Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis

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Abstract

Exercise training induces physical adaptations for heart failure patients with systolic dysfunction but less is known about those patients with preserved ejection fraction.

This study's aims were to establish if exercise training produces changes in peak VO_2 and related measures, quality of life, general health and diastolic function in heart failure patients with preserved ejection fraction (HFpEF).

We conducted a MEDLINE search (1985 to September 1, 2015), for exercise based rehabilitation trials in heart failure, using search terms 'exercise training, heart failure with preserved ejection fraction, heart failure with normal ejection fraction, peak VO_2 and diastolic heart dysfunction'. Eight intervention studies were included providing a total of 174 exercising subjects and 143 control subjects, a total of 317 participants.

Peak VO_2 increased by a mean difference (MD) 2.08 mL kg^{-1} min^{-1} (95% C.I. 1.51 to 2.65, p<0.00001) in exercise training versus sedentary control, equating to a 17% improvement from baseline. V_E/VCO_2 slope was not different between groups, MD -3.10 mL kg^{-1} min^{-1} (95% C.I. -7.47 to 1.27, p=0.16); maximum heart rate was significantly increased in exercise groups, MD 3.46 bpm (95% C.I. 2.41 to 4.51, p<0.00001); 6 Minute Walk Distance (6MWT) MD 32.1m (95% C.I. 17.2 to 47.1, p<0.0001); diastolic function; the ratio of early to late filling (E/A ratio) was improved after exercise training MD 0.07 (95% C.I. 0.02 to 0.12, p=0.006); as was filling pressure E/E' ratio MD -2.38 (95% C.I. -3.47 to -1.28, p<0.0001); Deceleration time (D_T) MD -13.2 msec (95% C.I. -19.8 to -6.5, p=0.0001); Minnesota Living with Heart Failure Questionnaire (MLHFQ) MD -6.77 (95% C.I. -9.70 to -3.84, p<0.00001); Short Form-36 Health Survey MD 11.38 (95% C.I. 5.28 to 17.48, p=0.0003). In 3222 patient-hours of training, not a single death was directly attributable to exercise.

Exercise training appears to effect several health-related improvements in people with heart failure and preserved ejection fraction.

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Introduction

Heart Failure with preserved Ejection Fraction (HFpEF) is defined as an inability of the ventricles to optimally accept blood from the atria with blunted end-diastolic volume response by limiting the stroke volume and cardiac output. Exercise intolerance and reduced quality of life are known as the primary chronic symptoms in HFpEF patients. HFpEF prevalence is higher in elderly and women and may be linked to hypertension, diabetes mellitus and atrial fibrillation [1,2]. Chronic Heart Failure (CHF) patients with either normal or abnormal systolic function have similar mortality rates [3]. In the United States, chronic heart failure affects approximately 5 million individuals with heart failure and over 555,000 are newly diagnosed with CHF annually [4]. Corresponding costs to the health care systems are enormous. A 2011 review by Smart [5] estimated the hospital-based exercise therapy treatment costs to prevent mortality in one systolic heart failure patient to be approximately US$60K *per annum*. A range of benefits are likely in patients with systolic heart failure undertaking exercise training [6-14]. Meta-analyses have shown exercise training to be beneficial in HFpEF patients in terms of improved cardio-respiratory fitness [15-17].

In people with HFpEF, as well as systolic heart failure, cardiorespiratory fitness (peak VO_2) is impaired [18,19]. Impaired peak VO_2 has been associated with increased mortality risk [20] and decreased quality of life in heart failure patients. As measured by traditional indices such as ejection fraction, systolic function appears largely normal under resting baseline conditions in HFpEF. However, studies have shown through global assessment of systolic function by other techniques, such as strain rate imaging, systolic abnormalities do exist in HFpEF patients [21]. Despite the preservation of systolic function at rest, mortality rates in HFpEF are similar to those observed in systolic failure [22], highlighting the clear need for effective treatment strategies for these patients.

Interestingly, conventional methods for treating heart failure have proven largely ineffective for HFpEF patients. Currently, effective therapeutic approaches for HFpEF are limited and focus primarily on managing cardiovascular risk factors, especially hypertension. Exercise therapy is a promising effective adjunct therapy that can delay disease progression, minimize pharmaceutical use and improve functional limitations and quality of life. While to date approximately 100 randomized, controlled

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trials of exercise training trials have been published in systolic heart failure patients, strikingly, only 10 such trials exist examining HFpEF [17].

