Exercise Training in Patients with Heart Failure and Preserved Ejection Fraction: A Meta-analysis of Randomized Control Trials.

Ambarish Pandey

Akhil Parashar

Dharam Kumbhani

Sunil Agarwal

Jalaj Garg MD
Lehigh Valley Health Network, jalaj.garg@lvhn.org

See next page for additional authors

Published In/Presented At

Pandey, A., Parashar, A., Kumbhani, D., Agarwal, S., Garg, J., Kitzman, D., & ... Berry, J. D. (2014). Exercise Training in Patients with Heart Failure and Preserved Ejection Fraction: A Meta-analysis of Randomized Control Trials. *Circulation. Heart Failure*, 8(1), 33-40.

Authors
Ambarish Pandey, Akhil Parashar, Dharam Kumbhani, Sunil Agarwal, Jalaj Garg MD, Dalane Kitzman, Benjamin Levine, Mark Drazner, and Jarett D Berry

HHS Public Access
Author manuscript
Circ Heart Fail. Author manuscript; available in PMC 2016 March 15.

Published in final edited form as:
Circ Heart Fail. 2015 January ; 8(1): 33–40. doi:10.1161/CIRCHEARTFAILURE.114.001615.

Exercise Training in Patients with Heart Failure and Preserved Ejection Fraction: A Meta-analysis of Randomized Control Trials

Ambarish Pandey, MD[#1], **Akhil Parashar, MD**[#2], **Dharam Kumbhani, MD, SM**[1], **Sunil Agarwal, MD, PhD**[3], **Jalaj Garg, MD**[4], **Dalane Kitzman, MD**[5], **Benjamin Levine, MD**[1], **Mark Drazner, MD, MSc**[1], and **Jarett Berry, MD, MS**[1]

[1]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, TX

[2]Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

[3]Division of General Internal Medicine, Department of Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[4]Division of Cardiology, Lehigh Valley Health Network, Allentown, PA

[5]Division of Cardiology, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC

[#] These authors contributed equally to this work.

Abstract

Background—Heart failure with preserved ejection fraction (HFPEF) is common and characterized by exercise intolerance and lack of proven effective therapies. Exercise training has been shown to be effective in improving cardiorespiratory fitness (CRF) in patients with systolic heart failure. In this meta-analysis, we aim to evaluate the effects of exercise training on CRF, quality of life and diastolic function in patients with HFPEF.

Methods and Results—Randomized controlled clinical trials that evaluated the efficacy of exercise training in patients with HFPEF were included in this meta-analysis. Primary outcome of the study was change in CRF (measured as change in peak oxygen uptake). Impact of exercise training on quality of life (estimated using Minnesota living with heart failure score), left ventricular systolic and diastolic function was also assessed. The study included 276 patients that were enrolled in 6 randomized controlled trials. In the pooled data analysis, HFPEF patients undergoing exercise training had significantly improved CRF (L/min) (Mean difference: 2.72; 95% CI: 1.79 to 3.65) and quality of life (Mean difference: −3.97; 95% CI: −7.21 to −0.72) as compared with the control group. However, no significant change was observed in the systolic function [Ejection Fraction – Weighted Mean difference (WMD): 1.26; 95% CI: −0.13% to 2.66%] or diastolic function [E/A - WMD: 0.08; 95% CI:−0.01 to 0.16] with exercise training in HFPEF patients.

Correspondence to: Jarett D. Berry, MD, MS, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, Ph: 214-645-7500, fax: 214-645-75201, jarett.berry@utsouthwestern.edu.

Disclosures
None.

Conclusions—Exercise training in patients with HFPEF is associated with an improvement in CRF and quality of life without significant changes in left ventricular systolic or diastolic function.

Keywords

heart failure with preserved ejection fraction; exercise training; meta-analysis

---

Heart failure with preserved ejection fraction (HFPEF) is common, representing approximately 50% of heart failure admissions.[1, 2] Exercise intolerance is the primary symptom among patients with HFPEF. [3] While pharmacological therapies such as ACE inhibitors and mineralocorticoid receptor antagonists have failed to a mortality benefit in HFPEF, [2, 4-6] there are a number of studies showing significant improvement in exercise capacity in response to these agents. [7, 8] Left ventricular diastolic dysfunction has been identified as one of the mechanisms underlying exercise intolerance in these patients.[9] As a result, there has been a significant interest in novel therapeutic approaches that could improve diastolic function and ameliorate exercise intolerance in HFPEF.

