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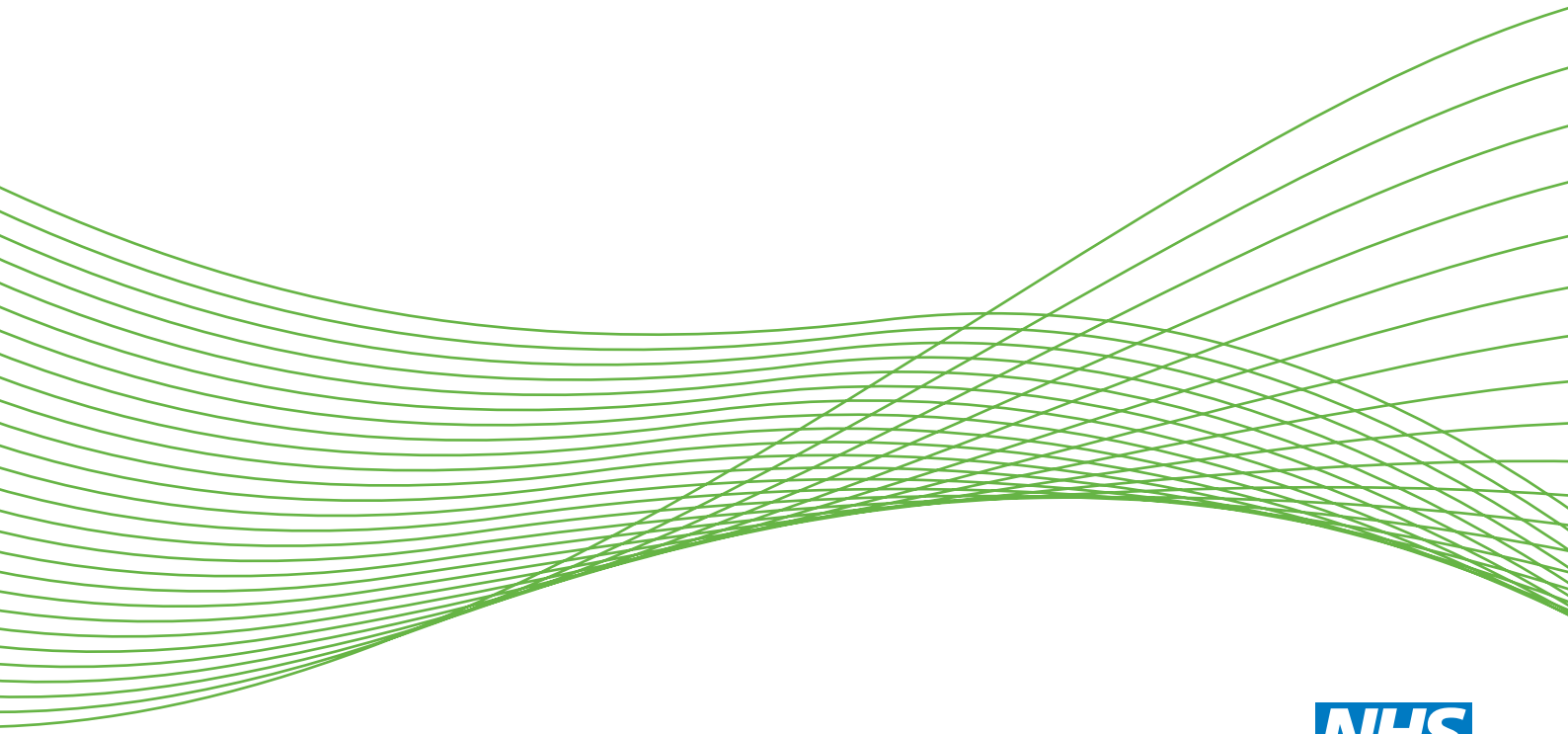

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Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis

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Abstract

Exercise-based cardiac rehabilitation for chronic heart failure: the EXTRAMATCH II individual participant data meta-analysis

Rod S Taylor,[1,2]* Sarah Walker,[1] Oriana Ciani,[1,3] Fiona Warren,[1] Neil A Smart,[4] Massimo Piepoli[5] and Constantinos H Davos[6]

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Background: Current national and international guidelines on the management of heart failure (HF) recommend exercise-based cardiac rehabilitation (ExCR), but do not differentiate this recommendation according to patient subgroups.

Objectives: (1) To obtain definitive estimates of the impact of ExCR interventions compared with no exercise intervention (control) on mortality, hospitalisation, exercise capacity and health-related quality of life (HRQoL) in HF patients; (2) to determine the differential (subgroup) effects of ExCR in HF patients according to their age, sex, left ventricular ejection fraction, HF aetiology, New York Heart Association class and baseline exercise capacity; and (3) to assess whether or not the change in exercise capacity mediates for the impact of the ExCR on final outcomes (mortality, hospitalisation and HRQoL), and determine if this is an acceptable surrogate end point.

Design: This was an individual participant data (IPD) meta-analysis.

Setting: An international literature review.

Participants: HF patients in randomised controlled trials (RCTs) of ExCR.

Interventions: ExCR for at least 3 weeks compared with a no-exercise control, with 6 months' follow-up.

Main outcome measures: All-cause and HF-specific mortality, all-cause and HF-specific hospitalisation, exercise capacity and HRQoL.

Data sources: IPD from eligible RCTs.

Review methods: RCTs from the Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH/ExTraMATCH II) IPD meta-analysis and a 2014 Cochrane systematic review of ExCR (Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, *et al*. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014;**4**:CD003331).

Results: Out of the 23 eligible RCTs (4398 patients), 19 RCTs (3990 patients) contributed data to this IPD meta-analysis. There was a wide variation in exercise programme prescriptions across included studies. Compared with control, there was no statistically significant difference in pooled time-to-event estimates in favour of ExCR, although confidence intervals (CIs) were wide: all-cause mortality had a hazard ratio (HR) of 0.83 (95% CI 0.67 to 1.04); HF-related mortality had a HR of 0.84 (95% CI 0.49 to 1.46); all-cause hospitalisation had a HR of 0.90 (95% CI 0.76 to 1.06); and HF-related hospitalisation had a HR of 0.98 (95% CI 0.72 to 1.35). There was a statistically significant difference in favour of ExCR for exercise capacity and HRQoL. Compared with the control, improvements were seen in the 6-minute walk test (6MWT) (mean 21.0 m, 95% CI 1.57 to 40.4 m) and Minnesota Living with Heart Failure Questionnaire score (mean –5.94, 95% CI –1.0 to –10.9; lower scores indicate improved HRQoL) at 12 months' follow-up. No strong evidence for differential intervention effects across patient characteristics was found for any outcomes. Moderate to good levels of correlation ($R^2_{trial} > 50\%$ and $p > 0.50$) between peak oxygen uptake (VO_2peak) or the 6MWT with mortality and HRQoL were seen. The estimated surrogate threshold effect was an increase of 1.6 to 4.6 ml/kg/minute for VO_2peak.

Limitations: There was a lack of consistency in how included RCTs defined and collected the outcomes: it was not possible to obtain IPD from all includable trials for all outcomes and patient-level data on exercise adherence was not sought.

Conclusions: In comparison with the no-exercise control, participation in ExCR improved the exercise and HRQoL in HF patients, but appeared to have no effect on their mortality or hospitalisation. No strong evidence was found of differential intervention effects of ExCR across patient characteristics. VO_2peak and 6MWT may be suitable surrogate end points for the treatment effect of ExCR on mortality and HRQoL in HF. Future studies should aim to achieve a consensus on the definition of outcomes and promote reporting of a core set of HF data. The research team also seeks to extend current policies to encourage study authors to allow access to RCT data for the purpose of meta-analysis.

Study registration: This study is registered as PROSPERO CRD42014007170.

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List of abbreviations

6MWT	6-minute walk test
CI	confidence interval
ExCR	exercise-based cardiac rehabilitation
ExTraMATCH/ ExTraMATCH II	Exercise Training Meta-Analysis of Trials for Chronic Heart Failure
HF	heart failure
HF-ACTION	Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
HRQoL	health-related quality of life
IPD	individual participant data
ISWT	incremental shuttle walk test
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NYHA	New York Heart Association
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
REACH-HF	Rehabilitation EnAblement in CHronic Heart Failure
SD	standard deviation
STE	surrogate threshold effect
TESTEX	Tool for the assEssment of Study qualiTy and reporting in EXercise
VO_2peak	peak oxygen uptake

Plain English summary

Exercise-based cardiac rehabilitation (ExCR) is currently recommended in both the UK and international clinical guidelines for people with heart failure (HF). However, it remains uncertain as to whether or not the effects of cardiac rehabilitation are consistent across patient subgroups (e.g. men vs. women). This study sought to review available scientific evidence using individual participant data (IPD) to look at this issue.

Electronic literature databases were searched for published studies and anonymised IPD from the researchers who conducted these research studies was sought. It was possible to bring together data from 3900 people with HF.

Although the analyses of these data show that participation in ExCR does not appear to have an impact on the risk of death or hospitalisation, participation does offer some improvement in the physical fitness and quality of life of people with HF. It was also found that these benefits were irrespective of a patient's age, sex, ethnicity, initial level of physical fitness or disease severity.

Scientific summary

Background

People with symptomatic heart failure (HF) are living for longer following the onset of their condition, increasing the importance of effective and accessible services for these patients. Exercise-based cardiac rehabilitation (ExCR) is recognised as integral to the comprehensive care of HF patients. ExCR is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health. Current national [National Institute for Health and Care Excellence. *Chronic Heart Failure in Adults: Management*. Clinical Guideline [CG108]. URL: www.nice.org.uk/guidance/CG108 (accessed 25 June 2018)] and international [Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;**128**:e240–327; Working Group on Cardiac Rehabilitation; Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise training in chronic heart failure patients. *Eur Heart J* 2001;**22**:125–35; and McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–847] guidelines on the management of HF recommend ExCR, but do not differentiate according to patient subgroups.

Objectives

The Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH/ExTraMATCH II) project aimed to determine which HF patient subgroups benefit most from ExCR using individual participant data (IPD) meta-analysis.

The project had three objectives:

1. To obtain definitive estimates of the impact of ExCR interventions compared with no exercise intervention (control) on mortality, hospitalisation, exercise capacity and health-related quality of life (HRQoL) in HF patients.
2. To determine the differential (subgroup) effects of ExCR in HF patients according to their:
    - age
    - sex
    - left ventricular ejection fraction
    - HF aetiology
    - New York Heart Association (NYHA) class
    - baseline exercise capacity.
3. To assess whether or not the change in patient exercise capacity mediates, and is an acceptable surrogate end point for, the impact of ExCR on final outcomes of mortality, hospitalisation and HRQoL.

The information gained from the ExTraMATCH II project will inform future UK and international clinical and policy decision-making on the use of ExCR in HF.

Methods

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) IPD statement. Randomised controlled trials were identified from the original ExTraMATCH IPD meta-analysis [Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004;**328**:189] and the 2014 Cochrane systematic review of ExCR for HF (Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, *et al*. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014;**4**:CD003331). ExTraMATCH and the Cochrane systematic review were based on searches of the following electronic databases: Cochrane Central Register of Controlled Trials in The Cochrane Library, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and the NHS Centre for Reviews and Dissemination. Conference proceedings and trial registers were also searched. In keeping with the original ExTraMATCH IPD meta-analysis, trials of exercise training (for at least 3 weeks) compared with no exercise control with ≥ 6 months' follow-up were included if they provided IPD on all-cause or HF-specific mortality, hospitalisation, exercise capacity or HRQoL. The data sets of IPD were combined into a single data set. One-stage fixed-effect meta-analyses of time-to-event end points were performed using Cox proportional hazards models, stratified by study. One-stage meta-analyses of continuous outcomes were performed using hierarchical linear models with adjustments for baseline values and a random effect on study. Two-stage models using fixed and random effects were also performed. Interaction terms between ExCR and participant characteristics were used to assess potential differential effects of ExCR across subgroups. Mediational analyses and meta-analytic regressions, with estimation of R^2 at the trial level, and surrogate threshold effect (STE), were performed to assess the question of surrogate validity for exercise capacity outcomes of peak oxygen uptake (VO_2peak) and the 6-minute walk test (6MWT).

Results

Of the 23 eligible trials (4398 patients), 19 trials contributed data to the IPD meta-analysis [18 trials (3912 patients) to the clinical events (mortality and hospitalisation) analysis, 13 trials (3332 patients) to exercise capacity and HRQoL analysis, and 10 trials (2656 patients) to the exercise capacity mediational/surrogate end-point analysis].