In this meta-analysis, our purpose was to assess the effects of exercise on a number of outcome measures that are commonly used to assess clinical status in HFpEF. First, we evaluated the impact of exercise training on changes to exercise capacity in HFPEF patients compared to sedentary controls through examination of peak VO_2, V_E/VCO_2, heart rate, and the 6-min walk test. Second, we studied clinical measures of diastology including early to late filling ratio (E/A), deceleration of early ventricular filling, and E/e' (a widely accepted noninvasive surrogate of left ventricular filling pressure). Third, we examined if exercise training produces better quality of life and/or general health through use of the Minnesota Living with Heart Failure Questionnaire [23] and the SF-36 (which has established norms) [24]. Finally, we examined if rates of serious events, mortality and hospitalization were more frequent with exercise training in HFPEF patients.

Methods

Search strategy

Studies were identified through a MEDLINE search (1985 to September 1, 2015), Cochrane Controlled Trials Registry (1966 to September 1, 2015), CINAHL, SPORTDiscus and Science Citation Index. The search strategy included a mix of MeSH and free text terms for key concepts related to exercise training, heart failure with normal ejection fraction and heart failure with preserved ejection fraction, peak VO_2 and diastolic heart failure for clinical trials of exercise training in heart failure patients. Studies were included if patients exhibited baseline Left Ventricular Ejection Fraction above 45%. These searches were limited to prospective randomized or controlled trials and human studies; with no language restrictions on publications. Manuscript reference lists and latest journal editions were scrutinised for new references. Full journal articles were assessed by three reviewers (NS, GD and HI) for relevance and eligibility. Methodological disagreements were resolved by reviewers through discussion. For two studies [25,26], authors were contacted and requested to provide further data about the protocol for implementing desired exercise intensity.

Study selection

Included were randomized controlled designs of exercise training in heart failure patients with normal or preserved ejection fraction. Studies of heart failure patients with abnormal, systolic function were excluded. All included studies are comparisons between exercise training and sedentary control. Records identified 33 papers through database searching. Six additional records from reference lists were added. Only principal studies, with the most subjects, were included where multiple publications existed from the same dataset. After initial screening, 19 studies were removed, which included overlapping, duplicates, duplicate data, abstracts, irrelevant articles (*e.g.* editorials and discussion papers). We further excluded 12 studies where the control group received additional intervention, non-relevant studies and acute exercise responses. Eight studies of exercise training intervention were included (Consort Statement, Figure 1).

Outcomes measures

We recorded the following; peak VO_2 (baseline and *post* exercise), V_E/VCO_2, maximum heart rate, 6 Minute Walk Test (6MWT), diastolic function [E/A and E/E' ratios, deceleration time (D_T)], Minnesota Living with Heart Failure Questionnaire (MLHFQ), the Short Form-36 Health Survey, participant completion rates, adverse medical events, hospitalization and mortality.

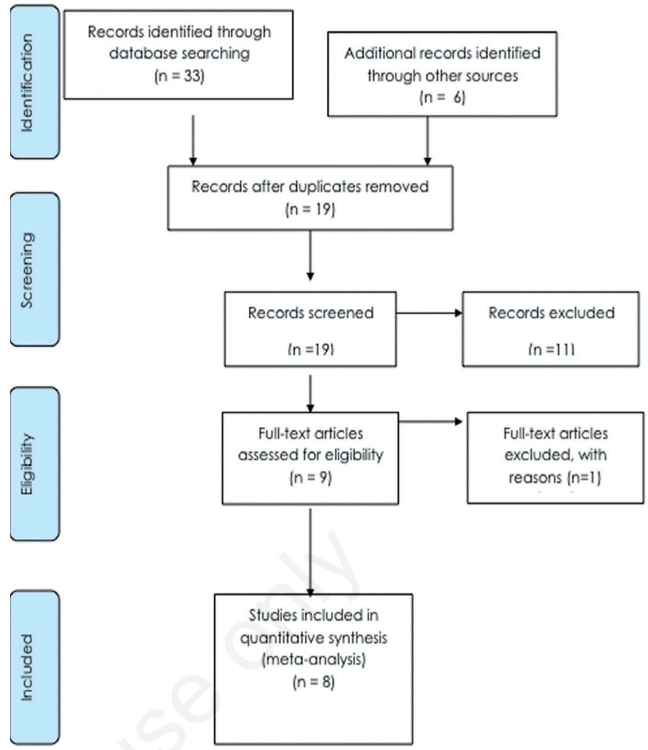

Figure 1. Consort statement.

Data synthesis

We calculated patient-hours of exercise training and percentage change in peak VO_2.

Assessment of study quality

We assessed study quality using the 15-point TESTEX scale [27], which is a validated study quality assessment tool specific to exercise training studies. Median TESTEX score was 10, with two studies scoring 8, three scoring 10 and two studies scoring 12.