Exercise training is one such therapeutic approach that is associated with significant improvement in cardiorespiratory fitness in patients with HFREF.[10, 11] While some studies have attributed this to exercise induced favorable changes in LV function and cardiac output, [11, 12] others have identified peripheral adaptations in the arterial and skeletal muscle function as the primary contributor to improvement in fitness after exercise training.[13, 14] Exercise training is also associated with improved exercise tolerance among sedentary, obese, and hypertensive subjects who are at high risk for HFPEF.[15] Several recent studies have evaluated exercise training as a therapeutic management strategy in patients with HFPEF.[16-21] While these studies were not designed to address clinical endpoints such as heart failure hospitalizations and mortality, they have demonstrated a variable degree of improvement in exercise tolerance and diastolic function in response to training. The aim of this meta-analysis is to assess the effects of exercise training on exercise tolerance, quality of life and diastolic function in patients with HFPEF.

Methods

Data sources and searches

A comprehensive computerized literature search of Medline, EMBASE, OVID, Web of Science, and Cochrane databases was conducted using MeSH terms and keywords including heart failure, diastolic heart failure, heart failure with normal ejection fraction, heart failure with preserved ejection fraction, exercise training, and cardiac rehabilitation. In addition, the institutional records were manually searched for available theses using the expertise of a medical librarian.

Study selection

We initially evaluated all comparative studies including randomized or non-randomized parallel group trials, pre-post within group design that enrolled adult patients (age ≥ 18 years) with diastolic heart failure of any etiology (Figure 1, Supplemental Table 1). However, only randomized controlled trials (RCT) were included in the final analysis to maintain consistency and obtain robust pooled estimates. Primary outcome of the study was change in cardiorespiratory fitness (measured as change in peak oxygen uptake in ml/kg/min). Secondary outcomes that were also assessed in the study included change in Minnesota living with heart failure (MLWHF) score, markers of diastolic function (changes in E/A ratio and early deceleration time), and left ventricular ejection fraction. Studies failing to report at least one of the above pre-defined study outcomes were excluded from our analysis.

Data extraction

Full text articles were retrieved for all title-abstracts that met the inclusion criteria. Data extraction was then independently performed by the co-primary authors (AP and AP) using a standardized questionnaire. All discrepancies concerning study inclusion or outcomes were resolved by the senior author (JB). In cases of multiple publications arising from a single trial, only the updated trial with the maximum number of patients was included.

Data synthesis and statistical analysis

Meta-analysis of the outcomes was conducted using *"Metan"* and *"Metareg"* functions available for *Stata*™ *version 12.1* statistical software *(Stata Corporation, College Station, TX).*[22] The meta-analysis has been reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) guidelines. [23] We primarily used fixed effects modeling to conduct the meta-analysis of outcomes from included studies. We assessed for heterogeneity using the I^2 test ($I^2 \geq 25\%$ was assumed to be a result of significant heterogeneity). In cases of significant heterogeneity, we reported a pooled estimate based on the random effects model. Weighted mean differences (WMD) and corresponding 95% confidence intervals were computed for all continuous outcomes. To assess the effect of demographic factors such as age and gender on treatment outcomes, random-effect meta-regression models were constructed for the primary outcome (change in cardiorespiratory fitness). Furthermore, to account for differences in the baseline measures of cardiorespiratory fitness and MLWHF score between control and training groups, we conducted additional meta-regression analysis for these outcomes (change in cardiorespiratory fitness and change in MLWHF score) adjusting for their baseline values. The variables included in the meta-regression model were identified *a priori* to safeguard against false-positive results because of an over-fitted model. Risk of bias analysis was performed using Cochrane collaboration's assessment tool in *RevMan version 5.2* software[24]. Publication bias was assessed using the funnel plots and quantified by Egger's regression test. All p-values were two-tailed with statistical significance specified at 0.05 and confidence intervals (CI) reported at the 95% level.

Results

We included a total of 276 participants enrolled in 6 randomized controlled trials, with a mean follow-up duration of 12–24 weeks (weighted mean duration = 19 weeks). The baseline demographic and clinical characteristics of the study participants are summarized in Table 1. All 6 trials included well compensated HFPEF patients (ejection fraction ≥45%), stabilized on cardiac medications with no recent hospitalizations. The HFPEF definition and exclusion criteria used in the included studies has been discussed in Table 2. The exercise training protocol, control group care and outcomes measured in the included trials has been discussed in Table 3. The study participants had an echocardiographic as well as cardiorespiratory fitness assessment at baseline and follow up.

