ORIGINAL RESEARCH

Exercise Training for Heart Failure With Preserved Ejection Fraction (ExTraMATCH III): Protocol for an Individual Patient Data Meta-Analysis

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ABSTRACT

Background: We will undertake an individual patient data (IPD) meta-analysis to assess the impact of exercise-based cardiac rehabilitation in patients with heart failure with preserved ejection fraction (HFpEF) on mortality and hospitalization and quality of life of exercise-based cardiac rehabilitation according to patient characteristics: age, sex, ethnicity, New York Heart Association functional class, ischemic etiology, ejection fraction, and exercise capacity. Despite emerging evidence supporting exercise training in HFpEF, uncertainties remain in the interpretation and understanding of this evidence base. Clinicians and health care providers seek definitive estimates of impact on mortality, hospitalization and health-related quality of life (HRQoL). This work is, therefore, important as HFpEF treatment options are evolving; however, efficacy of some medications is equivocal, so optimizing exercise rehabilitation is vital.

Methods: We conducted a systematic search to identify randomized trials of exercise training for at least 3 weeks compared with no exercise control with 6-month follow up or longer, providing IPD time to event on mortality or hospitalization (all-cause or heart failure-specific). IPD will be combined into a single dataset. We will use Cox proportional hazards models to investigate the effect of exercise-based cardiac rehabilitation and the interactions between exercise-based cardiac rehabilitation and participant characteristics. We will use a mix of one-stage and two-stage models. Original IPD will be requested from the authors of all eligible trials; we will check original data and compile a master dataset. IPD meta-analyses will be conducted using a one-step approach where the IPD from all studies are modeled simultaneously while accounting for the clustering of participants with studies.

Results: We expect our analyses to show improved mortality, hospitalization, cardiorespiratory fitness, and health-related quality of life.

Conclusion: This work will clarify exercise-based rehabilitation delivery methods to optimize benefits for people with HFpEF.

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Keywords: HFpEF, diastolic heart failure, mortality, quality of life

BACKGROUND

Patients with chronic heart failure (HF) and preserved ejection fraction (HFpEF) (left ventricular ejection fraction [LVEF] ≥50%), experience a marked reduction in their exercise capacity, health-related quality of life (HRQoL), and life expectancy (1). Typically exercise capacity of people with HFpEF is about 4 METS, and this is comparable to people with heart failure with reduced ejection fraction

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TABLE 1. Comparison of characteristics of people with HFpEF and HFrEF who have completed exercise training trials (RCTs).

Characteristic	HFpEF[a]	HFrEF [b]
Baseline left ventricular ejection fraction, %	≥45	<27 ± 8
Mean age, y	Typically > 70	61 ± 13
Male gender, %	> 50	75 or above

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; RCT = randomized controlled trials
[a]Per included trials
[b]As identified from ExTraMATCH II (5)

(HFrEF) (2). Structured exercise training, often delivered as part of a cardiac rehabilitation program, has been shown to redress some of the deficit in physical fitness (3). Treatment options are limited for HFpEF, and the cornerstone is often lifestyle therapy, including weight loss and structured physical activity. Optimization of exercise rehabilitation is vital as people with HFpEF are traditionally more likely to be female and older than their HFrEF counterparts. Uncertainty remains about the efficacy of exercise training in people with HFpEF because of the relatively small number of published trials compared with people with HFrEF. Despite some evidence supporting exercise training in HFpEF, uncertainties remain in the interpretation and understanding of the expected magnitude of improvement and optimal exercise prescription. Clinicians and health care providers seek definitive estimates of the impact on mortality, hospitalization, HRQoL, and which HFpEF patient phenotypes derive benefits. Several group-level meta-analyses examining the effect of exercise training for HFpEF have been conducted, but an individual participant data (IPD) meta-analysis will allow a more thorough investigation.

Justification for conducting this work is derived from studies that have compared HFpEF with HFrEF which repeatedly show patients of older age, and a higher prevalence of women (4) (Table 1).