Statistical analyses

Revman 5.1 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analysis. Continuous data were reported as mean and standard deviation. Revman 5.1 enabled calculation of post-intervention change from baseline for standard deviation, using change in mean values, number of subjects and p value or preferably 95% confidence intervals. In many cases where exact p-values were not provided, we used default values *e.g.* $p<0.05$ became $p=0.049$. Mean difference (MD) in these data from baseline were analyzed. We used a 5% level of significance and a 95% confidence interval to report change in outcome measures. Egger plots were produced to identify sources of publication bias [28].

Results

Included studies

Eight studies met selection criteria [18,25,26,29-33], providing a total of 174 exercising subjects and 143 control subjects, a total of 317 participants (Table 1). Total patient-hours of exercise training reported were 3222 hours.

Table 1. Patient and training characteristics for randomized control trials included in the meta-analysis on exercise training studies with HFpEF patients.

Study	Country	Sessions attended (%)	Participants include in the final analysis	Training characteristics	Outcomes measures
Alves (2012)	Portugal	100	Total patients N=98 Exercise (>55%): n=20, 22m/9f, mean age 62.9. Control group n=11. Exercise control (45%-54%): n=23, 24m/9f, mean age 63.6. Control group n=10, Exercise control (<45%): n=22, 27m/7f, mean age 62.0. Control group n=12 NYHA class I/II/III/IV	6 months of interval exercise training. First month, 3 sessions per week, and 15 min at 70%-75% of maximal heart rate. Following five months, 3 sessions per week, and 35 min at 70%-75% of maximal hear rate	LVEF Diastolic function
Edelmann (2011)	Germany	34 - Exercise training group participated in >90%, 52 in 70%-90% and 14% in <70% of the exercise sessions	Total patients N=64 Exercise: n=44, 24m/20f, mean age 64. Exercise control: n=20, 12m/8f, mean age 65 NYHA class II/III	32 sessions of continuous exercise training. Weeks 1-4, 2 sessions per week, 20-40 min at 50%-60% of peak VO_2. Week 5 onward, 3 sessions per week at 70% of peak VO_2 and resistance training, 15 reps at 60%-65% 1RM	LVEF Peak VO_2 Heart rate 6MWT MLHF SF36
Fu (2015)	Taiwan	100	Total patients N = 59 Exercise: n=30, 20m/10f, mean age 60.5. Control: n=29, 18m/11f, mean age 62.4 NYHA class II/III	3-min intervals of aerobic interval training at 40% and 80% VO_{2Peak} for 30 min/day, 3 days/week for 12 weeks	Systolic function Diastolic function Peak VO_2 V_E/CO_2 Heart rate MAP, SBP, DBP MLHF SF36
Gary (2004)	USA	100	Total patients N=28 Exercise: n=15, 15f, mean age 67. Control: n=13, 13f, mean age 69 NYHA class II/III	12 weeks of continuous exercise training (walking). 3 sessions per week, 20-40 min at 40% - 60% of the maximal heart rate	6MWT MLHF
Karavidas (2013)	Greece	100	Total patients N=30 Exercise: n=15, 6m/9f, mean age 69.4. Control: n=15, 6m/9f, mean age 68.5 NYHA class II/III	6 weeks of functional electrical stimulation (FES) training. 5 sessions per week, 30 min at 25 Hz for 5 s followed by 5 s rest	MLHF KCCQ BDI 6MWT Diastolic function BNP
Kitzmann (2013)	USA	86 Final testing 88 Exercise training	Total patients N=63 Exercise: n=24, 23m/9f, mean age 70. Control: n=30, 25m/6f, mean age 70 NYHA class II/III	4 months (~16 weeks of continuous exercise training. 3 sessions per week, 60 min at 40%-70% HRR	LVEF Peak VO_2 V_E/VCO_2 Heart rate 6MWT Diastolic function EDV & ESV SBP & DBP MLHF SF36

To be continued on next page

Table 1. Continued from previous page.

Study	Country	Sessions attended (%)	Participants include in the final analysis	Training characteristics	Outcomes measures
Palau (2013)	Australia	100	Total patients N=26 Exercise: n=14, 7m/7f, mean age 68. Control: n=12, 6m/6f, mean age 74 NYHA class II/III/IV	12 weeks of interval exercise training. 2 sessions per week, 20 min. Subjects started breathing at a resistance equal to 25-30% MIP for 1 week and each subsequent session was adjusted to 25-30% MIP	LVEF Peak VO_2 V_E/VCO_2 Heart rate 6MWT Diastolic function NT-proBNP MLHF
Smart (2012)	Australia	87.6	Total patients N=25 Exercise: n=12, 7m/5f, mean age 67. Control: n=13, 6m/7f, mean age 61 NYHA class I/II	16 weeks of interval exercise training. 3 sessions per week, 30 min at 60-70% peak VO_2	LVEF Peak VO_2 V_E/VCO_2 Heart rate Diastolic function MLHF