Quality Assessment

The Cochrane risk of bias assessment tool was used to perform quality assessment (Supplemental Figure 1). During quality assessment, random sequence generation was observed in all studies. Blinded assessment of outcomes was performed in 5 of the 6 included trials. Incomplete outcome data or selective reporting of results was not observed in any of the selected studies. We also didn't observe any significant publication bias in the formal analysis.

Effect of Exercise training on cardiorespiratory fitness

Four studies reported exercise capacity at baseline and after exercise training, using symptom-limited cardiopulmonary exercise testing on a bicycle ergometer or treadmill. A greater improvement in peak oxygen uptake was observed among HFPEF patients undergoing exercise training vs. usual care patients in all the included trials (Supplemental Table 2). There was no significant statistical heterogeneity across studies reporting peak oxygen uptake. Pooling across the 4 trials using fixed effects meta-analysis showed that exercise training is associated with a significant improvement in peak oxygen uptake (ml/kg/min) from baseline to follow-up among HFPEF patients (WMD: 2.72; 95% CI: 1.79 to 3.65; P-value = 0.0001; see Fig 2). Meta-regression analysis showed no significant effect of age, gender and baseline measure of peak oxygen uptake on the pooled WMD (Age: meta-regression coefficient = −0.23; P-value: 0.42, Gender: meta-regression coefficient = −0.04; p value: 0.48, Baseline line measure of peak oxygen uptake: meta-regression coefficient = 0.48; p value: 0.3)

Effect of exercise training on quality of life

All five studies reported an impact of exercise training on quality of life (determined using the MLWHF questionnaire). Clinically meaningful improvement in MLWHF total score (greater than 5 points reduction in MLWHF score from baseline to follow up) was observed among HFPEF patients undergoing exercise training in all the included trials (Supplemental Table 2). No significant heterogeneity was observed across the 5 trials. Pooling across the 5 studies using fixed effect meta-analysis showed a statistically significant improvement in the quality of life score from baseline to follow up as assessed by the MLWHF questionnaire among exercise training participants as compared to the usual care group (WMD: −3.97; 95% CI: −7.21 to −0.72; P-value = 0.02; see Fig 2). Meta-regression analysis showed no significant effect of baseline MLWHF score on the pooled WMD (meta-regression coefficient = −1.05; p value: 0.2)

Effect of exercise training on diastolic and systolic function

Five studies reported the impact of exercise training on diastolic function. E/A and deceleration time were reported as measures of diastolic function reported in 3 studies, whereas one study reported only E/A and another reported only E/e' (Supplemental Table 3). Pooling across all the available studies using fixed effect meta-analysis showed no significant change in E/A (WMD: 0.08; 95% CI: −0.01 to 0.16; P-value = 0.08; see Fig 3) or early deceleration time (ms) (WMD: 2.92; 95% CI: −18.56 to 24.41; P-value = 0.79; see Fig 3) with exercise training as compared with the control group subjects. Similarly, we did not observe any significant change in systolic function (ejection fraction) with exercise training on fixed effect meta-analysis of pooled data from the 5 studies (WMD: 1.26%; 95% CI: −0.13% to 2.66%; P-value = 0.08; see Fig 3, Supplemental Table 3).

Safety of Exercise Training

No major adverse effects of exercise training were reported in the included studies (Table 4).

Discussion

In the present meta-analysis, we observe two important findings. First, exercise training improves cardiorespiratory fitness and quality of life in patients with HFPEF. Second, exercise training in these patients is not associated with any significant change in resting diastolic or systolic function. Taken together, these findings suggest that exercise training may improve cardiorespiratory fitness in patients with HFPEF through mechanisms independent of left ventricular function.

Exercise training has been shown to improve fitness and quality of life in asymptomatic hypertensive subjects who are at risk for HFPEF. [15, 25] Similarly, in patients with heart failure with reduced ejection fraction, studies have shown a consistent improvement in fitness and quality of life after exercise training. [10, 26] In the present study, we have extended these findings showing a favorable effect of exercise training on fitness and quality of life among patients with HFPEF.

The mechanism by which exercise training improved exercise tolerance in HFPEF is not completely clear. Exercise training has been shown to improve systolic and diastolic function in patients with HFREF.[11, 27] However, in the present study, there was no significant change in diastolic function with exercise training in patients with HFPEF. It is important to note that for our meta-analysis, we used E/A and early deceleration time as measures of diastolic function because they were most commonly reported. E/E', a more specific measure of diastolic function, [28] was only reported in one included study by Edelmann et al, [18] and was not used for pooled analysis. Interestingly, Edelman et al did show a significant improvement in E/E' with exercise training.