The differing characteristics of people with HFpEF may impact exercise-based cardiac rehabilitation outcomes in the following ways:

1. Uptake rates may be different in older HFpEF patients, because of difficulty with access.
2. Adherence rates may differ between HFpEF and HFrEF.
3. The expected change in quality of life and physical fitness may be different to HFrEF as often HFpEF patients are older.
4. Time to events and number of events may show differences between people with HFpEF and HFrEF.

METHODS

Search Methods for Identification of Studies

Randomized controlled trials for inclusion in the ExTraMATCH III project have been identified from recent meta-analyses, the 2019 updated Cochrane Review (6), and the most recent database search.

Eligibility Criteria for Studies

Studies will be included if they meet the following inclusion criteria:

1. Study design: Randomized controlled trials
2. Population:
   a. Studies that include adult patients (18 years and older) with a diagnosis of HFpEF with a LVEF ≥45%.
   b. Studies with an inclusion criteria that allows for any HF patient (HFpEF and HFrEF) but provides no LVEF% inclusion or exclusion criteria, but reports a mean LVEF >40%; however only IPD for participants with LVEF ≥45% will be extracted (subanalyses will also be conducted; see subgroup analysis).
   c. Studies reporting a mean LVEF >40% at baseline, but with a stated study inclusion/exclusion criterion of LVEF <45%, will be excluded
3. Intervention: Exercise training of 4 weeks' duration or more, with no restriction on type of training
4. Context: Patients managed in any setting, that is, home, hospital, university, community facility, supervised or unsupervised
5. Comparator: a no-exercise group, defined as no exercise, normal daily activities, usual care, attention control, and/or education
6. Sample size: no restriction on sample size

Tables 2 and 3 list the characteristics of the studies identified for possible inclusion in IPD meta-analysis. Table 4 outlines the status of clinical trials in HFpEF patients, previously identified in 2019 Cochrane Review.

MAIN VARIABLES AND OUTCOMES

This list of proposed variables and outcomes at a patient level has been generated from the ExTraMATCH II protocol (38). In accordance with the research objectives, IPD will be sought for the following variables and outcomes from eligible trials:

1. Baseline & clinical characteristics:
   a. Age
   b. Gender
   c. Body Mass Index
   d. Ethnicity
   e. LVEF and cardiac dimensions, diastology (Doppler) and HF etiology
   f. New York Heart Association Class
   g. Etiology and Comorbidities (e.g., hypertension, diabetes)
   h. Baseline BNP and serum creatinine and hemoglobin
   i. Medication class and dosage
2. Outcomes:
   a. Exercise capacity (irrespective of assessment method) (at baseline and all follow up); including peak VO_2, respiratory exchange ratio, V_E/VCO_2 slope, resting/maximal/delta heart rate, resting/maximal blood pressure.
   b. Disease-specific HRQoL, at baseline and all follow up, irrespective of assessment tool;

TABLE 2. HFpEF: possible studies for inclusion in IPD meta-analysis.