Characteristics and quality of included trials

Patient characteristics at baseline were well balanced between ExCR and control group patients. The majority of patients were male (74%), had a mean age of 61 years, had experienced heart failure with reduced ejection fraction (HFrEF) (mean baseline left ventricular ejection fraction 26.7%), and most patients were in NYHA functional class II (59%) or III (37%). No included trials recruited patients with HF with a preserved ejection fraction of > 45%. Trials were conducted in Europe and North America and were published between 1990 and 2012, and the sample sizes ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention, which was most commonly delivered in either an exclusively centre-based setting or a centre-based setting in combination with some home exercise sessions. The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 12–90 weeks, with between two and seven sessions per week (median session duration was between 15 and 120 minutes, including warm-up and cool-down). The intensity of exercise ranged between 50% and 85% VO_2peak. The overall quality of included trials was measured using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX), a measure of study quality and reporting. Most studies were judged as being moderate to good, with a median TESTEX score of 11 (range 9–14) out of a maximum score of 15.

Impact of ExCR on mortality and hospitalisation

Compared with control, there was no statistically significant difference in pooled time-to-event estimates in favour of ExCR, although confidence intervals (CIs) were wide: all-cause mortality had a hazard ratio (HR) of 0.83 (95% CI 0.67 to 1.04); HF-related mortality had a HR of 0.84 (95% CI 0.49 to 1.46); all-cause

hospitalisation had a HR of 0.90 (95% CI 0.76 to 1.06); and HF-related hospitalisation had a HR of 0.98 (95% CI 0.72 to 1.35). No strong evidence for differential intervention effects across patient characteristics was found.

Impact of ExCR on exercise capacity and health-related quality of life

Compared with the control, there was a statistically significant difference in favour of ExCR for exercise capacity and HRQoL. For example, at 12 months' follow-up, improvements were seen in the 6MWT (mean 21.0 m, 95% CI 1.57 to 40.4 m; $p = 0.034$, $\tau^2 = 491$, $I^2 = 78\%$) and the Minnesota Living with Heart Failure Questionnaire score (mean –5.94, 95% CI –1.0 to –10.9; $p = 0.018$, $\tau^2 = 77$, $I^2 = 88\%$); lower scores indicate improved HRQoL. No strong evidence for differential intervention effects across patient characteristics was found.

Validation of exercise capacity as a surrogate end point

Moderate to good levels of correlation ($R^2_{trial} > 50\%$ and $p > 0.50$) between exercise capacity VO_2peak or 6MWT with mortality and HRQoL were seen. Estimated STE was an increase of 1.6 to 4.6 ml/kg/minute for VO_2peak. The results indicate that an increase in VO_2peak or an improvement in the 6MWT with ExCR is a potentially weak mediator of final outcomes.

Discussion

In HFrEF patients, ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation. However, uncertainty around effect estimates and lack of IPD on exercise adherence precludes drawing definitive conclusions in these event outcomes. ExCR significantly improves exercise capacity and HRQoL. No consistent differences were found in ExCR effects across patient subgroups. The results provide indicative evidence that VO_2peak and the 6MWT may be suitable surrogate end points for the treatment effect of ExCR on final outcomes in HF.

Recommendations for further research

Two central aspects of future data collection are (1) a consensus on the definition, collection and reporting of core sets of outcome data, concomitant disease/comorbidities and metrics of therapy delivery/uptake; and (2) the capture of data on patient-level adherence to the amount of exercise training during the ExCR intervention period. More generally, the research community should continue to implement policies that encourage primary study authors to make their data sets available, by either depositing in publicly available repositories or sharing with IPD meta-analysis collaborations when directly requested.

Study registration

This study is registered as PROSPERO CRD42014007170.

Funding

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Chapter 1 Background

Chronic heart failure (HF) is a burgeoning global health challenge that affects 1–2% of adults in the Western world.[1] Although survival after HF diagnosis has improved, prognosis is poor, with 30–40% of patients dying within a year of diagnosis.[2] Patients with HF experience limitations to their exercise capacity and activities of daily living, reduced health-related quality of life (HRQoL), and an increased risk of hospital admission rate and all-cause mortality.[3,4]

The cost of management of HF to the UK NHS was reported to be approximately £1B in 2010.[5] According to the Office for National Statistics, the proportion of the UK population aged ≥ 85 years is projected to double between 2016 and 2041.[6] Owing to increases in both the incidence and the prevalence in HF with increasing age,[7] more demands will be placed on the NHS in this time frame. An increase in the prevalence of comorbidities in an older population will lead to a greater number of hospitalisations in HF patients.[8]

With increasing numbers of people living longer with symptomatic HF, the effectiveness and accessibility of health services for HF patients have never been more important. Exercise-based cardiac rehabilitation (ExCR) is recognised as being integral to the comprehensive care of HF patients. Cardiac rehabilitation is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health.[9] Although exercise training is at the centre of cardiac rehabilitation, it is accepted that programmes should be comprehensive in nature and include education and psychological input, focusing on health and lifestyle behaviour change and psychosocial well-being.[2–4,9]

Previous systematic reviews and meta-analyses have shown exercise-based rehabilitation offers important health benefits for patients.[9–12] Including 33 trials across 4740 HF patients, the 2014 Cochrane review[10] shows no difference in pooled all-cause mortality with ExCR [relative risk 0.93, 95% confidence interval (CI) 0.69 to 1.27]; reduced risk of overall hospitalisation (relative risk 0.75, 95% CI 0.62 to 0.92) and HF-specific hospitalisation (relative risk 0.61, 95% CI 0.46 to 0.80); and a clinically important improvement in disease-specific HRQoL on the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (mean difference –5.8 points, 95% CI –9.2 to –2.4 points). ExCR for HF is therefore recommended by the National Institute for Health and Care Excellence[3] and is a class I recommendation of the joint American College of Cardiology Foundation and the American Heart Association guidelines and the European Society of Cardiology guidelines.[13–15] These guidelines do not differentiate by patient subgroup but, rather, recommend cardiac rehabilitation to all HF patients 'who are able to participate to improve functional status'.[13]

Despite this evidence and recommendation by clinical guidelines, the uptake of ExCR for HF remains poor. Only 16% of UK cardiac rehabilitation centres have a specific rehabilitation programme for HF.[16] The recent ExtraHF Survey reported that only 40% of centres from across 42 European countries implemented an exercise programme for HF.[17] Cardiac rehabilitation centres report a lack of resources as the major barrier to providing rehabilitation services for HF (i.e. lack of finances, staff and equipment).[16,17] A key potential solution (if supported by evidence) could be targeting exercise-based rehabilitation services to those HF patients who might experience the greatest benefit in outcomes. Such a differential effect of treatment across HF patients could improve the overall clinical effectiveness and cost-effectiveness of rehabilitation for HF and drive improvements in patient uptake of rehabilitation.

Although meta-analyses demonstrate important health benefits with ExCR, there is uncertainty as to whether or not there are differential effects across HF patient subgroups. Three data sources currently provide evidence on this issue, but all have weaknesses. First, in 2004, the Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH/ExTraMATCH II) Collaborative Group published an individual participant data (IPD) meta-analysis based on nine randomised trials of 801 HF patients, which showed ExCR to reduce all-cause mortality [hazard ratio (HR) 0.65, 95% CI 0.46 to 0.92], and no subgroup [age, sex, HF aetiology, New York Heart Association (NYHA) class, ejection fraction or exercise capacity] effects.[18]

Given the small number of trials, patients and events (193 deaths), these subgroup analyses are likely to be underpowered. Furthermore, a number of trials have been published since, including Heart Failure: A Controlled Trial Investigating Outcomes of exercise Training (HF-ACTION), a large US National Institutes of Health (NIH)-funded randomised trial (2331 HF patients across 82 centres).[19] Second, the original analysis of HF-ACTION found no interactions between treatment allocation (ExCR or no exercise control) and patient characteristics (age, sex, HF aetiology, NYHA class, ejection fraction or depression score) for the composite outcome of mortality or hospital admission.[19] Although the largest ExCR trial to date, to our knowledge, the power of this study to detect small subgroup effects remains limited. Finally, meta-regression analysis in the 2014 Cochrane review found no association between trial-level patient characteristics (age, sex, ejection fraction) and the impact of ExCR.[10] However, such analysis is highly prone to study-level confounding (ecological fallacy) and should be interpreted with great caution. The methodology of IPD meta-analysis allows more robust analysis of treatment effects in subgroups and consistent analysis of outcome data across trials, such as enabling time-to-event data analyses adjusted for baseline covariates.

Chapter 2 Aims and objectives

The ExTraMATCH II project aimed to determine which HF patient subgroups benefit most from ExCR using IPD meta-analysis.

The project objectives were to:

- obtain definitive estimates of the impact of ExCR interventions compared with no exercise intervention (control) on all-cause mortality, hospitalisation, HRQoL and exercise capacity in HF patients
- determine the differential (subgroup) effects of exercise-based interventions in HF patients according to their:
  - age
  - sex
  - left ventricular ejection fraction
  - HF aetiology
  - NYHA class
  - baseline exercise capacity
- assess whether or not the change in patient exercise capacity mediates and acts as a surrogate end point for the impact of the ExCR on all-cause mortality, all-cause hospitalisation and disease-specific HRQoL.

The information gained from the ExTraMATCH II project will inform future national and international clinical and policy decision-making on the use of ExCR in HF.

Chapter 3 Methods

This project was undertaken and reported according to current reporting guidelines for IPD meta-analyses[20–22] and was registered with PROSPERO (CRD42014007170).[23] The project management committees are listed in *Appendix 1*.

Identification of trials for inclusion

Trials were identified from the ExTraMATCH IPD meta-analysis and the 2014 Cochrane systematic review of ExCR for HF.[10,18] The Cochrane review searched (to January 2013) the following electronic databases: Cochrane Central Register of Controlled Trials in The Cochrane Library, EMBASE, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO and the NHS Centre for Reviews and Dissemination (see *Appendix 2* for the search strategy). Conference proceedings were searched on Web of Science. Trial registers (controlled-trials.com and ClinicalTrials.gov) and reference lists of all eligible trials and identified systematic reviews were also checked. No language limitations were imposed. Details of the search strategy used are reported elsewhere[23] and are included in *Appendix 2*.

Trials were included if they met the following criteria.

Study design
Randomised controlled trials (RCTs) with a follow-up period of ≥ 6 months (in accordance with the 2014 Cochrane review[10]).

Target population
Adult patients, aged ≥ 18 years, with a diagnosis of heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), based on an objective assessment of the left ventricular ejection fraction and on clinical findings.

Setting/context
Patients managed in any setting (i.e. hospital, community facility or patient's home).

ExCR intervention
An ExCR intervention that included at least an aerobic exercise training component performed by the lower limbs, lasting a minimum of 3 weeks,[24] either alone or as part of a comprehensive cardiac rehabilitation programme, which may also include health education and/or a psychological intervention.

Comparator
A non-exercise group receiving standard medical care or an attention placebo.

Sample size
A sample size of > 50 patients to ensure that the logistical effort in obtaining, cleaning and organising the data were commensurate with the contribution of the data set to the analysis.[25,26]

Identified RCTs meeting the inclusion criteria are shown in *Appendix 3*. Study selection for the 2014 Cochrane review and ExTraMATCH IPD meta-analysis was performed by the original research teams that performed these studies.[10,18] For the purposes of this project, a single researcher (RST) compared the included studies from these two previous studies and applied the above inclusion criteria.

Investigator requests

The principal investigators of eligible studies were invited (collaboration invitation) to participate in this IPD meta-analysis and share their anonymised trial data. The list of variables that principal investigators were asked to provide was reported in the study protocol[27] (see *Appendix 4*).

Exclusion of trials from individual participant data analysis

Trials were excluded if:

- authors did not respond to the invitation to provide IPD for the ExTraMATCH II analysis in spite of repeated contact attempts being made
- authors were unable to provide IPD, because the data had been either lost or destroyed
- patients were included in the trial who may also have appeared in another IPD data set.

Ethics approval

The ethics of obtaining data were carefully considered and advice was sought from NHS Digital in April 2016. The original trials had each obtained ethics/institutional review board committee approval and obtained individual patient consent. Given the fully anonymised nature of all the trial data sets (i.e. no inclusion of data, such as patient name or date of birth, that would allow individual patients to be identified), NHS Digital confirmed that there was no further legal/ethics or contractual requirements for use of these data for the purpose of this project. A revision of the HF-ACTION[19] data was obtained via the NIH data portal, which required that we obtain a letter of approval from the University of Exeter Medical School Research Ethics Committee. A letter was received on 13 November 2017.