Peak VO_2, maximal oxygen consumption; FES, functional electrical stimulation; peak HR, maximal heart rate; MHR, maximum heart rate; HRR, heart rate reserve; m/f, male/female; MIP, inspiratory muscle trainer; 1RM, 1 repetitive maximum; 6MWT, 6 minute walk test; LVEF, left ventricular ejection fraction; EDV, end diastolic volume; ESV, end systolic volume; MLHF, Minnesota living with heart failure questionnaire; SF 36, the short form (36) Health survey; V_E/VCO_2, ventilatory equivalent for carbon dioxide; KCCQ, Kansas City cardiomyopathy questionnaire; BDI, Beck depression inventory; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain natriuretic peptide; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Exercise training parameters

Program length for high intensity training varied from 6-26 weeks and frequency from 2-5 sessions weekly. Three studies used walking and cycle training, one used only walking, two used cycling only, one used functional electrical stimulation and one inspiratory muscle training.

Outcome measures

Change in peak VO_2

Data from five studies showed a significant improvement in peak VO_2, mean difference (MD) 2.08 mL $kg^{-1}min^{-1}$ (95% C.I. 1.51 to 2.65, p<0.00001) in exercise *versus* control (Figure 2).

Change in peak V_E/VCO_2 slope

Data from four studies showed V_E/VCO_2 slope was not significantly changed, MD was -3.10 units (95% C.I. -7.47 to 127, p=0.16) in exercise *versus* control (Figure 3).

Change in heart rate

Data from five studies showed maximum heart rate was significantly reduced, MD 3.46 bpm (95% C.I. 2.41 to 4.51, p<0.00001), in exercise *versus* control (Figure 4).

Change in 6-min walk test (6MWT)

Data from four studies for 6-min walk test (6MWT) reported a significant increase in walking distance, MD of 32.1 metres (95% C.I. 17.20 to 47.05, p<0.0001) in exercise *versus* control (Figure 5).

Change in diastolic function

Change in E/A ratio

Data from four studies showed the ration of early diastolic filling (E/A ratio) was significantly improved, MD 0.07 (95% C.I. 0.02 to 0.12, p=0.006) with exercise versus control (Figure 6).

Change E/E' ratio

Data from five studies showed a significant reduction in diastolic filling pressure (E/E' ratio), MD was -2.38 (95% C.I. -3.47 to -1.28, p<0.0001) with exercise *versus* control (Figure 7).

Change in deceleration time

Data from three studies showed a significant reduction in diastolic deceleration time (D_T), MD of -13.2ms (95% C.I. -19.8 to -6.5, p=0.0001) with exercise *versus* control (Figure 8).

Change in quality of life

Data from seven studies showed a significant improvement in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, MD -6.77 units (95% C.I. -9.70 to -3.84, p<0.00001) with exercise *versus* control (Figure 9).

Change in the Short Form-36 health survey

Data from three studies showed a significant improvement in physical dimension of the Short Form-36 health survey was 11.38 units (95% C.I. 5.28 to 17.48, p=0.0003) with exercise *versus* control (Figure 10).

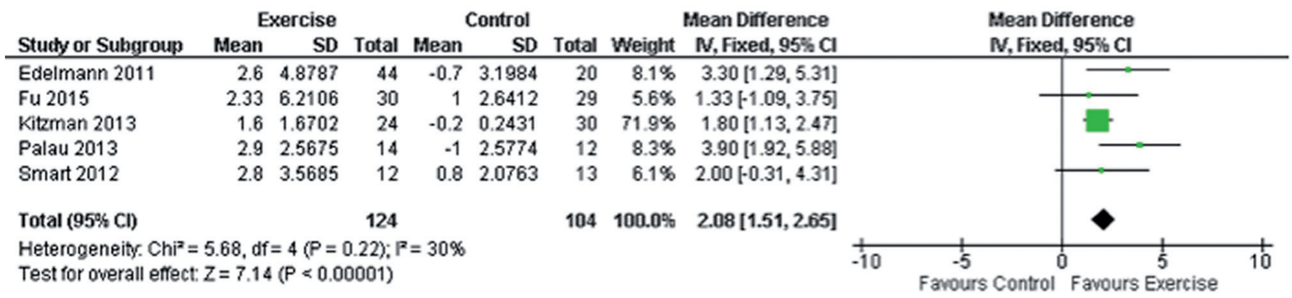

Figure 2. Change in Peak VO_2 for exercise training studies with HFpEF patients.

