance with ethical standards

**Conflict of interest** Dr. Ohte has received lecture fees from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Co., Ltd., Bayer GA, AstraZeneca plc, and Boehringer Ingelheim and grant support from Takeda Pharmaceutical Co. Ltd., Bayer GA, Daiichi Sankyo Co., Ltd., MSD, Novartis International AG, Boehringer Ingelheim, Astellas Pharma Inc., and Otsuka Pharmaceutical Co., Ltd. No other disclosures were reported.

**Ethical approval** This article does not contain any studies with human participants performed by any of the authors.

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