Data management

Data files were received in a variety of formats depending on the security concerns of the host institutions. In most cases, data transfer was by e-mail of a password-protected file, with a separate e-mail containing the password. Each raw data file was saved in its original format on receipt and then converted to a Stata® file (version 14.2, StataCorp LP, College Station, TX, USA). Data cleaning was carried out in each pseudonymised data set prior to being combined in a master data set. Within the individual data sets, data for each variable (at the patient level) was checked for accuracy in range, extreme values, internal consistency, missing values and consistency with published reports. Data discrepancies or missing information were discussed with trial investigators and corrected, if appropriate.

All data files were stored on a secure password-protected computer server managed in accordance with the data management standard operating procedures of the UK Clinical Research Collaboration-registered Exeter Clinical Trials Unit. Access to data at all stages of cleaning and analysis was restricted to core members of the research team (OC, RST, FW and SW).

Patient and public involvement

As part of the National Institute for Health Research (NIHR) *Programme Grants for Applied Research* report [Rehabilitation EnAblement in CHronic Heart Failure (REACH-HF), reference number RP-PG-1210-12004; www.journalslibrary.nihr.ac.uk/programmes/pgfar/RP-PG-1210-12004/#/ (accessed 1 January 2019)], a patient and public involvement (PPI) group was established in 2009, which consisted of eight active members (five with lived experience of HF and three patient caregivers). The PPI group are familiar with the ongoing portfolio of Cochrane systematic reviews in cardiac rehabilitation.

This IPD meta-analysis was proposed to the PPI group meeting in Truro on 1 November 2015, in which views were sought on the proposed research questions. Following receipt of funding from NIHR, the ExTraMATCH II project was presented to the PPI group at a further meeting (held in March 2017). Members of the group gave views on how the results could be best presented and disseminated to patients, caregivers and clinicians to have an impact on clinical practice and patient understanding of HF. Kevin Paul (PPI group chairperson) was a co-applicant for the REACH-HF study and was also a member

of the REACH-HF Programme Steering Committee. Kevin is a core colleague and valued member of our team and agreed to act as conduit between the Project Advisory Group for ExTraMATCH II and the established PPI group. The PPI group was asked to contribute to, and give views on, (1) the ExTraMATCH II protocol (e.g. whether or not the most appropriate outcomes were prioritised), (2) lay summaries of the ExTraMATCH II project, (3) the implications for clinical practice and future research and (4) the planned dissemination strategy.

Kevin commented on the plain English summary of the original application and also offered advice on the plain English summary of the final report. Based on the INVOLVE guidelines,[28] we paid expenses that included the cost of his time to attend Project Advisory Group meetings, plus travel costs.

Statistical analysis

All analyses were carried out in accordance with the principle of intention to treat (i.e. patients were analysed according to randomised treatment assignment for which complete data was available at follow-up). When missing data were noted within an individual trial, contact with the author was attempted and data added if available. Given the relatively small levels of missing outcome and covariate data within trials, we did not undertake data imputation. When possible, all one- and two-stage analyses used random-effects models, as the overall data set is likely to include a high degree of clinical heterogeneity across the individual studies (differences in population, ExCR intervention and comparator).[29] All analyses were undertaken using Stata.

Main outcomes

In accordance with the study research objectives, it was sought, from eligible trials, IPD for the following outcomes:

- Mortality – incidence and time-to-event data for all deaths (we also sought to obtain data on the cause of death).
- Hospital admission – incidence, time to event and duration of hospitalisation (we also sought to obtain data on the cause of the hospitalisation).
- Disease-specific HRQoL (as assessed by the MLHFQ and other validated HRQoL outcomes) – value at baseline (pre randomisation) and at 6, 12, 24 and > 24 months post randomisation.
- Exercise capacity [as assessed by peak oxygen uptake (VO_2peak) and other validated exercise capacity measures] – as measured at baseline and at 6, 12, 24 and > 24 months post randomisation.

Patient subgroups

We also requested individual patient demographic and clinical data, including age, sex, ejection fraction, NYHA class, HF aetiology (ischaemic vs. non-ischaemic), race/ethnicity and exercise capacity at baseline. Details of exercise training prescription (i.e. session frequency, duration, intensity and overall programme duration) was collected as part of the 2014 Cochrane review.[10]

Statistical analysis plans

A detailed statistical analysis plan was produced for each of the three analyses described below:

1. the impact of ExCR on mortality and hospitalisation outcomes
2. the impact of ExCR on HRQoL and exercise capacity outcomes
3. the validation of exercise capacity as a surrogate outcome.

Descriptive statistics

For each analysis, patient-level characteristics were compared for those patients in the ExCR and control groups of the included studies. Descriptives of trial-level characteristics by group are also reported.

Assessment of study quality and risk of bias

We checked for potential small-study bias by visually assessing funnel plot asymmetry and using Egger's test.[30] Study quality and risk of bias was assessed using the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX).[31] Statistical heterogeneity was assessed using the I^2-statistic.[29]

Impact of ExCR on mortality and hospitalisation

Inclusion of trials

Trials were included in the mortality and hospitalisation analyses if IPD was provided for the one or more of the outcomes of interest detailed below.

Outcomes of interest

The final patient-relevant outcomes of interest in this study were time to event to:

- all-cause mortality
- HF-related mortality
- all-cause hospital admission
- HF-related hospital admission.

Owing to the inconsistency of reporting in IPD sets, we were able to consider only time-to-event outcomes and not incidence or duration of events. Insufficient data were made available to allow analyses on 'sudden death' to be carried out.

Each of the outcomes described above was analysed separately. Each trial contributed to between one and four analyses.

Primary analysis

In the primary analysis, a two-stage IPD meta-analysis approach was taken. A Cox regression model was performed on the data from each trial individually and the resulting HRs used in a random-effects meta-analysis. For the meta-analysis of treatment–covariate interactions, the same approach was used, with a Cox regression model applied to the data from each trial and the resulting HR for the interaction effect used to inform the meta-analysis. A random-effects model was used to account for the high degree of clinical heterogeneity across the individual studies due to differences in population, ExCR intervention and comparator.[29] An overall estimate of the effect of ExCR for each outcome, both by trial and as a pooled estimate, was presented as a HR and 95% CI. Additionally, the and I^2 and τ^2 statistics were reported alongside the associated p-value for the results of the main analyses.[29,32] The Cochrane handbook advises that using specific threshold values for the interpretation of the I^2-statistic can be misleading.[33]

Secondary analysis

The secondary analysis used a one-stage IPD meta-analysis Cox regression model, stratified by trial. Stratification allowed the baseline hazard to vary between studies, rather than forcing the hazard in individual studies to be proportionate to each other.[34] No distributional assumptions about this baseline hazard were made. Owing to failure of convergence in the one-stage random-effect models, probably due to the low level of heterogeneity between studies, a fixed-effect approach was used.

The within-trials interaction term used here identifies any patient characteristics that influence the effectiveness of ExCR on an individual level, necessary for making inferences for stratified medicine, as recommended by Riley *et al.*[35] The within-trial interaction effect is fixed across trials. Continuous covariates were centred on the mean value within each trial; binary covariates were centred on the proportion within each trial.

Sensitivity analyses

To test the robustness of the primary and secondary analyses, we undertook a number of prespecified sensitivity analyses: we excluded the largest trial (HF-ACTION[19]); truncated outcomes at 1, 2 and 5 years' follow-up; and included trial-level outcome data for studies that could not provide IPD.[26]

Impact of ExCR on health-related quality of life and exercise capacity

Inclusion of trials

Trials were included in the HRQoL and exercise capacity analyses if IPD was provided for the one or more of the outcomes of interest detailed below.

Outcomes of interest

The final patient-relevant outcomes of interest in this study were:

- HRQoL measured using the MLHFQ score
- HRQoL measured through any validated scale
- exercise capacity measured using VO_2peak (ml/kg/minute)
- exercise capacity measured using the 6-minute walk test (6MWT) (m)
- exercise capacity measured using a standardised exercise capacity score calculated from any of the four validated exercise capacity measures [i.e. VO_2peak, 6MWT, incremental shuttle walk test (ISWT) and workload on cycle ergometer].

Health-related quality of life: scales of measurement

Health-related quality of life measured using one of the following three validated measures was included in this analysis:

1. the MLHFQ[36]
2. the Kansas City Cardiomyopathy Questionnaire[37]
3. the Guyatt *et al.*[38] Chronic Heart Failure Questionnaire scale.

The first HRQoL analysis was carried out for trials providing the MLHFQ data; the second analysis used a standardised score calculated from any of the three measures above.

Exercise capacity: scales of measurement

Exercise capacity measured using one of four validated measures was included in this analysis:

1. VO_2peak (ml/kg/minute)
2. distance (m) walked on the 6MWT
3. distance (m) walked in an ISWT
4. workload on cycle ergometer (watts).

Exercise capacity analysis was carried out for:

- trials providing VO_2peak
- trials providing the 6MWT
- a standardised exercise capacity score, calculated from any of the validated exercise capacity measures listed above.

One study, HF-ACTION,[19] provided data on both VO_2peak and the 6MWT, and was included in all analyses, with the VO_2peak measure taking precedence for the standardised exercise capacity analysis.

Primary analysis

The primary analyses included one- and two-stage IPD meta-analyses carried out at 6 and 12 months. At each time point, we used the observation closest to and prior to the time point. All one-stage IPD models used a hierarchical random-effects regression model, adjusted for the baseline value of the outcome measure. All two-stage models used random treatment effects. We performed a series of models to estimate the overall treatment effect and to investigate potential interactions between ExCR and predefined patient subgroups (i.e. age, sex, left ventricular ejection fraction, HF aetiology, NYHA class and baseline exercise capacity[23,27]). Each model investigated one interaction effect only. The I^2 and τ^2 statistics were reported alongside the associated *p*-value for the results of the main analyses.[29,32]

Secondary analysis

The secondary analyses used a random-effects hierarchical model for repeated measures at multiple time points. These models utilised HRQoL and exercise capacity outcome data at all available time points. Adjustments for baseline values of the outcome measure were made; no other covariates were included in the model. This model included a time-by-treatment interaction term.

Sensitivity analyses

To test the robustness of the primary analyses, prespecified sensitivity analyses were carried out:

- the primary analysis was repeated after exclusion of the largest trial (HF-ACTION[19])
- data was added from studies that did not provide IPD.

Surrogate analyses

Inclusion of trials

All studies in the ExTraMATCH II meta-analysis were eligible for inclusion in the surrogate analyses, dependent on the availability of data on exercise capacity and final patient-relevant outcomes, as explained below.

Outcomes of interest

The final patient-relevant outcomes of interest in this validation study were:

- HRQoL measured by MLHFQ score
- HRQoL measured through any validated scale
- time to all-cause mortality
- time to all-cause hospital admission.

For this study, three approaches to exercise capacity definition were used:

1. direct assessed VO_2peak
2. 6MWT
3. direct and indirect VO_2peak (conversion from the 6MWT and the ISWT; no conversion was possible for watts as it is dependent on the body weight of individual patients).

Distances recorded as either 6MWT or ISWT at baseline were converted to VO_2peak using previously reported methods.[39–43] Details can be found in *Appendix 5*.

Follow-up time considerations

The following outcome follow-up times were considered: $\leq$ 6 months for exercise capacity outcomes, $\leq$ 12 months for HRQoL outcomes and all available follow-up time for mortality and hospitalisation. This approach was consistent with the assumption of temporal antecedence for a causal relationship between the surrogate end point and the final outcomes.

Mediation analysis

Mediation is known as the phenomenon whereby a cause affects an intermediate variable (also called mediator), and the change in the intermediate variable goes on to affect the outcome.[44,45] The effect of the cause on the outcome that operates through the intermediate of interest is sometimes referred to as an indirect or mediated effect. Mediation analysis usually refers to the set of techniques by which a researcher assesses the relative magnitude of these direct and indirect effects. The product method specification of this approach was used to determine whether or not a change in VO_2peak (ΔVO_2peak) or a change in the 6MWT result (Δ6MWT) mediate the relationship between treatment assignment (i.e. ExCR vs. no ExCR), and each of the final outcomes of interest. Linear or Cox regression analyses were conducted to evaluate the following four hypotheses:

1. Treatment assignment (i.e. ExCR vs. control) has a significant effect on ΔVO_2peak or Δ6MWT from baseline to 6 months' follow-up.
2. ΔVO_2peak or Δ6MWT have a significant effect on ΔMLHFQ or ΔHRQoL, or on the hazards of developing a clinical event.
3. Treatment assignment (i.e. ExCR vs. control) has a significant effect on ΔMLHFQ or ΔHRQoL, or on the hazards of developing a clinical event.
4. The effect of treatment assignment (i.e. ExCR vs. control) on ΔMLHFQ or ΔHRQoL, or on the hazards of developing a clinical event, is attenuated when ΔVO_2peak or Δ6MWT is added to the model.