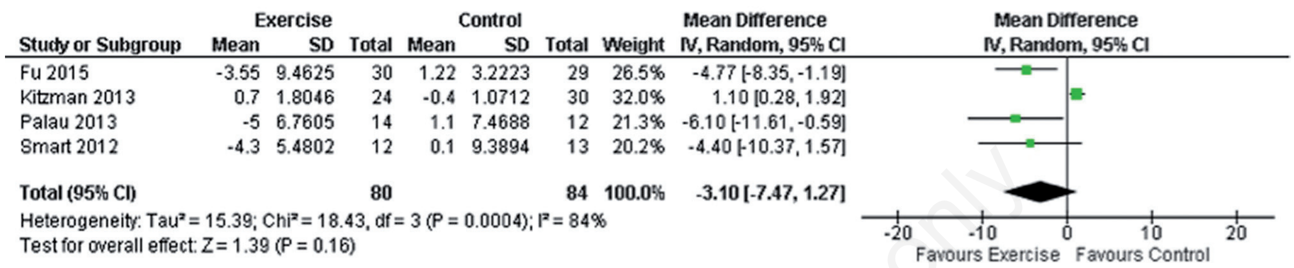

Figure 3. Change in V_E/VCO_2 for exercise training studies with HFpEF patients.

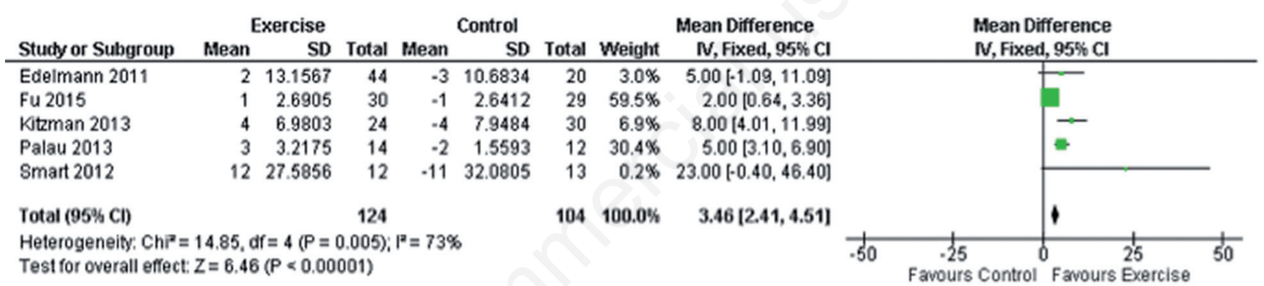

Figure 4. Change in maximum heart rate for exercise training studies with HFpEF patients.

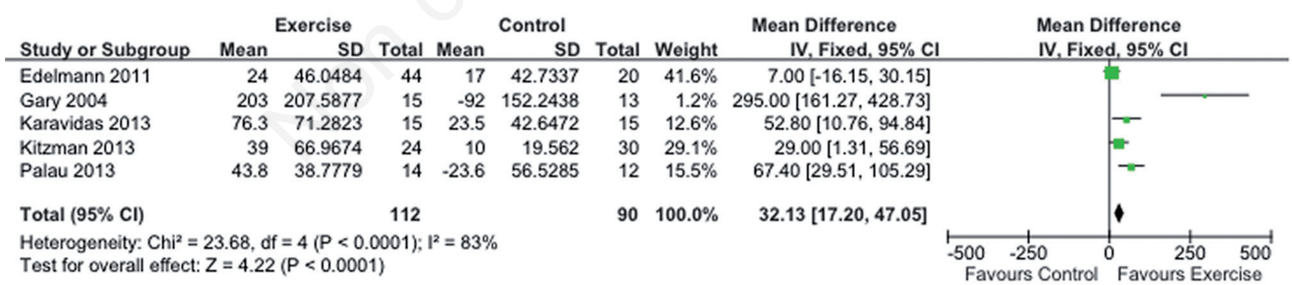

Figure 5. Change in 6-minute walk test (6MWT) for exercise training studies with HFpEF patients.