Increased arterial stiffness and endothelial dysfunction have also been shown to contribute to exercise intolerance in patients with HFPEF. [21, 29-31] However, in a recent study by Kitzman et al,[21] exercise training failed to improve the endothelial function and arterial stiffness in such patients. Another potential mechanism by which exercise training has been shown to improve cardiorespiratory fitness in asymptomatic, sedentary subjects is through physiological remodeling and associated improvement in stroke volume and cardiac output. However, recent works by Fujimoto et al [32] and Haykowsky et al [33] have shown that exercise training in HFPEF subjects is not associated with any significant change in cardiac output. The impact of exercise training on arterial stiffness, endothelial function and cardiac output could not be assessed in the present meta-analysis because these outcomes were not reported in the majority of the clinical trials. Taken together, the available literature suggests that exercise training may improve exercise tolerance through peripheral mechanisms leading to an improved oxygen extraction in the active skeletal muscles.[21, 33, 34] If so, this would mirror to some extent the results of studies investigating the mechanisms of improvement in exercise capacity following exercise training in patients with HFREF. [14, 35-37]

Exercise intolerance is the primary symptom of HFPEF and an important determinant of quality of life. [3, 38] While pharmacological interventions have been ineffective in reducing HFPEF patient mortality, a substantial improvement in exercise capacity without a significant change in diastolic function was reported in a recent meta-analysis of all HFPEF drug trials. [8] Similar results were observed in the present meta-analysis using exercise training in these subjects. These findings suggest that exercise training can be utilized as an alternative therapeutic strategy for the improvement of symptoms in patients with HFPEF.

Findings in our study are similar to those in the meta-analysis of Taylor et al [39] who evaluated the impact of exercise training on HFPEF. However, more recent randomized control trials have been published since the latter study was completed in November 2011.[19-21] The present work, with twice as many study subjects, represents an updated and more comprehensive evaluation of the impact of exercise training in patients with HFPEF. Moreover, the previous meta-analysis included both randomized and non-randomized clinical trials that may have lead to potential bias because it was impossible to completely remove interference of unknown confounding factors.

There are several limitations in this study. First, we only have 6 clinical trials included in the meta-analysis reflecting the scarcity of randomized control trials in literature addressing this issue. This could be due to several challenges that are associated with exercise training trials among HFPEF patients. These include non-adherence and high drop out rates among training participants, time and resource intense nature of intervention, and difficulties with selection of right patient population that will benefit from exercise training. Furthermore, the sample size of some included trials was small resulting in wide confidence intervals for point estimates associated with study outcomes. This highlights the significance of pooled analysis that has been conducted in the present study. Second, the standard measure of diastolic function E/E' was not consistently reported in all the included clinical trials and was therefore not used for pooled analysis. Third, echocardiographic parameters are reported in only 4 of the 6 included studies and the meta-analysis may not be adequately powered to draw definitive conclusions about the impact of exercise training on echocardiographic parameters. Future studies with larger sample size are needed to determine the impact of exercise training on echocardiographic outcomes. Fourth, the mean follow-up duration in these clinical trials was relatively short (12–24 weeks) and longer duration follow-up may be needed to observe significant changes in left ventricular remodeling and diastolic function. Fifth, none of the included trials reported clinical outcomes such as heart failure, hospitalization, or mortality; therefore, we were unable to assess these points. Furthermore, it is difficult to evaluate the sustainability of effects of exercise training intervention on CRF among HFPEF patients in the present meta-analysis since all the trials measured outcomes at the end of follow up. Finally, as with all meta-analyses, selection bias cannot be completely ruled out because articles were only retrieved from published trials.

Taken together, the findings from our study suggest that exercise training in patients with HFPEF improves cardiorespiratory fitness and quality of life without a significant change in LV diastolic function. Future studies among HFPEF patients with well characterized phenotype that have longer follow up duration, use more efficient and less resource intense exercise training protocols, and assess relevant clinical end-points are needed to determine if exercise training can be used as an effective management strategy for these patients in the real world.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of Funding

Dr. Berry receives funding from (1) the Dedman Family Scholar in Clinical Care endowment at University of Texas Southwestern Medical Center, (2) grant 13GRNT14560079 from the American Heart Association and (3) grant 14SFRN20740000 from the American Heart Association prevention network.