All regression models took into account the clustering within trials to allow for study-level differences in treatment effect and unstructured covariance between random intercept and random slope. Regression models were adjusted for baseline of either exercise capacity values or baseline HRQoL values. No other adjustments were made, because patients were randomly assigned to intervention or control arm. In testing hypothesis (2), no adjustment is made for potential confounding variables.

It was assumed necessary to reject the null for at least the first of these hypotheses (i.e. the treatment assignment is associated with the mediator), to support the validation of ΔVO_2peak or Δ6MWT as mediator end points and proceed further with the estimation of proportion explained or proportion mediated.

Meta-analytic approach: R^2 and surrogate threshold effect

Although mediation analysis considers pathways by which treatment effects may arise, surrogacy principally concerns whether or not we are able to predict the effect of treatment on the final end point by using the effect of treatment on the surrogate.

Given the issues described with the proportion explained and indirect effects approaches in identifying consistent surrogates, the meta-analytic approach may offer the most promise for assessing surrogate outcomes and for making policy and treatment decisions.[46,47] This approach requires multiple studies, or at least multiple subgroups (e.g. centres within a trial), which we have through the ExTraMATCH II IPD meta-analysis. As a true and strong association between the treatment effect on the final end point and the treatment effect on the surrogate is considered to be the hallmark of surrogacy,[47] this approach proceeds as follows. Let ϕ_j denote the estimate of the effect of treatment on the final outcome in the jth study, let θ_j denote the estimate of the effect of treatment on the surrogate outcome in the jth study, both derived from RCTs. For a good surrogate, a monotonic relationship would exist between ϕ_j and θ_j and, in a regression of ϕ_j on θ_j, there would be limited variability around the regression line. If the relationship between ϕ_j and θ_j is approximately linear, a reasonable measure of surrogacy is the R^2_{trial} of the regression of ϕ_j on θ_j. Another intuitive measure recommended as a surrogacy metric is the surrogate threshold effect (STE), which takes into account the variability around the regression line and represents the intercept of the prediction band of the regression line with the zero effect line on the final outcome.[46] For each trial, we estimated study-level treatment effects by conducting linear regression or Cox proportional hazards regression models. Adjustment was made for baseline exercise capacity or HRQoL values. Then we conducted linear meta-regressions to relate estimated difference in exercise capacity to

the estimated effect on change in HRQoL: log(HR) of all-cause mortality or log(HR) of all-cause hospitalisation events. The square of the inverse standard error was used as a weight to account for uncertainty in the estimated patient-relevant outcomes effect. We calculated commonly reported indicators of surrogate validation.[48] The correlation coefficient (*p*-value) and the R^2 for the relationship between treatment effect difference on exercise capacity and each of the final outcomes was estimated individually using weighting by the inverse of the variance (for the treatment effect on final outcomes). In order to estimate STE, prediction bands were calculated based on approximate prediction intervals.[48,49]

Chapter 4 Characteristics and quality of included studies

Identification of trials for inclusion in the ExTraMATCH II master data set

A total of 23 trials were deemed eligible for the ExTraMATCH II IPD meta-analysis. Data from six trials had been analysed previously and were available from the ExTraMATCH database.[50–55] Fourteen investigators responded positively and shared their de-identified trial data directly.[19,56–68]

Exclusion of eligible trials from the ExTraMATCH II master data set

We were unable to include data from three trials (355 patients): for two trials data were no longer available[69,70] and the investigators of the other trial could not be contacted.[71] After obtaining IPD, a further trial[72] was excluded, as it was determined that it included patient data that overlapped with another trial.[62] We therefore had a total of 19 trials in the ExTraMATCH II study,[19,50–67] with a total of 3900 patients. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[22] flow diagram to show inclusion and exclusion of trials in the ExTraMATCH II study is shown in *Figure 1*. Further flow diagrams to show inclusion and exclusion of trials and participants within individual analyses are given in the appropriate results sections.

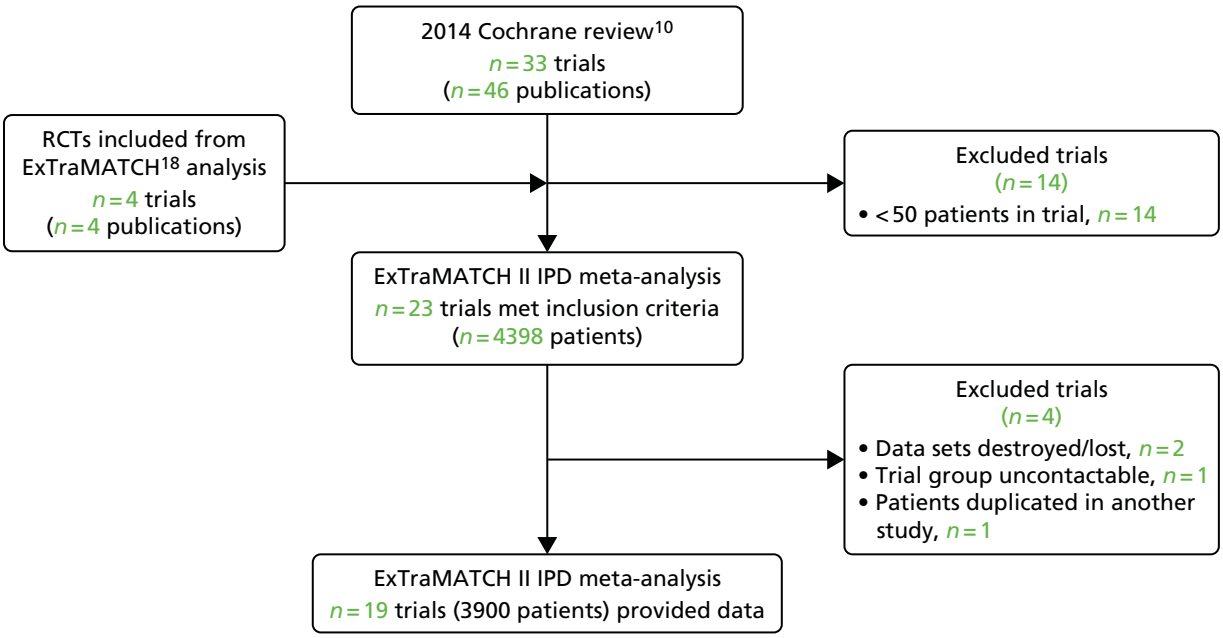


FIGURE 1 The PRISMA flow diagram summarising the selection of studies for the ExTraMATCH II study.

Characteristics of included patients

Patient characteristics at baseline were well balanced between ExCR and control patients. The majority of patients were male (74%), with a mean age of 61 years [standard deviation (SD) 13 years]. The mean baseline left ventricular ejection fraction was 26.7% (SD 8.1%), and most patients were in NYHA functional class II (59%) or III (37%) (*Table 1*). No included trials recruited patients with HFpEF (i.e. an ejection fraction of > 45%).

Characteristics of included trials

Trials were from Europe and North America and were published between 1990 and 2012. Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention, which was most commonly delivered in either an exclusively centre-based setting or a centre-based setting in combination with some home exercise sessions. The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 12–90 weeks, with between two and seven sessions per week (median session duration was between 15 and 120 minutes, including warm-up and cool-down). The intensity of exercise ranged between 50% and 85% VO_2peak (*Table 2*).

Assessment of study quality and risk of bias in included trials

The overall quality of included trials was judged to be moderate to good, with a median TESTEX score of 11 (range 9–14) out of a maximum score of 15 (*Table 3*).

TABLE 1 Baseline characteristics of patients in the ExTraMATCH II master data set

Characteristic	ExCR (*N* = 1986)	Control (*N* = 2003)	All (*N* = 3989)
Age (years), mean (SD)	61.4 (12.8)	61.5 (13.1)	61.4 (13.0)
Gender, *n* (%)			
Male	1455 (73.3)	1511 (75.4)	2966 (74.4)
Female	531 (26.7)	492 (24.6)	1023 (25.7)
Baseline ejection fraction (%); mean (SD)	27.2 (8.8)	26.9 (8.7)	26.9 (8.7)
NYHA status, *n* (%)			
Class I	25 (1.3)	29 (1.5)	54 (1.4)
Class II	1124 (58.6)	1148 (59.5)	2272 (59.0)
Class III	721 (37.6)	728 (37.7)	1449 (37.7)
Class IV	47 (2.5)	26 (1.4)	73 (1.9)
Aetiology, *n* (%)			
Ischaemic	1067 (57.3)	1055 (56.1)	2122 (56.7)
Non-ischaemic	796 (42.7)	826 (43.9)	1622 (43.3)
Ethnicity, *n* (%)			
White	1130 (70.2)	1163 (71.8)	2293 (71.0)
Non-white	480 (29.8)	458 (28.3)	938 (29.0)
VO_2peak (ml/kg/minute), mean (SD)	14.9 (4.3)	15.0 (4.6)	15.0 (4.4)

Note
Percentages may not sum to 100 because of rounding.

TABLE 2 Characteristics of included trials in the ExTraMATCH II master data set

Study characteristic	*n* (%), unless otherwise stated
Publication year	
1990–99	2 (10.5)
2000–9	12 (63.2)
2010–12	4 (21.0)
Unpublished	1 (5.3)
Main study location	
Europe	14 (73.7)
North America[a]	5 (26.3)
Study centre	
Single	13 (68.4)
Multiple	5 (26.3)
Not reported	1 (5.3)
Sample size	
0–99	11 (57.9)
100–999	7 (36.8)
≥ 1000	1 (5.3)
Duration of follow-up in data set (months), median (interquartile range)	
Mortality	29 (24–40)
Intervention characteristic	
Intervention type	
Exercise-only programmes	13 (68.4)
Comprehensive programmes	5 (26.3)
Not reported	1 (5.3)
Type of exercise	
Aerobic exercise only	12 (63.2)
Aerobic plus resistance training	6 (31.6)
Not reported	1 (5.3)
Dose of intervention	
Duration of intervention (weeks), median (range)	30 (15–90)
Frequency (sessions/week), median (range)	2.5 (2–6.5)
Length of exercise session (minutes), median (range)	24 (4–120)
Exercise intensity (range)	50–85% VO_2peak
	11–15 Borg rating
Setting	
Centre based	14 (73.7)
Home based	4 (21.1)
Not reported	1 (5.3)

Borg, Borg Scale of Perceived Exertion.
a HF-ACTION study[19] was categorised as North America, but was also delivered to a small number of patients in France.

TABLE 3 Assessment of quality using TESTEX scale for trials in ExTraMATCH II

First author/ study (year)	Eligibility criteria specified	Randomisation specified	Allocation concealed	Groups similar at baseline	Blinding of assessors	Outcome measures in > 85% of participants[a]	Intention-to-treat analysis[b]	Between-group statistical comparisons reported[c]	Point measures and measures of variability reported	Activity monitoring in control group	Relative exercise intensity reviewed	Exercise volume and energy expended	Overall TESTEX score (maximum score of 15)
Belardinelli *et al.* (1999)[50]	1	0	0	1	0	3	1	1	1	0	0	1	9
Belardinelli *et al.* (2012)[56]	1	0	0	1	0	3	1	1	1	0	0	1	9
DANREHAB (2008)[57]	1	1	0	1	1	3	1	2	1	0	0	0	11
Dracup *et al.* (2007)[58]	1	0	0	1	0	3	1	2	1	1	1	1	10
Gary *et al.* (2010)[59]	1	1	0	1	1	3	1	2	1	0	0	0	11
Giannuzzi *et al.* (2003)[60]	1	0	0	1	0	2	1	2	1	0	1	1	10
Hambrecht *et al.* (2000)[51]	1	1	0	1	0	3	0	2	1	0	1	1	11
HF-ACTION (2009)[19]	1	1	1	1	1	3	1	2	1	1	0	1	14
Jolly *et al.* (2009)[61]	1	1	1	1	0	2	1	2	1	0	1	1	12
McKelvie *et al.* (2002)[52]	1	1	1	1	1	2	1	1	1	0	1	1	12
Mueller *et al.* (2007)[62]	1	0	0	1	0	2	1	2	1	0	1	1	10
Nilsson *et al.* (2008)[63]	1	1	0	1	1	2	1	2	1	0	0	1	11
Passino *et al.* (2006)[67]	1	0	0	1	0	2	1	2	1	0	1	1	10
Wielenga *et al.* (1999)[53]	1	0	0	1	0	2	1	2	1	0	0	1	9
Willenheimer *et al.* (2001)[54]	1	0	0	1	1	2	1	2	1	0	0	1	9
Witham *et al.* (2005)[64]	1	1	0	1	1	3	1	2	1	0	1	0	12
Witham *et al.* (2012)[65]	1	1	0	1	1	3	1	2	1	0	1	0	12
Yeh *et al.* (2011)[66]	1	1	0	1	1	3	1	2	1	1	0	0	12
Zanelli *et al.* (1997)[55]	No score[d]												

DANREHAB, DANish Cardiac ReHABilitation trial.

a Three points possible.

b If intention to treat was not specifically mentioned, but it was noted that no participants withdrew and all were analysed, then 1 point was awarded.

c Two points possible.

d Not scored as no full publication.