Author	N = Baseline (Completed)	HFpEF: LVEF Inclusion Criteria	Mean ± SD LVEF%	NYHA	Mean Age, y	Male, %	Intervention Length and (Longest FU)	Intervention
Alves 2012 (7), Israel	31[a] (33)	LVEF >55% (Mild group 45-54%)[a]	56.3 ± 2.5 49.3 ± 1.9[a] Total[b]	I-III	62.9 ± 10.2 63.6 ± 10.9[a]	71 73[a]	6 mo (6 mo)	Aerobic training (treadmill or cycle) vs usual care
Edelmann 2011 (8), Ex-DHF—Pilot, Germany	67 (64)	LVEF ≥50%	68 ± 7 Ex 67 ± 7 Con[b]	I-III	64 ± 8 65 ± 6	45 40	3 mo (3 mo)	Endurance (cycle ergometer)/ resistance training (added week 5) vs usual care
Gary 2004 (9), USA	32 (28)	LVEF ≥45%	54 ± 7 Ex 57 ± 9 Con	II-III	67 ± 11 69 ± 11	0	12 wk (12 wk)	Aerobic training (walking) vs control group (education)
Karavidas 2013 (10), Greece	30 (30)	LVEF >50%	63.6 ± 7.6 Ex 62.6 ± 4.5 Con	II-III	69.4 ± 8.6 68.5 ± 7.9	40	6 wk (6 wk)	FES vs placebo
Kinugasa 2020 (11)	20	LVEF ≥45%			76 ± 10	85	24 wk	Inspiratory muscle training vs usual care
Kitzman 2010 (12), USA	53 (46)	LVEF ≥50%	61 ± 5 Ex 60 ± 10 Con[c]	II-III	70 ± 6 69 ± 5	17 9	16 wk (16 wk)	Aerobic (endurance—walking/cycle) training vs attention control
Kitzman 2013 (13), USA	63 (54)	LVEF ≥50%	58 ± 6 Ex 56 ± 5 Con[c]	II-III	70 ± 7	28 20	16 wk (16 wk)	Aerobic (endurance) training vs attention control
Kitzman 2016 (14), USA	51 (46)	LVEF ≥50%	60.7 ± 6.1 Ex 62.5 ± 5.5 Con	II-III	67.5 ± 5.9 65.6 ± 4.8	19 20	20 wk (20 wk)	Aerobic training (primarily walking) vs attention control
Lang 2018 (15), Scotland	50 (45)	LVEF ≥45%	LVEF ≥45%	I-III	71.8 ± 9.9 78.0 ± 6.6	36 56	12 wk (6 mo)	Exercise training (walking or chair based) vs usual care
Mueller 2021 (16)	180	LVEF ≥50%	LVEF ≥50%	II-III	70 ± 7 High 70 ± 8 Mod 69 ± 10 Con	29 40 32	52 wk (12 mo)	High vs moderate Intensity vs control
Palau 2014 (17), Spain	27 (26)	LVEF >50%	69 (63-77) Ex 76 (68-83) Con[c]	III-IV	68 (60-76) 74 (73-77)	50	12 wk (12 wk)	IMT vs usual care
Palau 2019 (18), Spain	59 (59)	LVEF >50%	70 ± 9 Ex1 68 ± 11 Ex2 63 ± 11 Ex3 68 ± 8 Con		75 ± 10 72 ± 9 73 ± 10 75 ± 9	47 40 50 31	12 wk (24 wk)	IMT vs FES vs IMT + FES vs usual care
Smart 2012 (19), Australia	30 (25)	LVEF >45%	58.9 ± 11.9 Ex 56.7 ± 7.7 Con[c]	I-II	67 ± 5.8 61.9 ± 6.9	58 46	16 wk (16 wk)	Aerobic training (cycle ergometry) vs control

Con = control; Ex = exercise; FES = functional electrical stimulation; FU = follow up; HFpEF = heart failure preserved ejection fraction; IPD = individual patient data; IMT = inspiratory muscle training; LVEF = leftventricualr ejection fraction; NYHA = New York Heart Association

[a]Alves 2012 also included mild ejection fraction in addition to preserved

[b]Data is for completed/analyses sample size

[c]Results not published, but trial is indicated as completed

TABLE 3. Heart failure studies with baseline LVEF >40%: possible studies for inclusion in IPD meta-analysis.