References

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; 355:251–9. [PubMed: 16855265]
2. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med. 2006; 355:260–9. [PubMed: 16855266]
3. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA. 2002; 288:2144–50. [PubMed: 12413374]
4. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, Investigators IP. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359:2456–67. [PubMed: 19001508]
5. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Investigators C, Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003; 362:777–81. [PubMed: 13678871]
6. Bergstrom A, Andersson B, Edner M, Nylander E, Persson H, Dahlstrom U. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004; 6:453–61. [PubMed: 15182771]
7. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo DHFI. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. JAMA. 2013; 309:781–91. [PubMed: 23443441]

8. Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction. A meta-analysis. J Am Coll Cardiol. 2011; 57:1676–86. [PubMed: 21492765]

9. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. 1991; 17:1065–72. [PubMed: 2007704]

10. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL, Investigators H-A. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301:1439–50. [PubMed: 19351941]

11. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol. 2007; 49:2329–36. [PubMed: 17572248]

12. Hambrecht R, Gielen S, Linke A, Fiehn E, Yu J, Walther C, Schoene N, Schuler G. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: A randomized trial. JAMA. 2000; 283:3095–101. [PubMed: 10865304]

13. Jette M, Heller R, Landry F, Blumchen G. Randomized 4-week exercise program in patients with impaired left ventricular function. Circulation. 1991; 84:1561–7. [PubMed: 1914097]

14. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with severe left ventricular dysfunction. Hemodynamic and metabolic effects. Circulation. 1988; 78:506–15. [PubMed: 3409495]

15. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA. 2007; 297:2081–91. [PubMed: 17507344]

16. Gary RA, Sueta CA, Dougherty M, Rosenberg B, Cheek D, Preisser J, Neelon V, McMurray R. Home-based exercise improves functional performance and quality of life in women with diastolic heart failure. Heart Lung. 2004; 33:210–8. [PubMed: 15252410]

17. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail. 2010; 3:659–67. [PubMed: 20852060]

18. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M, Pieske B. 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; 58:1780–91. [PubMed: 21996391]

19. Alves AJ, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana JL, Duarte JA, Sagiv M, Oliveira J. Exercise training improves diastolic function in heart failure patients. Med Sci Sports Exerc. 2012; 44:776–85. [PubMed: 22005747]

20. Smart NA, Haluska B, Jeffriess L, Leung D. 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. [PubMed: 22536983]

21. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. 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; 62:584–92. [PubMed: 23665370]

22. Harris RJ, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JA. Metan: fixed- and random-effects meta-analysis. Stata J. 2008; 8:3–28.

23. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339:b2535. [PubMed: 19622551]

24. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G and Cochrane Statistical Methods G. The Cochrane

Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343:d5928. [PubMed: 22008217]

25. Martin CK, Church TS, Thompson AM, Earnest CP, Blair SN. Exercise dose and quality of life: a randomized controlled trial. Archives of internal medicine. 2009; 169:269–78. [PubMed: 19204218]
26. van Tol BA, Huijsmans RJ, Kroon DW, Schothorst M, Kwakkel G. Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis. Eur J Heart Fail. 2006; 8:841–50. [PubMed: 16713337]
27. Sandri M, Kozarez I, Adams V, Mangner N, Hollriegel R, Erbs S, Linke A, Mobius-Winkler S, Thiery J, Kratzsch J, Teupser D, Mende M, Hambrecht R, Schuler G, Gielen S. Age-related effects of exercise training on diastolic function in heart failure with reduced ejection fraction: the Leipzig Exercise Intervention in Chronic Heart Failure and Aging (LEICA) Diastolic Dysfunction Study. Eur Heart J. 2012; 33:1758–68. [PubMed: 22267243]
28. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschope C. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007; 116:637–47. [PubMed: 17646587]
29. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 2006; 114:2138–47. [PubMed: 17088459]
30. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010; 56:845–54. [PubMed: 20813282]
31. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. J Am Coll Cardiol. 2001; 38:796–802. [PubMed: 11527636]
32. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. Am Heart J. 2012; 164:869–77. [PubMed: 23194487]
33. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. J Am Coll Cardiol. 2012; 60:120–8. [PubMed: 22766338]
34. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, Levine BD. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. Eur J Heart Fail. 2011; 13:1296–304. [PubMed: 21979991]
35. Kitzman DW, Haykowsky MJ. Invited editorial commentary for American Heart Journal mechanisms of exercise training in heart failure with preserved ejection fraction: central disappointment and peripheral promise. Am Heart J. 2012; 164:807–9. [PubMed: 23194479]
36. Rehn TA, Munkvik M, Lunde PK, Sjaastad I, Sejersted OM. Intrinsic skeletal muscle alterations in chronic heart failure patients: a disease-specific myopathy or a result of deconditioning? Heart Fail Rev. 2012; 17:421–36. [PubMed: 21996779]
37. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway J, Sleight P. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. Circulation. 1992; 85:2119–31. [PubMed: 1591831]
38. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G, American Heart Association Committee on Exercise R; Prevention of the Council on Clinical C; American Heart Association Council on Cardiovascular N. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation. 2007; 116:329–43. [PubMed: 17576872]

39. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K, Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. Int J Cardiol. 2012; 162:6–13. [PubMed: 22664368]

Patients with HFPEF are older and most commonly present with symptoms of exercise intolerance. While exercise training is well accepted as a management strategy for heart failure with reduced ejection fraction, its role in management of HFPEF patients is not well established. In the present meta-analysis we observed that exercise training is associated with significant improvements in cardiorespiratory fitness and quality of life among HFPEF patients. These findings suggest that exercise training could be used as an alternative therapeutic strategy for management of HFPEF patients. This study also provides some insight into the potential mechanisms through which training may improve fitness among these patients. We did not observe any significant changes in left ventricular diastolic function with exercise training suggesting that other mechanisms may play an important role in exercise training associated improvement of fitness among these patients. Future studies that use more efficient, less resource intense training protocol and assess relevant clinical end-points such as HF hospitalization and mortality are needed to determine if exercise training can be established as an effective management strategy for HFPEF in the real world.

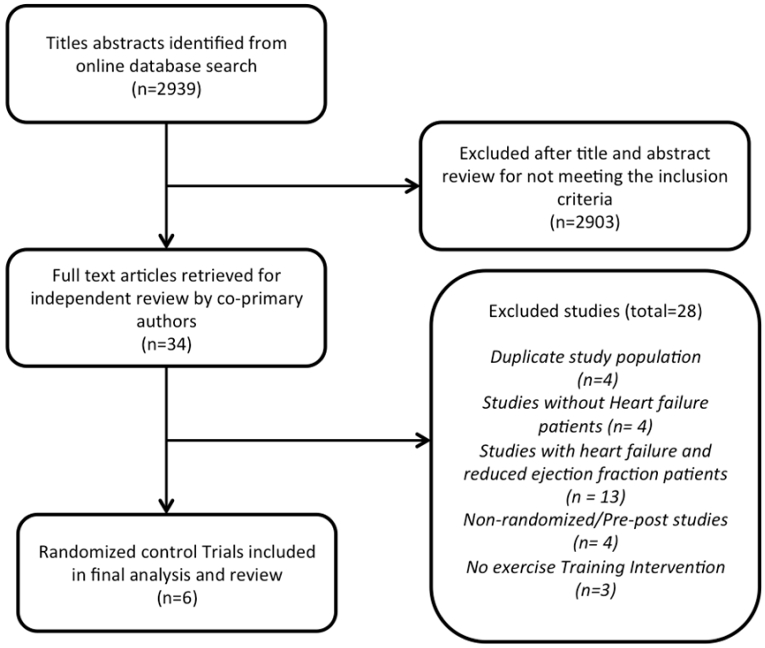

Figure 1.

Flow diagram for inclusion of studies in the Meta-analysis

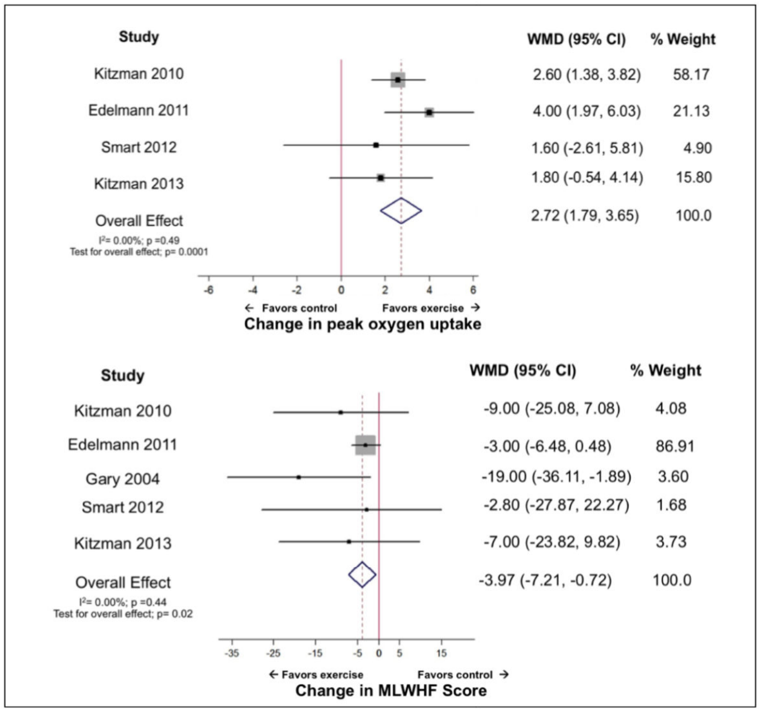

Figure 2.