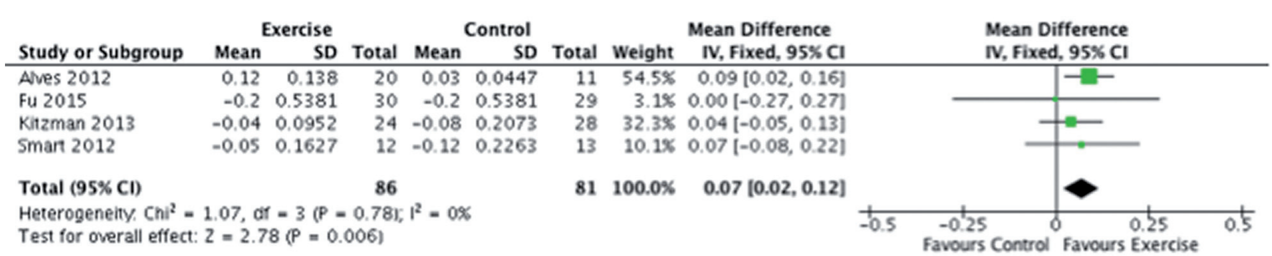

Figure 6. Change in E/A ratio for exercise training studies with HFpEF patients.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Edelmann 2011	-2.3	2.3024	44	0.6	2.3504	20	79.3%	-2.90 [-4.13, -1.67]
Fu 2015	-4.9	13.061	30	-1.4	3.7667	29	5.1%	-3.50 [-8.37, 1.37]
Karavidas 2013	-3.25	5.898	15	-2.06	3.7384	15	9.7%	-1.19 [-4.72, 2.34]
Palau 2013	-3.3	9.4503	14	-5.5	10.2501	12	2.1%	2.20 [-5.42, 9.82]
Smart 2012	4.4	9.8491	12	0.001	0.0017	13	3.9%	4.40 [-1.17, 9.97]
Total (95% CI)			**115**			**89**	**100.0%**	**-2.38 [-3.47, -1.28]**

Heterogeneity: Chi² = 8.39, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 4.24 (P < 0.0001)

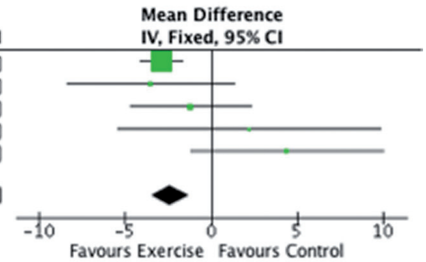

Figure 7. Change in E/E' ratio for exercise training studies with HFpEF patients.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Alves 2012	-14	16.1042	20	-2.1	3.1424	11	82.5%	-11.90 [-19.20, -4.60]
Kitzman 2013	-6	14.2763	24	17	44.0463	28	14.7%	-23.00 [-40.29, -5.71]
Smart 2012	5	60.5067	12	3	37.8638	13	2.8%	2.00 [-37.95, 41.95]
Total (95% CI)			**56**			**52**	**100.0%**	**-13.15 [-19.78, -6.52]**

Heterogeneity: Chi² = 1.91, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)

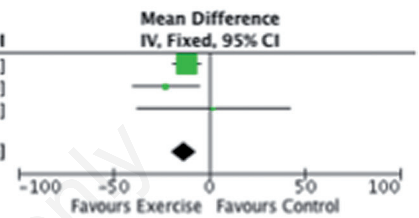

Figure 8. Change in deceleration time for exercise training studies with HFpEF patients.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Edelmann 2011	-8	14.4115	41	-2	6.4007	19	30.9%	-6.00 [-11.27, -0.73]
Fu 2015	-18.5	49.3118	30	-1.9	5.1119	29	2.7%	-16.60 [-34.34, 1.14]
Gary 2004	-17	17.3842	15	1	1.6548	13	11.0%	-18.00 [-26.84, -9.16]
Karavidas 2013	-28.5	40.766	15	-8.7	15.7885	15	1.8%	-19.80 [-41.92, 2.32]
Kitzman 2013	-10	65.0378	20	-3	22.7887	27	1.0%	-7.00 [-36.77, 22.77]
Palau 2013	-11	10.6849	14	-3.5	10.5306	12	12.8%	-7.50 [-15.67, 0.67]
Smart 2012	-4.8	7.5547	12	-2	3.3096	13	39.9%	-2.80 [-7.44, 1.84]
Total (95% CI)			**147**			**128**	**100.0%**	**-6.77 [-9.70, -3.84]**

Heterogeneity: Chi² = 11.63, df = 6 (P = 0.07); I² = 48%
Test for overall effect: Z = 4.53 (P < 0.00001)

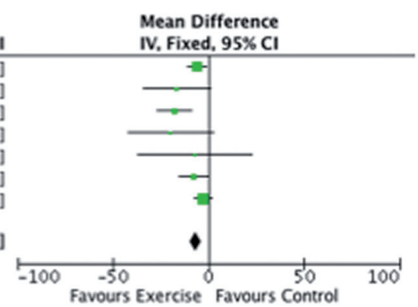

Figure 9. Change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) for exercise training studies with HFpEF patients.