Author	N = Baseline (Completed)	Inclusion Criteria	Mean LVEF Reported	NYHA	Mean Age, y	Male, %	Intervention Length and (Longest FU)	Intervention
Antonicelli 2016 (20)	343 (313)	Reduced or Preserved Ejection Factions NYHA ≥II	48.4±13.4 Total (37%[a] LVEF <40%) 47.9 ± 13.3 Ex 49.0 ± 13.4 Con	≥ II	76.90 ± 5.67	56.9	6 mo (6 mo)	Aerobic training (cycling) vs usual care
Aksoy 2015 (21)	57 (45)	HF LVEF 35-55% NYHA II-III	50.33 ± 6.93 Ex1 52.0 ± 4.92 Ex2 51.67 ± 6.17 Con	II-III	60.2 ± 9.3	86.7	10 wk	Aerobic training (interval) vs aerobic training (continous) vs control
Chen 2018a (22) China	62 (60)	HF Diagnosis NYHA II-IV	43.5 ± 13.5 Total 39.9 ± 13.4 Ex 47.1 ± 13.4 Con	II-IV	61.7 ± 14.4	59.7	26 wk	Combined (aerobic & strengthening) vs standard care
Chen 2018b (23)	80 (63)	HF NYHA Class I-II	58.61 ± 15.56 Total 56.68 ± 17.5 Ex 60.44 ± 13.35 Con	I-II	70.29 ± 13.53	52.5	12 wk (12 wk)	Baduanjin vs control
Gary 2019 (24)	41[a] (28)	LVEF ≥10% NYHA II-III	34 ± 14 Ex 36 ± 14 Con Range 10-65%	II-III	60 ± 10 59 ± 11	41 37	12 wk (6 mo)	Aerobic vs usual care Attention control (vs aerobic + cognitive training)
Giallauria 2008 (25)	61	Post STEMI	41.6 ± 11.3 Ex 42.0 ± 7.6 Con		55.9 ± 3.1 55.1 ± 3.7	72	6 mo	Aerobic training vs usual care
Jaarsma 2020 (26)	605	CHF Diagnosis	Ex (21% HFpEF) Con (24% HFpEF)	I-IV	66 ± 12 67 ± 11	72 70	3 mo 6 mo 12 mo	Exergame vs control (motivational support)
Jónsdóttir 2006 (27)	43	CHF Diagnosis	41.5 ± 13.5 Ex 40.6 ± 13.7 Con	II-III	68 ± 6.6 69 ± 5.3	79	5 mo	Combined vs usual care
Kaltsatou 2014 (28)	57 (51)	Male HF NYHA Class II-III	49.1 ± 2.4 Ex 49.3 ± 3.4 Dance 49.6 ± 3.5 Con	II-III	67.1 ± 5.5	100	32 wk	Combined vs dance vs control
Norman 2020 (29)	204	Diagnosis Stage C HF	39.3 ± 12.1 Ex (19.6% HFpEF) 40.5 ± 14.0 (24.5% HFpEF)	I-IV	59.8 ± 12.6 60.9 ± 10.3	55.9 54.9	6 mo 12 mo 18 mo	Combined vs enhanced usual care
Redwine 2019 (30)	70	HFpE & HFrF (Stage C symptomatic HF)	46 ± 14 Ex1 45% HFpEF) 44 ± 13 Ex2 (44% HFpEF) 46 ± 12 Con (37% HFpEF)	Stage C	65 ± 9 63 ± 9 67 ± 7	86 92 87	16 wk	Resistance vs tai chi vs usual care
Reeves 2017 (31)	27 (24)	HFrEF & HFpEF ADHF dx by Acute Worsening HF Symptoms	40 ± 13 Ex (42% HFpEF) 34 ± 18 Con (40% HFpEF)		72.7 ± 10.8 71.8 ± 9.1	47 33	12 wk (6 mo)	Combined vs usual care
Wall 2010 (32)	19	NYHA Class I-III; EF ≤60%	≤60	II	69 ± 4.4 70 ± 4.05	58	12 mo	Aerobic vs usual care

ADHF = acute decompensated heart failure; CHF = chronic heart failure; Con = control; EF = ejection fraction; Ex = exercise; FU = follow up; HF = heart failure; HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction; IPD = individual patient data; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STEMI = ST segment elevation myocardial infarction

[a]Attention control and exercise only, excludes exercise + cognitive training group

TABLE 4. HFpEF clinical trials as identified from 2019 Cochrane Review.

Trials	Intervention	Comments
ACTR12608000263392, Mudge et al. 2018 (33)	HFpEF/HFrEF	**Excluded: No nonexercise control group**—both groups exercised; centre-based supervised exercise program compared with home-based program; ~23.3% HFpEF
ISRCTN86879094, EX-DHF, Edelman Trial (34)	HFpEF	**Noted as completed;** no published data
NCT02696486 (35)	HFpEF	**Excluded: Single group assignment per trial register** Noted as completed; register last updated January 2017
NCT01914315 (36)	HFpEF	**Noted as still recruiting** at last register update November 2014
NCT02196038 (37), REHAB-HF (31)	HFpEF	**Estimated completion date November 2020 Included: Reeves 2017—pilot of REHAB-HF**
NCT03041376 (38)	HFpEF	**Estimated completion date January 2020**