Forest Plot showing effect of exercise training on cardiorespiratory fitness, measured as peak oxygen uptake (ml/kg/min) and quality of life, estimated using Minnesota living with heart failure (MLWHF) score, among participants with heart failure and preserved ejection fraction. WMD indicated weighted mean difference.

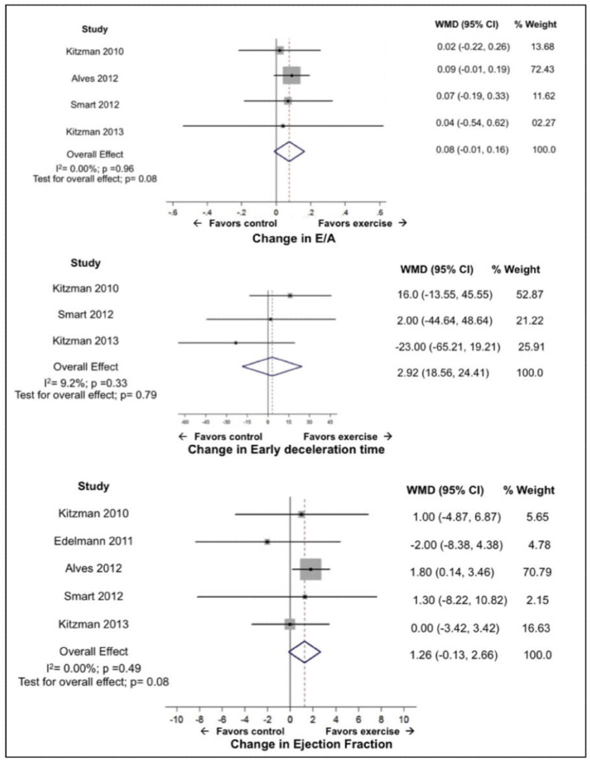

Figure 3.

Forest plot showing effect of exercise training on left ventricular diastolic function (E/A ratio and early deceleration time) and left ventricular ejection fraction (LVEF) among participants with heart failure and preserved ejection fraction. WMD indicated weighted mean difference.

Table 1

Baseline characteristics of the studies included in meta-analysis

	Gary et al 2004[16]	**Kitzman et al 2010**[17]	**Edelmann et al 2011**[18]	**Smart et al 2012**[20]	**Alves et al 2012**[19]	**Kitzman et al 2013**[21]
Total participants (control/training)	16/16	27/26	20/44	13/12	11/20	31/32
Women (%)	100	75	36	48	29	76
Caucasian (%)	59	70	NA	NA	NA	68
Mean age, years	68 ± 11	69.5 ± 5.5	65 ± 7	64.4 ± 6.4	62.9 ±10.2	70 ± 7
Mean Body mass index, Kg/m^2	33.5 ± 6.5	0.5 ± 6.5	31 ± 5	32.1 ± 6.4	28.4 ± 4.5	32.1 ± 6.6
NYHA Class II (%) NYHA Class III (%)	41 59	51 21	84 16	64 0	39 55	51 49
Hypertension (%)	88	68	86	16	68	89
Diabetes (%)	31	17	14	16	35	24
Baseline Systolic BP, mm Hg	NA	147± 20	140 ± 19	131±11	NA	146 ± 17
Baseline Heart Rate, beats/min	NA	69 ± 13	66 ± 11	NA	NA	NA
Presentation EF (%)	≥ 45	≥ 50	≥ 50	≥ 45	≥ 55	≥ 50
Exercise capacity Assessment	6 min walk test	Cycle Ergometer	Cycle Ergometer	Cycle Ergometer	Exercise treadmill test	Cycle Ergometer
6 min walk at baseline, feet	832 ± 366	1452 ± 332	1794 ± 282	NA	NA	1450 ± 300
Peak oxygen uptake baseline, ml/kg/min	NA	13.3 ± 2.6	16.3 ± 4.8	13.2 ± 3.9	13.6 ± 4.9	14.1± 3.0
Blinded assessment of outcomes	No	Yes	Yes	Yes	Yes	Yes

NYHA: New York Heart Association; BP: Blood Pressure; EF: Ejection Fraction; Data represented as mean ± SD