Chapter 5 Impact of exercise-based cardiac rehabilitation on mortality and hospitalisation

One trial that provided IPD was not included in the mortality and hospitalisation analyses, as no data were provided to allow calculation of survival time or time to hospitalisation.[59] This resulted in the inclusion of 18 trials,[19,50,51,53–58,60–67,73] comprising 3912 patients (1948 ExCR patients and 1964 control patients), with a median follow-up of 19 months for mortality outcomes and 11 months for hospitalisation outcomes. *Figure 2* summarises the study selection process for the mortality and hospitalisation analyses.

Characteristics of included patients and trials

Patient baseline characteristics were well balanced between ExCR patients and control patients (*Table 4*). The majority of patients were male (75%), with a mean age of 61 years (SD 13 years). The mean baseline left ventricular ejection fraction was 27% (SD 8.1%), no included studies recruited patients with HFpEF (i.e. an ejection fraction of > 45%), and most patients were in NYHA functional class II (59%) or III (37%). Studies were published between 1999 and 2012 across a number of countries (see *Table 2*). Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention; six also included resistance training.[52,57,58,61,64,65] Exercise training was most commonly delivered in either an exclusively centre-based setting or a centre-based setting in combination with some home exercise sessions (*Table 5*). Three trials were conducted in an exclusively home-based setting.[52,54,58] The dose of exercise training ranged widely across studies, with an average session duration of 15–120 minutes (including warm-up and cool-down), two to seven sessions per week, of exercise intensity equivalent of 50–85% VO_2peak and delivery duration of 12–90 weeks.

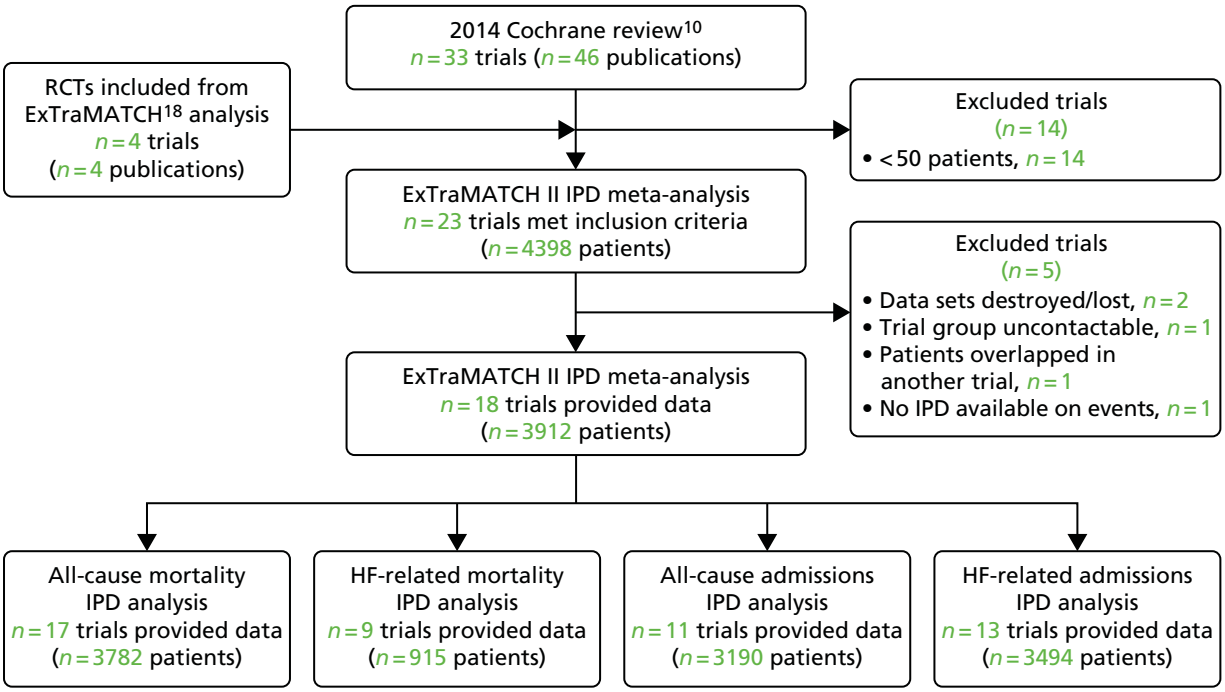


FIGURE 2 The PRISMA flow diagram summarising the selection of studies for mortality and hospitalisation analyses.

TABLE 4 Baseline characteristics of patients in the mortality and hospitalisation analyses

Characteristic	ExCR (*N* = 1948)	Control (*N* = 1964)	All (*N* = 3912)
Age (years), mean (SD)	61.3 (12.7)	61.4 (13.2)	61.3 (13.0)
Gender, *n* (%)			
Male	1442 (74)	1489 (76)	2931 (75)
Female	506 (26)	475 (24)	981 (25)
Baseline ejection fraction (%), mean (SD)	26.8 (8.2)	26.7 (8.1)	26.7 (8.1)
NYHA status, *n* (%)			
Class I	25 (1)	28 (1)	53 (1)
Class II	1107 (59)	1130 (60)	2237 (59)
Class III	700 (37)	708 (37)	1408 (37)
Class IV	47 (3)	26 (1)	73 (2)
Aetiology, *n* (%)			
Ischaemic	1094 (57)	1080 (56)	2174 (57)
Non-ischaemic	809 (43)	838 (44)	1647 (43)
Ethnicity, *n* (%)			
White	1100 (70)	1140 (72)	2240 (71)
Non-white	472 (30)	445 (28)	917 (29)
VO_2peak (ml/kg/minute), mean (SD)	14.9 (4.4)	15.0 (4.6)	14.9 (4.5)

Note
Percentages may not sum to 100 because of rounding.

TABLE 5 Characteristics of included trials in the mortality and hospitalisation analyses

Study characteristic	*n* (%), unless otherwise stated
Publication year	
1990–9	2 (11)
2000–9	12 (67)
2010–12	3 (17)
Unpublished	1 (6)
Main study location	
Europe	14 (78)
North America[a]	4 (22)

TABLE 5 Characteristics of included trials in the mortality and hospitalisation analyses (*continued*)

Study characteristic	*n* (%), unless otherwise stated
Study centre	
Single	12 (67)
Multiple	5 (28)
Not reported	1 (6)
Sample size	
0–99	10 (56)
100–999	7 (39)
≥ 1000	1 (6)
Duration of follow-up in data set (months), median (range)	
Mortality	18.6 (11.8–419)
Hospitalisation	11.2 (2.6–98)
Intervention characteristic	
Intervention type	
Exercise-only programmes	5 (28)
Comprehensive programmes	12 (67)
Not reported	1 (6)
Type of exercise	
Aerobic exercise only	12 (67)
Aerobic plus resistance training	6 (33)
Dose of intervention	
Duration of intervention (weeks), median (range)	30 (12–90)
Frequency (sessions/week), median (range)	2.8 (2–7)
Length of exercise session (minutes), median (range)	24 (15–120)
Exercise intensity (range)	40–80% maximum heart rate
	50–85% VO_2peak
	12–18 Borg rating
Setting	
Centre based	6 (33)
Home based	3 (17)
Centre and home based	8 (44)
Not reported	1 (6)

Borg, Borg Scale of Perceived Exertion.
a HF-ACTION study[19] was categorised as North America, but was also delivered to a small number of patients in France.
Note
Percentages may not sum to 100 because of rounding.

Assessment of study quality and risk of bias

There was no evidence of significant small-study bias for the four outcomes (*Figure 3*). The overall quality of included trials was judged to be moderate to good, with a median TESTEX[31] score of 11 (range 9–14) out of a maximum score of 15 (*Table 6*). The criteria of allocation concealment and physical activity monitoring in the control groups were met in only three studies;[19,58,66] the other TESTEX criteria were met in ≥ 50% of the trials.

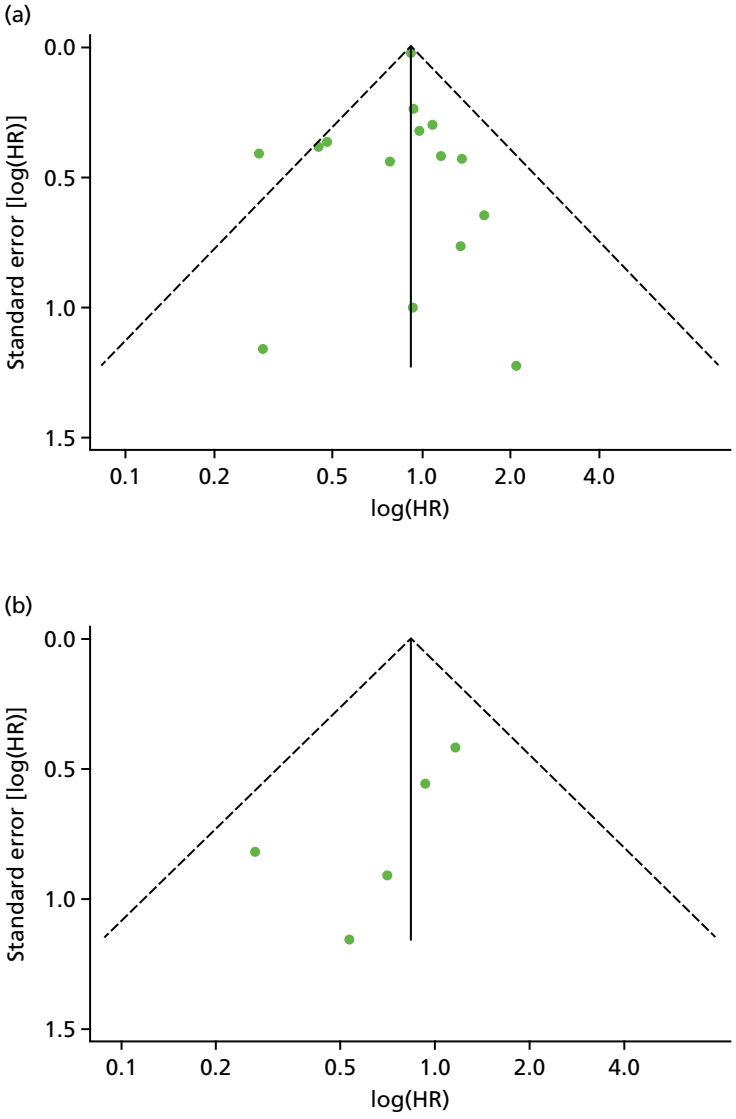


FIGURE 3 Funnel plots for mortality and hospitalisation analyses. (a) All-cause mortality, Egger's test –0.26, $p = 0.458$; (b) HF-specific mortality, Egger's test –1.60, $p = 0.147$; (c) all-cause hospitalisation, Egger's test 0.16, $p = 0.739$; and (d) HF-specific hospitalisation, Egger's test 0.32, $p = 0.610$. (*continued*)