HFpEF = heart failure preserved ejection fraction; HFrEF = heart failure reduced ejection fraction

c. Mortality (all-cause, death due to HF); incidence and time-to-event;
d. Hospital admission/readmission (all cause, HF-specific); incidence, duration, reason for censoring, and time-to-event

Collection of Data and Data Management

Investigator Contacts

Principal investigators of included trials will be contacted via email by IPD authors to inform them of the IPD analysis and to ask if they are willing to share their original IPD. Members of the ExTraMATCH III Executive Management Group (see list of members in the Acknowledgments) have links with several study investigators, so if no response is received to the initial invitation, members of the group will be assigned to make further contact. If after this time study investigators have not responded or are unwilling to contribute their data, a final note will be sent enquiring why they are unable to participate.

Data Format

The procedure for collection and collation of data will be coordinated by the project secretariat at the University of New England, Armidale, NSW Australia. All participating study authors will be asked to provide deidentified datasets. Where possible, electronic versions of datasets will be sought together with written details of the coding of the variables. A standardized data template will be provided to all study authors; however, as primary study authors are unable to use the template, we will accept databases in all formats.

Data Transfer and Storage

Receipt of raw data from study investigators will vary depending on any concerns as to security of their host institution. In most cases, we anticipate data will be sent via an encrypted data file by email to the project secretariat. Once received data will be stored on a secure password-protected computer server managed in accordance with the data management standard operating procedures of the University of New England. Raw datasets will be stored in their original format and then converted and combined into one overall master dataset.

Data Checking

Data from each study will be evaluated and compared with the data in the original publications. We will check original data to make sure all values are reasonable and assess any missing data. Data from each trial will be checked on range, extreme values, internal consistency, missing values, and consistency with published reports. Where there is missing information, errors, or data discrepancies, the relevant study author will be contacted and asked to check their data and ensure the IPD dataset tallies with the published article. Access to data at all stages of cleaning and analysis will be restricted to core members of the research team (N.A.S., M.J.P., J.C., and R.T.).

Once all original data is checked and verified, individual study data will be combined to form a new master dataset. Data from individual datasets remain the property of the ExTraMATCH III Collaborators who have provided IPD.

Statistical Analysis

For dichotomous outcomes the number of people in each group allocation and the number of successes/failures (e.g., alive/dead) will be analyzed. For continuous variables the pre/post training mean/SD for change in these values will be calculated or imputed using standard methods (39,40). Due to the complexity of the statistical analysis the following represents the planned principal analyses; some modifications and additional analyses are likely to emerge during the project. Where there are sufficient numbers of studies using the same HrQOL tool, we will group and analyze these using the default mean difference function. Where there are a number of mixed HrQOL tools, these will be grouped and the standardized mean difference function will be used as opposed to the default mean difference function.

A detailed statistical analysis will be produced prior to the analysis. Analyses will be conducted in accordance with current recommendations for IPD meta-analyses (41).

Study and patient level characteristics of included studies will be presented. IPD meta-analyses will be conducted

using a one-step approach where the IPD from all studies are modeled simultaneously while accounting for the clustering of participants with studies. All analyses will follow the principle of intention-to-treat as closely as possible. Continuous outcomes will be analyzed using linear models with adjustments for baseline values. Time-to-event endpoints will be analyses using Cox proportional hazard models.

Analyses will be undertaken using Stata v 16; Stata Statistical Software, Release 16, StataCorp LLC, College Station, TX, and study data will not be used for any other purpose without the permission of collaborators.