Table 2

Heart Failure with Preserved Ejection Fraction definition and exclusion criteria use in the studies included in the meta-analysis

Trial	Criteria used for Defining HFPEF	Exclusion Criteria
Gary et al 2004[16]	• NYHA Class II or III Diastolic Heart Failure on chart review. • Ejection Fraction > 50% • Stabilized on cardiac medications for at least 3 months	Significant coronary artery disease Renal insufficiency, uncontrolled hypertension
Kitzman et al 2010[17] & Kitzman et al 2013[21]	• Symptoms and signs defined by NHANES HF score >3 • History of acute pulmonary edema OR At least 2 of the following symptoms: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, lower-extremity edema, or exertional fatigue. • Well compensated, stabilized on cardiac medications for at-least 6 weeks	Significant coronary artery disease, valvular heart disease or pulmonary disease, anemia
Edelmann et al 2011[18]	• Symptomatic (NYHA II/III) with ejection fraction > 50% • Echo determined diastolic dysfunction in sinus rhythm, • At least 1 cardiovascular risk factor • Stabilized on cardiac medications for at least 4 weeks	Significant coronary artery disease, valvular heart disease or pulmonary disease, anemia, uncontrolled Hypertension, arrhythmia
Smart et al 2012[20]	• Significant Dyspnea on exertion with Delayed relaxation or Pseudonormal filling on echo.	Hx of coronary artery disease COPD, Valvular disease
Alves et al 2012[19]	• Signs and symptoms of heart failure with ejection fraction > 55%	Uncontrolled Hypertension, unstable angina, abnormal hemodynamic response, arrhythmias, ischemic EKG changes during treadmill test

Table 3

Control and exercise group interventions used in the studies included in the meta-analysis

	Exercise Training group Intervention	**Control group Intervention**	**Duration**	**Outcome Measured**
Gary et al 2004[16]	• Self-monitored community based walking intervention + home education program. • Walking intervention with ambulatory Heart rate monitoring, initially at an intensity of 40% of target heart rate for week 1 with gradual increase to 60% as tolerated.	Weekly visits with home education program	12 weeks	1. Exercise capacity as 6-min walk test 2.Quality of life
Kitzman et al 2010[17] & Kitzman et al 2013[21]	• Supervised endurance training (track walking + cycling) 3 times per week • Week 1-2: exercise at 40-50% of peak VO_2 with gradually increasing duration • Week 3-16: exercise exercise intensity at 60-70% of peak VO_2 and duration increased to 15-20 min.	Telephone call follow-up every 2 weeks without addressing exercise behavior	16 weeks	1. Peak Oxygen uptake. 2. Systolic, diastolic function by Echo 3. LV dimensions 4. Quality of life
Edelmann et al 2011[18]	• Supervised, endurance (cycling) + resistance training • Week 1-4: aerobic endurance training at 50-60% of baseline peak VO_2 • Week 5-12: aerobic endurance at 70% of baseline peak VO_2 + resistance training	Usual care and maintenance of usual activities	24 weeks	1. Peak Oxygen uptake. 2. Systolic, diastolic function by Echo 3. LV dimensions 4. Quality of life
Alves et al 2012[19]	• Supervised endurance training on treadmill/cycle ergometer. • Week 1-4: training at 70-75% of peak VO_2. • Week 5-24: training at 70-75% of peak VO_2.	Usual care with regular cardiologist follow-up.	24 weeks	1. Peak Oxygen uptake. 2. Systolic, diastolic function by Echo 3. LV dimensions 4. Quality of life
Smart et al 2012[20]	• Supervised, outpatient, cycle ergometer exercise training. • Initial intensity of 60-70% peak VO_2. • Exercise intensity uptitrated by 2 to 5 Watts/week as tolerated	Usual care and maintenance of usual activity levels.	16 weeks	1. Peak Oxygen uptake. 2. Systolic, diastolic function by Echo 3. LV dimensions 4. Quality of life

Peak VO_2: Peak Oxygen Uptake; LV: left ventricle

Table 4

Exercise associated adverse events as reported in the studies included in the meta-analysis

Studies	Exercise associated Adverse Events
Gary et al 2004[16]	No adverse events
Kitzman et al 2010[17]	No adverse events
Edelmann et al 2011[18]	No serious adverse events. Palpitations (n = 2); dyspnea (n = 2); Muscle discomfort (n = 9)
Kitzman et al 2013[21]	1 exercise patient with transient hypoglycemia
Smart et al 2012[20]	Not reported