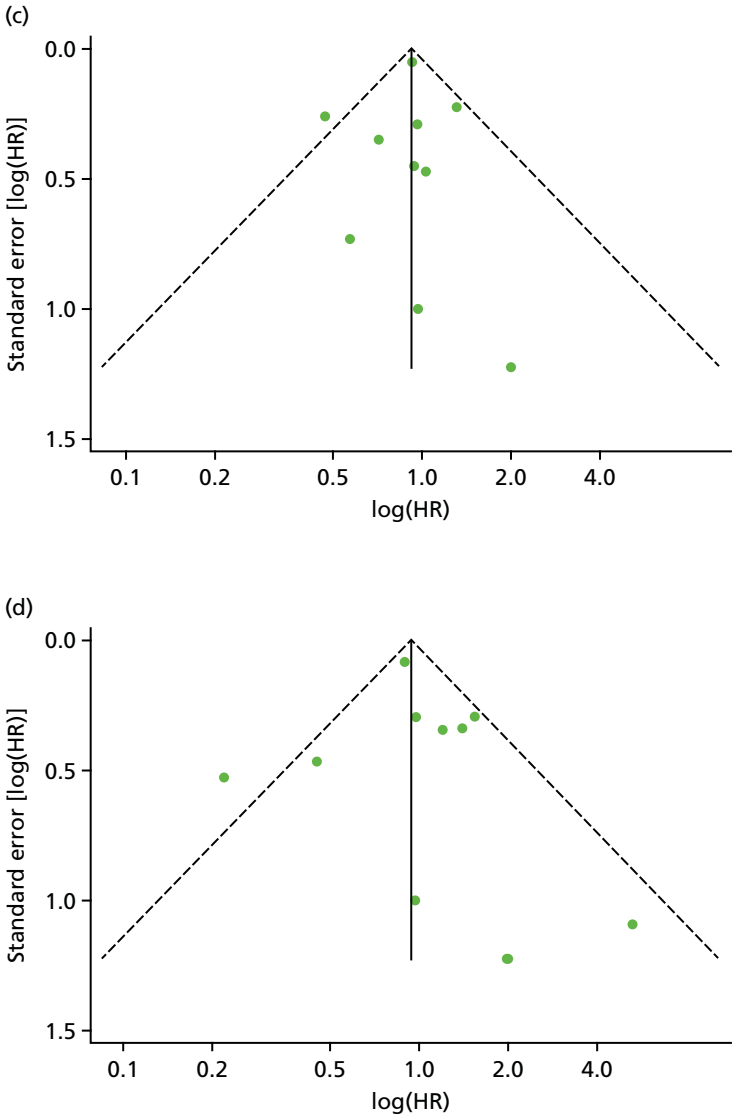


FIGURE 3 Funnel plots for mortality and hospitalisation analyses. (a) All-cause mortality, Egger's test –0.26, $p = 0.458$; (b) HF-specific mortality, Egger's test –1.60, $p = 0.147$; (c) all-cause hospitalisation, Egger's test 0.16, $p = 0.739$; and (d) HF-specific hospitalisation, Egger's test 0.32, $p = 0.610$.

Findings

Primary analysis

Compared with control, all time-to-event mean treatment effects from the two-stage random-effects IPD meta-analysis were in favour of ExCR, but had wide CIs and were not statistically significant [all-cause mortality: HR 0.83 (95% CI 0.67 to 1.04; $p = 0.107$, 17 studies,[19,50–55,57,58,60–67] 3782 patients, $\tau^2 = 0.04$, $I^2 = 26\%$); HF-specific mortality: HR 0.84 (95% CI 0.48 to 1.46; $p = 0.527$, 9 studies,[51–54,58,60,64,65,67] 915 patients, $\tau^2 = 0.00$, $I^2 = 0\%$); all-cause hospitalisation: HR 0.90 (95% CI 0.76 to 1.06; $p = 0.210$, 11 studies,[19,51,54,55,57,58,60,61,64–66] 3190 patients, $\tau^2 = 0.01$, $I^2 = 12.4\%$); and HF-specific hospitalisation: HR 0.98 (95% CI 0.72 to 1.35; $p = 0.902$, 13 studies,[19,50,51,52,56–58,60,61,64–67] 3494 patients, $\tau^2 = 0.10$, $I^2 = 45\%$)] (*Figure 4* and *Tables 7–10*).

TABLE 6 Assessment of quality using TESTEX scale[31] of included studies in mortality and hospitalisation analysis

First author/ study (year)	Eligibility criteria specified	Randomisation specified	Allocation concealed	Groups similar at baseline	Blinding of assessors	Outcome measures in > 85% of participants[a]	Intention-to-treat analysis[b]	Between-group statistical comparisons reported[c]	Point measures and measures of variability reported	Activity monitoring in control group	Relative exercise intensity reviewed	Exercise volume and energy expended	Overall TESTEX score (maximum score of 15)
Belardinelli *et al.* (1999)[50]	1	0	0	1	0	3	1	1	1	0	0	1	9
Belardinelli *et al.* (2012)[56]	1	0	0	1	0	3	1	1	1	0	0	1	9
DANREHAB (2008)[57]	1	1	1	1	1	3	1	2	1	0	0	0	12
Dracup *et al.* (2007)[58]	1	0	0	1	0	3	1	2	1	1	1	1	10
Giannuzzi *et al.* (2003)[60]	1	0	0	1	0	2	1	2	1	0	1	1	10
Hambrecht *et al.* (2000)[51]	1	1	0	1	0	3	0	2	1	0	1	1	11
HF-ACTION (2009)[19]	1	1	1	1	1	3	1	2	1	1	0	1	14
Jolly *et al.* (2009)[61]	1	1	1	1	0	2	1	2	1	0	1	1	12
McKelvie *et al.* (2002)[52]	1	1	1	1	1	2	1	1	1	0	1	1	12
Mueller *et al.* (2007)[62]	1	0	0	1	0	2	1	2	1	0	1	1	10
Nilsson *et al.* (2008)[63]	1	1	0	1	1	2	1	2	1	0	0	1	11
Passino *et al.* (2006)[67]	1	0	0	1	0	2	1	2	1	0	1	1	10
Wielenga *et al.* (1999)[53]	1	0	0	1	0	2	1	2	1	0	0	1	9
Willenheimer *et al.* (2001)[54]	1	0	0	1	1	2	1	2	1	0	0	1	9
Witham *et al.* (2005)[64]	1	1	0	1	1	3	1	2	1	0	1	0	12
Witham *et al.* (2012)[65]	1	1	0	1	1	3	1	2	1	0	1	0	12
Yeh *et al.* (2011)[66]	1	1	0	1	1	3	1	2	1	1	0	0	12
Zanelli *et al.* (1997)[55]	No score[d]												

DANREHAB, DANish Cardiac ReHABilitation trial.

a Three points possible.

b If intention to treat was not specifically mentioned, but it was noted that no participants withdrew and all were analysed, then 1 point was awarded.

c Two points possible.

d Not scored as no full publication.

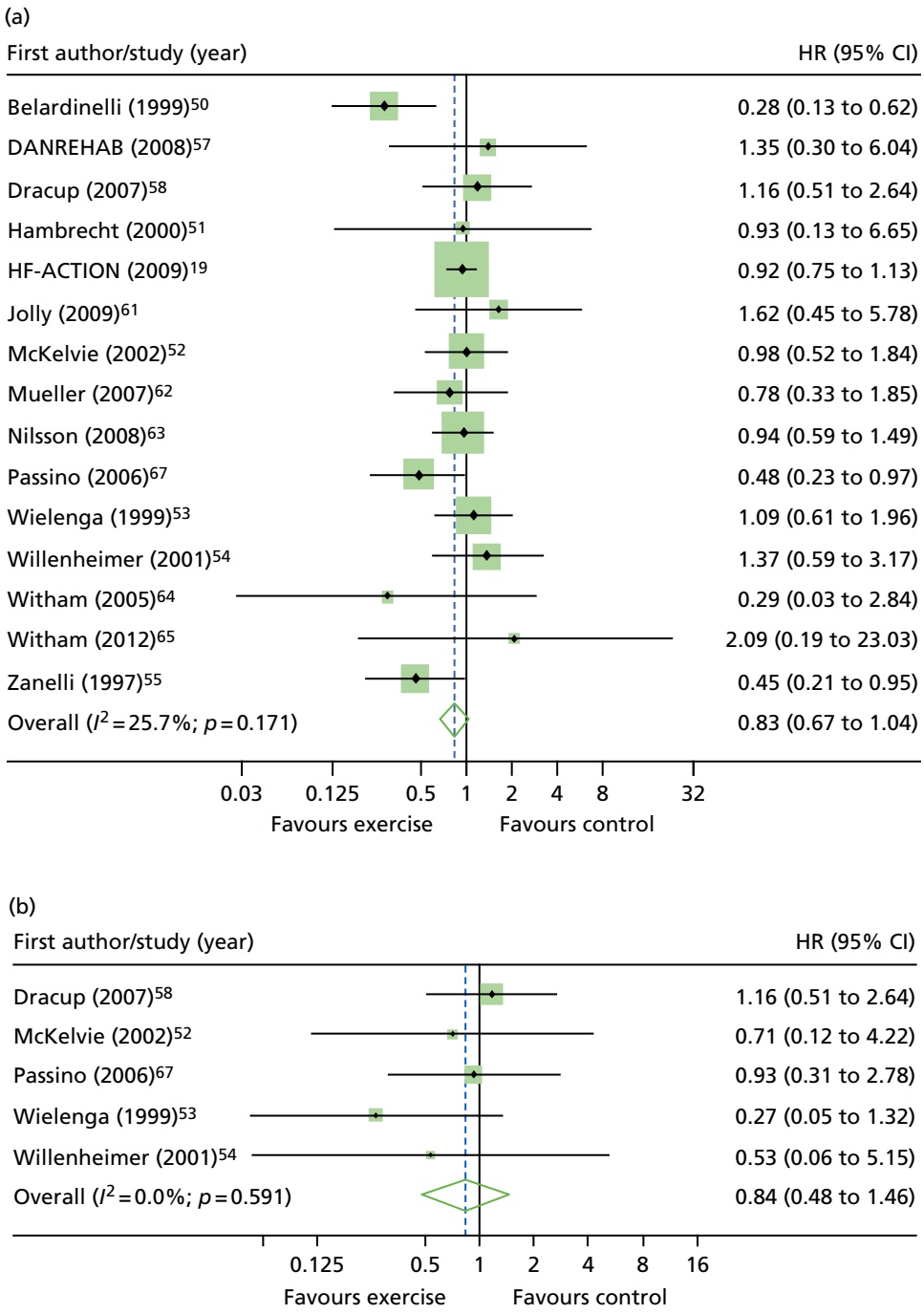


FIGURE 4 Effect of ExCR on mortality and hospitalisation across patient subgroups: two-stage IPD meta-analysis. (a) All-cause mortality; (b) HF-specific mortality; (c) all-cause hospitalisation; and (d) HF-specific hospitalisation. DANREHAB, DANish Cardiac ReHABilitation trial. (*continued*)