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Edelmann 2011	14	24.8605	40	-4	16.7888	20	32.8%	18.00 [7.35, 28.65]
Fu 2015	9.1	24.2561	30	2.9	7.8024	29	44.7%	6.20 [-2.93, 15.33]
Kitzman 2013	15	28.5985	20	3	7.5837	27	22.5%	12.00 [-0.86, 24.86]
Total (95% CI)			**90**			**76**	**100.0%**	**11.38 [5.28, 17.48]**

Heterogeneity: Chi² = 2.73, df = 2 (P = 0.26); I² = 27%
Test for overall effect: Z = 3.65 (P = 0.0003)

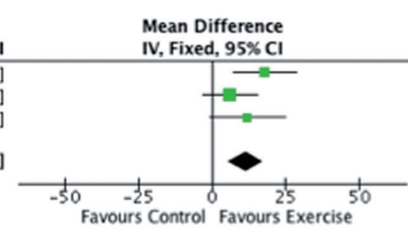

Figure 10. Change in the physical dimension of the Short Form-36 health survey for exercise training studies with HFpEF patients.

Adverse events

All studies reported adverse events; deaths, hospitalizations, and cardiovascular events (Table 2). There were no deaths reported from exercise training or control groups in any of the included studies. One hospital admission was reported from an exercise training patient. Overall, there were 3222 patient-hours of exercise training reported. There were insufficient adverse event data to justify analyses.

Study quality

Median TESTex score was 11 out of 15 for all studies (Table 3). Funnel (Egger) plots of the analysis showed minimal evidence of publication bias.

Heterogeneity

Only the analyses of V_E/VCO_2 slope and six minute walk distance showed high heterogeneity.

Table 2. Study withdrawals and adverse events in the included exercise training studies with HFpEF patients.

Study	Withdrawals		Adverse events	
	Exercise	Control	Exercise	Control
Alves (2011)	2	3	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events
Edelmann (2011)	2	1	0 deaths or hospitalizations, 5 cardiac events (palpitations or dyspnea)	0 deaths, hospitalizations or cardiac events
Fu (2015)	0	1	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events
Gary (2004)	1	3	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events
Karavidas (2013)	0	0	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events
Kitzmann (2013)	8	1	0 deaths, 1 hospitalization and 0 cardiac events	0 deaths, hospitalizations or cardiac events
Palau (2013)	2	2	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events
Smart (2012)	4	1	0 deaths, hospitalizations or cardiac events	0 deaths, hospitalizations or cardiac events

Table 3. Study quality assessment of included studies using the tool for the assessment of study quality in exercise training (TESTEX).

Study name	Eligibility criteria specified	Randomly allocated participants	Allocation concealed	Groups similar at baseline	Assessorsblinded	Outcome measures assessed >85% of participants*	Intention to treat analysis	Reporting of between group statistical comparisons	Point measures and measures of variability reported°	Activity monitoring in control group	Relative exercise Intensity review	Exercise volume and nenergy expended	Overall TESTEX
Alves (2011)	YES	YES	NO	YES	NO	YES (2)	NO	YES	YES (2)	NO	YES	NO	9
Edelmann (2011)	YES	YES	Unclear	YES	NO	YES(2)	N/A	YES	YES(2)	YES	YES	YES	12
Fu (2015)	YES	NO	Unclear	YES	YES	YES (1)	Unclear	YES	YES (2)	Unclear	YES	Unclear	8
Gary (2004)	YES	YES	Unclear	YES	NO	YES (2)	NO	YES	YES (2)	Unclear	YES	NO	9
Karavidas (2013)	YES	YES	Unclear	YES	YES	YES (2)	Unclear	YES	YES (2)	NO	YES	NO	10
Kitzman (2013)	YES	YES	Unclear	YES	NO	YES (3)	YES	YES	YES (2)	YES	YES	YES	13
Palau (2013)	YES	YES	NO	YES	YES	YES (2)	Unclear	YES	YES (2)	YES	YES	YES	12
Smart (2012)	YES	YES	NO	YES	NO	YES(3)	YES	YES	YES (2)	YES	YES	YES	13
Median score 11													
Total out of 15 points													

*Three points possible: 1 point if adherence>85%, 1 point if adverse events reported, 1 point if exercise attendance is reported; °two points possible: - 1 point if primary outcome is reported, 1 point if all other outcomes reported; N/A, not applicable.

Discussion

This meta-analysis indicates that, in HFpEF patients, the magnitude of gain in cardio-respiratory fitness is similar to that seen in systolic heart failure patients exercising at moderate intensity [6,7]. In HFpEF, exercise training elicits in improvements in cardiac (diastolic) function, health related quality of life, general health, maximum heart rate and six minute walk distance which complement improvements seen in cardio-respiratory fitness.