Subanalyses will include the following:

1. Meta-regression: Where 8 or more studies provide relevant data, meta-regression will be performed to examine the effect of confounding variables (e.g., age, gender) on the findings.
2. Subgroup analyses: Over the years clinical trials in HFpEF have used LVEFs of 40% to 49% to define the cut-off and inclusion of HFpEF patients. Recent European Society of Cardiology guidelines suggest that HF patients with a LVEF 40% to 49% be classified as having heart failure with mid-range ejection fraction (HFmrEF) and only HFpEF when LVEF is ≥50% (42). Initial IPD analysis will include data from all HF patients with a LVEF ≥45%. Subgroup analyses will then be conducted removing patients with a LVEF 45% to 49%.
3. Sensitivity analysis: Where indicated sensitivity analyses will be undertaken to assess the effect of various characteristics (e.g., gender, age, renal function) on the findings.

Study Quality Assessment

Study quality assessment of included studies was undertaken using the validated TESTEX scale (43).

Publication Bias

Publication bias will be assessed for the IPD analysis will be assessed in accordance with recommended methods (44).

Project Management and Ethics

The *ExTraMATCH III Executive Management Group* refers to the core team of researchers who will oversee the strategic direction of the study. The Executive Management Group will act as liaison between the *ExTraMATCH III Collaborators*. The *ExTraMATCH III Collaborators* refers to all those linked to the project and includes trial teams who provide data sets for the study. The Collaborative Group will be composed of 1 representative from each of the included studies. As new eligible studies are completed, new collaborators will be invited.

The roles of the ExTraMATCH III Executive Management Group are to

1. agree on the research questions of the collaboration and develop the initial protocol;
2. agree on the data collection proforma;
3. oversee arrangements for secure data handling;
4. review the publication strategy for the collaboration;
5. ensure that data are only used, and any additional research (including updating of the combined data sets with emerging evidence) only proceeds, following consultation and agreement with the Collaborative Group; and lead future applications for research funding.

Collaborative Group

The Executive Management Group will act as a liaison between members of the Collaborative Group. The Collaborative Group will be composed of a representative from each of the included trials. We will invite new collaborators as new eligible studies are completed.

Members of the collaborative will be given opportunities to participate in decision- making regarding the study design and analyses. We intend members of the collaborative will have opportunities to network and identify future ExTraMATCH III research questions suitable for analysis with the IPD dataset. Once the Collaborative Group and initial dataset are established, we will develop mechanisms for communication and input on methodological issues.

Data Ownership and Confidentiality

Participants in the individual trials have previously consented to participation in their respective trial. Given that the analyses proposed are simply an extension of the core analysis of the constituent trials, we do not anticipate that additional ethical permission will be required. We will ensure that datasets shared as part of the project include no patient-identifiable information (such as names and addresses), that all data storage is in accordance with the regulations governing research at the University of New England, and we will obtain a signed data sharing agreement with all authors to outline procedures for the transmission, storage, analysis, and dissemination. The collaborators remain the custodians of their own data and retain the right to withdraw their data from the analysis at any time.

Publication Policy

We will follow recommendations for authorship in IPD analyses and multicenter studies (45,46). Where possible, we will follow the policy of members of the Executive Management Group and the Collaborative Group being listed as authors and names of other participating collaborators listed in the acknowledgments. Requirements for authorship will follow those of the International Committee of Medical Journal Editors (47).

A primary publication of the results of this review will be prepared by the Executive Management Group. This and all other ExTraMATCH II manuscript drafts will be circulated to the Collaborative Group for comment, revision, and approval.

DISCUSSION

The information from ExTraMATCH III will help inform future national and international clinical and policy

decision-making on the use of exercise-based interventions in HF and improve the quality, design, and reporting of future trials in this field. Despite encouraging evidence supporting exercise training in HFpEF, only data from about 20 trials have been published to date. So uncertainties remain in the interpretation and understanding of this evidence base. Providers of medical care seek more precise estimates of impact on mortality, hospitalization, cardiorespiratory fitness, and HRQoL. A pooled IPD analysis will allow predictions to be made between patient characteristics and change in the clinical outcomes, following exercise-based cardiac rehabilitation. This work is, therefore, important as HFpEF treatment options are evolving; however, efficacy of some medications is equivocal, so optimizing exercise rehabilitation is vital as people with HFpEF are traditionally more likely to be female and older than their HFrEF counterparts. The IPD analysis may reveal that some of these subtle HFpEF vs HFrEF differences in patient characteristics may have implications for optimization of exercise programming.

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