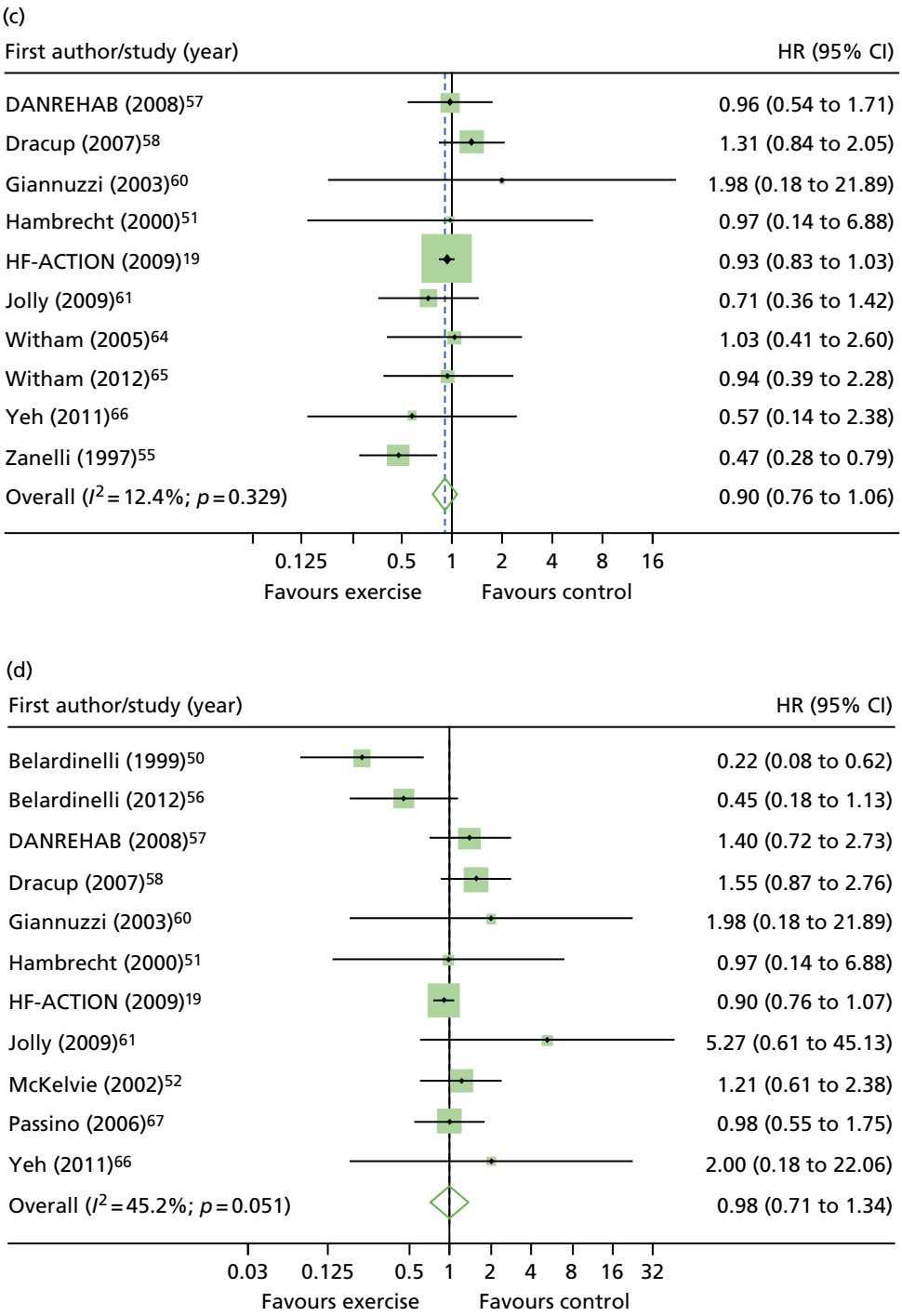


FIGURE 4 Effect of ExCR on mortality and hospitalisation across patient subgroups: two-stage IPD meta-analysis. (a) All-cause mortality; (b) HF-specific mortality; (c) all-cause hospitalisation; and (d) HF-specific hospitalisation. DANREHAB, DANish Cardiac ReHABilitation trial.

TABLE 7 All-cause mortality: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analysis, HR (95% CI); *p*-value	Secondary analysis, HR (95% CI); *p*-value	Sensitivity analyses, HR (95% CI); *p*-value				
	Two-stage model, random effects	One-stage Cox model, stratified by study with fixed treatment effect	Two-stage model, random effects excluding HF-ACTION[19]	One-stage Cox model, stratified by study with fixed effect excluding HF-ACTION[19]	Two-stage model, random effects 1-year truncation	Two-stage model, random effects 2-year truncation	Two-stage model, random effects 5-year truncation
Overall effect	0.83 (0.67 to 1.04); 0.107	0.85 (0.73 to 0.99); 0.034	0.81 (0.61 to 1.06); 0.129	0.79 (0.64 to 0.97); 0.027	0.87 (0.58 to 1.31); 0.507	0.86 (0.67 to 1.10); 0.217	0.84 (0.66 to 1.06); 0.140
Interaction term							
Age (years)	0.99 (0.98 to 1.00); 0.165	0.99 (0.98 to 1.01); 0.254	0.98 (0.96 to 1.01); 0.144	0.99 (0.96 to 1.01); 0.228	0.98 (0.95 to 1.00); 0.077	0.98 (0.96 to 1.00); 0.034	0.99 (0.97 to 1.00); 0.097
Gender (male vs. female)	1.10 (0.73 to 1.66); 0.660	1.06 (0.70 to 1.60); 0.783	0.71 (0.35 to 1.43); 0.341	0.70 (0.36 to 1.36); 0.300	0.76 (0.34 to 1.68); 0.490	0.96 (0.55 to 1.67); 0.872	1.17 (0.75 to 1.82); 0.481
Ejection fraction (%)	0.99 (0.97 to 1.01); 0.250	0.99 (0.97 to 1.01); 0.332	0.98 (0.95 to 1.01); 0.124	0.98 (0.96 to 1.01); 0.201	1.04 (1.00 to 1.08); 0.055	0.99 (0.97 to 1.02); 0.688	0.99 (0.97 to 1.01); 0.506
NYHA class (NYHA class I/II vs. NYHA class III/IV)	0.80 (0.58 to 1.11); 0.182	0.79 (0.57 to 1.08); 0.134	0.82 (0.49 to 1.38); 0.459	0.75 (0.46 to 1.22); 0.244	0.50 (0.23 to 1.07); 0.073	0.84 (0.54 to 1.30); 0.431	0.83 (0.59 to 1.18); 0.297
HF aetiology (ischaemic vs. non-ischaemic)	0.73 (0.38 to 1.39); 0.335	1.19 (0.86 to 1.64); 0.297	0.69 (0.36 to 1.31); 0.255	0.87 (0.54 to 1.41); 0.575	0.69 (0.19 to 2.54); 0.574	0.79 (0.38 to 1.67); 0.542	0.70 (0.33 to 1.47); 0.345
Ethnic group (white vs. non-white)	1.12 (0.74 to 1.69); 0.593	1.11 (0.74 to 1.68); 0.604	[a]	1.05 (0.25 to 4.31); 0.949	0.72 (0.34 to 1.53); 0.396	0.83 (0.50 to 1.38); 0.468	1.12 (0.74 to 1.69); 0.593
Exercise capacity							
Baseline VO_2peak directly measured	1.00 (0.95 to 1.05); 0.937	0.99 (0.95 to 1.04); 0.783	0.98 (0.90 to 1.08); 0.712	0.99 (0.91 to 1.07); 0.777	0.97 (0.88 to 1.06); 0.456	0.99 (0.93 to 1.05); 0.780	0.98 (0.91 to 1.06); 0.630
Baseline VO_2peak directly measured and predicted	1.00 (0.95 to 1.06); 0.903	1.00 (0.96 to 1.04); 0.954	1.00 (0.91 to 1.08); 0.923	1.00 (0.93 to 1.07); 0.984	0.99 (0.90 to 1.08); 0.734	1.00 (0.94 to 1.06); 0.961	1.00 (0.93 to 1.07); 0.924
Standardised scores using baseline VO_2peak, 6MWT, ISWT units and watts score	1.03 (0.83 to 1.27); 0.802	1.02 (0.85 to 1.22); 0.851	0.99 (0.71 to 1.39); 0.955	1.01 (0.75 to 1.35); 0.967	0.97 (0.66 to 1.41); 0.858	1.00 (0.78 to 1.30); 0.972	1.01 (0.76 to 1.35); 0.938

a Study estimate not available as too few studies provide data.

TABLE 8 Heart failure-specific mortality: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analysis, HR (95% CI); *p*-value	Secondary analysis, HR (95% CI); *p*-value	Sensitivity analyses, HR (95% CI); *p*-value		
	Two-stage model, random effects	One-stage Cox model, stratified by study with fixed treatment effect	Two-stage model, random effects 1-year truncation	Two-stage model, random effects 2-year truncation	Two-stage model, random effects 5-year truncation
Overall effect	0.84 (0.48 to 1.46); 0.527	0.75 (0.44 to 1.28); 0.294	[a]	1.30 (0.59 to 2.87); 0.515	0.84 (0.49 to 1.53); 0.575
Interaction term					
Age (years)	0.96 (0.91 to 1.02); 0.206	0.96 (0.92 to 1.01); 0.162	[a]	0.91 (0.84 to 0.98); 0.017	0.95 (0.90 to 1.00); 0.066
Gender (male vs. female)	0.53 (0.08 to 3.73); 0.524	0.61 (0.11 to 3.49); 0.583	[a]	[b]	[b]
Ejection fraction (%)	0.95 (0.89 to 1.02); 0.159	0.96 (0.90 to 1.02); 0.179	[a]	1.01 (0.82 to 1.24); 0.912	0.96 (0.89 to 1.04); 0.309
NYHA class (NYHA class I/II vs. NYHA class III/IV)	0.54 (0.07 to 4.28); 0.562	0.78 (0.23 to 26.65); 0.691	[a]	[b]	0.54 (0.07 to 4.28); 0.562
HF aetiology (ischaemic vs. non-ischaemic)	Data only available for one study	3.30 (1.02 to 10.7); 0.047	[a]	[b]	[b]
Ethnic group (white vs. non-white)	[b]	[b]	[a]	[b]	[b]
Exercise capacity					
Baseline VO_2peak directly measured	0.90 (0.76 to 1.07); 0.232	0.93 (0.78 to 1.09); 0.362	[a]	0.98 (0.73 to 1.31); 0.893	0.86 (0.69 to 1.06); 0.146
Baseline VO_2peak directly measured and predicted	0.91 (0.77 to 1.07); 0.263	0.94 (0.80 to 1.10); 0.423	[a]	0.98 (0.76 to 1.26); 0.854	0.88 (0.72 to 1.06); 0.184
Standardised scores using baseline VO_2peak, 6MWT, ISWT units and watts score	0.69 (0.35 to 1.35); 0.276	0.82 (0.43 to 1.56); 0.545	[a]	0.86 (0.31 to 2.37); 0.773	0.61 (0.28 to 1.32); 0.210

a HF-ACTION[19] did not provide HF mortality so sensitivity analysis of omission not undertaken.
b Study estimate not available as too few studies provide data.

TABLE 9 All-cause hospitalisation: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analysis, HR (95% CI); *p*-value	Secondary analysis, HR (95% CI); *p*-value	Sensitivity analyses, HR (95% CI); *p*-value				
	Two-stage model, random effects	One-stage Cox model, stratified by study with fixed treatment effect	Two-stage model, random effects excluding HF-ACTION[19]	One-stage Cox model, stratified by study with fixed treatment effect excluding HF-ACTION[19]	Two-stage model, random effects 1-year truncation	Two-stage model, random effects 2-year truncation	Two-stage model, random effects 5-year truncation
Overall effect	0.90 (0.76 to 1.06); 0.210	0.91 (0.83 to 1.01); 0.072	0.86 (0.64 to 1.14); 0.293	0.85 (0.68 to 1.09); 0.210	0.94 (0.75 to 1.18); 0.583	0.91 (0.74 to 1.11); 0.330	0.90 (0.76 to 1.06); 0.210
Interaction term							
Age (years)	1.00 (0.99 to 1.01); 0.794	1.00 (0.99 to 1.01); 0.854	1.00 (0.98 to 1.03); 0.808	1.00 (0.98 to 1.02); –0.969	1.00 (0.99 to 1.01); 0.636	1.00 (0.99 to 1.01); 0.798	1.00 (0.99 to 1.01); 0.794
Gender (male vs. female)	1.09 (0.87 to 1.36); 0.454	1.09 (0.88 to 1.36); 0.424	0.66 (0.38 to 1.14); 0.136	0.68 (0.39 to 1.16); 0.158	1.05 (0.80 to 1.37); 0.745	1.15 (0.91 to 1.46); 0.239	1.09 (0.87 to 1.35); 0.454
Ejection fraction (%)	1.00 (0.98 to 1.01); 0.629	1.00 (0.98 to 1.01); 0.646	1.00 (0.96 to 1.04); 0.857	1.00 (0.96 to 1.05); 0.831	1.00 (0.98 to 1.01); 0.632	0.99 (0.98 to 1.01); 0.343	1.00 (0.98 to 1.01); 0.629
NYHA class (NYHA class I/II vs. NYHA class III/IV)	0.91 (0.74 to 1.12); 0.370	0.90 (0.73 to 1.10); 0.308	0.89 (0.43 to 1.87); 0.763	0.79 (0.39 to 1.60); 0.508	0.81 (0.63 to 1.05); 0.110	0.87 (0.70 to 1.09); 0.235	0.91 (0.74 to 1.12); 0.355
HF aetiology (ischaemic vs. non-ischaemic)	0.96 (0.71 to 1.31); 0.810	1.00 (0.82 to 1.22); 0.988	0.73 (0.39 to 1.39); 0.340	0.73 (0.40 to 1.31); 0.284	1.08 (0.84 to 1.38); 0.562	1.04 (0.84 to 1.29); 0.723	1.01 (0.83 to 1.24); 0.910
Ethnic group (white vs. non-white)	1.02 (0.83 to 1.26); 0.860	1.02 (0.83 to 1.26); 0.852	1.02 (0.47 to 2.21); 0.959	1.06 (0.49 to 2.32); 0.879	1.14 (0.88 to 1.48); 0.322	1.06 (0.85 to 1.33); 0.607	1.02 (0.83 to 1.26); 0.860
Exercise capacity							
Baseline VO_2peak directly measured	1.01 (0.99 to 1.04); 0.259	1.02 (0.99 to 1.04); 0.234	1.05 (0.95 to 1.16); 0.352	1.06 (0.96 to 1.17); 0.262	1.03 (0.99 to 1.06); 0.124	1.02 (0.99 to 1.04); 0.243	1.01 (0.99 to 1.04); 0.259
Baseline VO_2peak directly measured and predicted	1.02 (0.99 to 1.04); 0.153	1.02 (0.99 to 1.04); 0.134	1.07 (0.98 to 1.17); 0.125	1.08 (0.99 to 1.17); 0.078	1.03 (1.00 to 1.06); 0.057	1.02 (0.99 to 1.05); 0.129	1.02 (0.99 to 1.04); 0.153
Standardised scores using baseline VO_2peak, 6MWT, ISWT units and watts score	1.09 (0.98 to 1.22); 0.095	1.10 (0.99 to 1.22); 0.088	1.30 (0.93 to 1.83); 0.120	1.32 (0.95 to 1.82); 0.097	1.16 (1.02 to 1.33); 0.027	1.11 (0.99 to 1.24); 0.077	1.09 (0.98 to 1.22); 0.095