Change in peak VO_2,V_E/VCO_2 slope, maximum heart rate and 6-minute walk distance

The improvements in peak VO_2 observed with exercise training are complemented with changes in maximum heart rate, but not in V_E/VCO_2 slope. This current analysis produced peak VO_2 changes of similar effect size seen previously [16]. Although two trials have shown an improvement in V_E/VCO_2 slope, our analysis does not identify an improvement with exercise training. A previous meta-analysis did not analyze change in V_E/VCO_2 slope in HFpEF patients [16]. A previous report established a strong prognostic relationship between peak VO_2, V_E/VCO_2 slope and mortality in heart failure patients with reduced systolic function [34]. Our analysis showed maximum heart rate to be higher after exercise training; the resultant increase in maximal cardiac output would at least partially explain why peak VO_2 improved with training. Although V_E/VCO_2 slope did not become lower in our analysis, a reduction would imply improved ventilatory efficiency and would likely contribute to improved cardio-respiratory fitness. A mean 10-12 bpm increase in maximum heart rate after training has been reported in systolic heart failure and HFpEF in previous trials [18,35].

Diastolic function

Our analysis of E/A ratio is the first to identify that exercise training may significantly improve this aspect of diastolic function. Neither individual studies, nor pooled analyses published previously have shown a post-exercise training benefit. Our analysis of E/E' confirms the finding of Edelmann *et al.* [30] but not the findings of the pooled analysis of Taylor *et al.* [16]. E/E' is a surrogate for filling pressure and our analysis suggests a small reduction (improvement) is elicited with exercise training in HFpEF patients. We suspect that these changes in E/E' do not account for all of the improvement in peak VO_2, we therefore acknowledge that some changes may be due to improved endothelial function [36]. Deceleration time (D_T) was also significantly reduced in our analysis; this is the first analysis to demonstrate such a benefit. Together these three measures of diastolic function have shown a trend towards normalization after exercise training. While improved diastolic function due to exercise training has been previously demonstrated in healthy people [37], previous work in HFpEF has failed to show a trend towards improved E/A and D_T in people with HFpEF [32]. Unfortunately study-level (as opposed to patient-level) meta-analyses do not allow examination of the relationship between changes in non-invasive measures of cardiac function to other comprehensive measures of systole/diastole generated by catheterization, *e.g*., pressure-volume loops. Further well designed and appropriately powered studies of HFpEF are required to provide clarification of how non-invasive and catheter based techniques interrelate to avoid speculation regarding the probable long-term consequences of chronically increased left ventricular pressures [38].

Quality of life and general health

Our analysis showed HFpEF patients exhibited reductions (improvements) in Minnesota Living with Heart Failure scores of similar magnitude to those seen in patients with systolic heart failure [39]. Our analyses also showed HFpEF patients exhibited increased (improved) SF-36 scores. The effect size was of a similar magnitude to improvements seen previously in heart failure patients with normal (HFpEF) and abnormal systolic function [35].

Limitations

The major limitation of this analysis is that only eight datasets currently exist and associated sample sizes were generally small. In terms of study quality the median TESTEX score for the included studies indicated of good study quality and comprehensive reporting. There were insufficient data to warrant analysis of study withdrawal, adverse events, hospitalization and mortality rates.

Heterogeneity scores indicated the majority of our analyses were justified, but those of V_E/VCO_2 slope and 6 MWT may exhibit heterogeneity at levels too high to justify these analyses.

Meta-analysis of continuous data is problematic; for example data sampling duration can alter peak VO_2 values in heart failure [40]. We adjusted for baseline difference in primary outcomes between allocation groups by measuring pre- *versus* post-intervention change. Often we were accurately able to calculate change in standard deviation, but in cases where exact p-values were not provided by study reports we used default values *e.g.* $p<0.05$ or $p<0.001$ in our calculations which may introduce errors. Our funnel plots appear to suggest negligible risk of publication bias. We suspect that unpublished datasets with perhaps negative results do not exist.

Finally, we acknowledge that factors related to volume of exercise may explain some of the outcomes reported, for example, intuitively one suspects longer study duration variations may yield better results, but the small number of included studies precluded sub-analyses of exercise volume parameters.

Previous work by one of our authors shows that people with HFpEF tend to typically be 5 or more years older and more likely to be female than their systolic dysfunction counterparts [35]. While the precise volume of screening to identify people with HFpEF for this work were not published, it can be revealed that screening of over 4000 echocardiograms yielded less than 20 exercise training participants. The explanation of this low yield is because for the purposes of scientific rigor, trials of HFpEF need to demonstrate participants do not have ischemic heart disease. Isolation from any hint of ischemic heart disease is rare in HFpEF and therefore makes suitable trial participants extremely difficult to find. This is possibly the primary explanation why over 100 randomized exercise training trials exist in systolic heart failure patients, but only 8 exist to date in HFpEF.

Conclusions

Exercise training does yield improvements in cardio-respiratory fitness, diastolic function, quality of life and general health in heart failure patients with preserved ejection fraction.

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