TABLE 10 Heart failure-specific hospitalisation: overall treatment effect and subgroup (interactions) effects in studies included in IPD meta-analysis

Baseline variable	Primary analysis, HR (95% CI); *p*-value	Secondary analysis, HR (95% CI); *p*-value	Sensitivity analyses, HR (95% CI); *p*-value				
	Two-stage model, random effects	One-stage Cox model, stratified by study with fixed treatment effect	Two-stage model, random effects excluding HF-ACTION[19]	One-stage Cox model, stratified by study with fixed treatment effect excluding HF-ACTION[19]	Two-stage model, random effects 1-year truncation	Two-stage model, random effects 2 year truncation	Two-stage model, random effects 5 year truncation
Overall effect	0.98 (0.72 to 1.35); 0.902	0.94 (0.81 to 1.08); 0.368	1.00 (0.65 to 1.54); 0.999	1.03 (0.79 to 1.35); 0.829	1.08 (0.88 to 1.33); 0.470	1.06 (0.83 to 1.34); 0.658	0.97 (0.70 to 1.34); 0.855
Interaction term							
Age (years)	1.00 (0.99 to 1.02); 0.603	1.00 (0.99 to 1.02); 0.632	1.00 (0.98 to 1.03); 0.958	1.00 (0.97 to 1.02); 0.906	1.00 (0.99 to 1.02); 0.640	1.00 (0.99 to 1.02); 0.611	1.00 (0.99 to 1.02); 0.580
Gender (male vs. female)	1.03 (0.73 to 1.46); 0.865	0.99 (0.71 to 1.39); 0.949	0.70 (0.32 to 1.53); 0.372	0.65 (0.33 to 1.29); 0.215	0.76 (0.46 to 1.24); 0.274	1.06 (0.68 to 1.66); 0.803	0.93 (0.49 to 1.75); 0.815
Ejection fraction (%)	0.51 (0.14 to 1.79); 0.291	0.99 (0.97 to 1.01); 0.325	0.99 (0.96 to 1.03); 0.540	0.99 (0.97 to 1.01); 0.350	0.99 (0.97 to 1.02); 0.569	0.99 (0.97 to 1.01); 0.350	0.99 (0.97 to 1.02); 0.569
NYHA class (NYHA class I/II vs. NYHA class III/IV)	1.55 (0.79 to 3.02); 0.200	1.14 (0.84 to 1.54); 0.399	2.05 (0.86 to 4.92); 0.107	1.74 (0.92 to 3.29); 0.089	0.81 (0.51 to 1.29); 0.375	1.17 (0.68 to 2.03); 0.573	1.21 (0.72 to 2.04); 0.475
HF aetiology (ischaemic vs. non-ischaemic)	1.20 (0.64 to 2.25); 0.577	1.28 (0.94 to 1.74); 0.111	0.95 (0.31 to 2.95); 0.928	1.10 (0.57 to 2.16); 0.771	1.47 (0.94 to 2.29); 0.128	1.28 (0.90 to 1.84); 0.172	1.29 (0.79 to 2.12); 0.309
Ethnic group (white vs. non-white)	1.18 (0.85 to 1.65); 0.318	1.19 (0.86 to 1.66); 0.291	[a]	1.79 (0.60 to 5.37); 0.301	1.25 (0.79 to 1.98); 0.334	1.20 (0.83 to 1.74); 0.327	1.18 (0.85 to 1.65); 0.318
Exercise capacity							
Baseline VO_2peak directly measured	0.97 (0.88 to 1.07); 0.538	0.97 (0.93 to 1.01); 0.149	0.94 (0.80 to 1.11); 0.467	0.98 (0.90 to 1.07); 0.658	0.99 (0.90 to 1.10); 0.882	0.99 (0.93 to 1.06); 0.769	0.98 (0.89 to 1.08); 0.685
Baseline VO_2peak directly measured and predicted	0.97 (0.89 to 1.07); 0.539	0.97 (0.93 to 1.01); 0.116	0.95 (0.82 to 1.10); 0.483	0.97 (0.89 to 1.05); 0.424	0.98 (0.92 to 1.05); 0.610	0.99 (0.94 to 1.03); 0.535	0.98 (0.90 to 1.07); 0.670
Standardised scores using baseline VO_2peak, 6MWT, ISWT units and watts score	0.88 (0.62 to 1.26); 0.483	0.86 (0.72 to 1.03); 0.093	0.83 (0.46 to 1.49); 0.527	0.81 (0.56 to 1.16); 0.246	0.92 (0.69 to 1.23); 0.576	0.93 (0.75 to 1.16); 0.517	0.91 (0.69 to 1.20); 0.505

a Study estimate not available as too few studies provide data.

Interaction analyses for the two-stage model revealed no consistent interaction between the effect of ExCR and any of the predefined subgroups (age, sex, ejection fraction, NYHA class, HF aetiology, ethnicity or baseline exercise capacity) for all-cause mortality, HF-related mortality, all-cause hospitalisation or HF-related hospitalisation (see *Tables 7–10*). In order to make further comparisons of mortality and hospitalisation rates within each subgroup, the HR and associated 95% CI from individual subgroup one-stage IPD meta-analyses are shown in *Figure 5*. The *p*-values from the interaction test in the two-stage IPD meta-analyses are presented alongside these estimates.

(a)

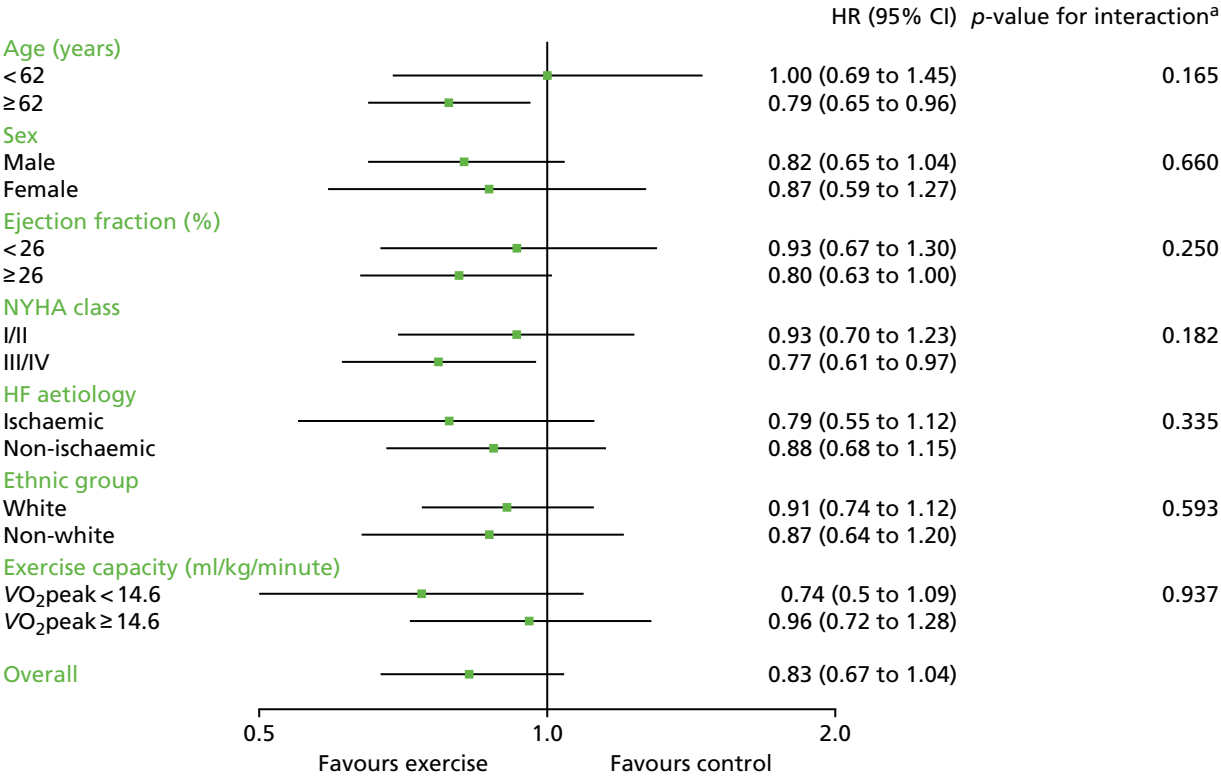
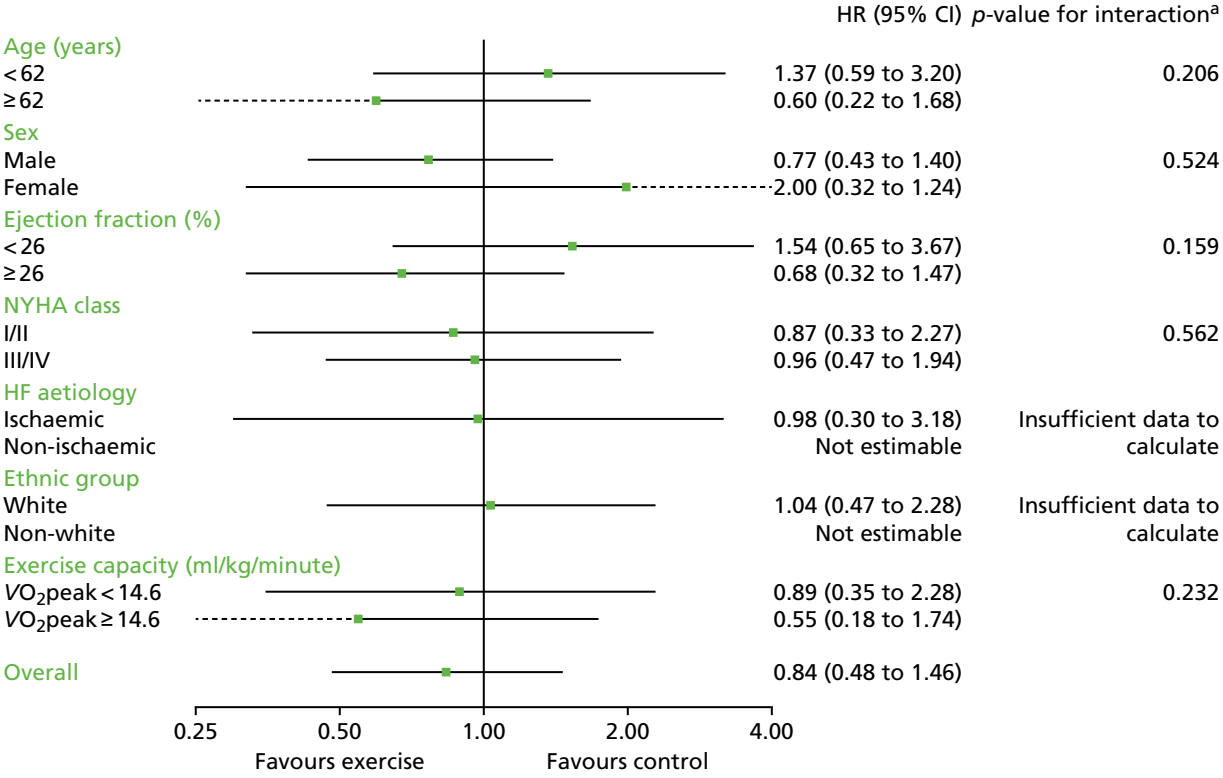


FIGURE 5 Effect of ExCR on mortality and hospitalisation across patient subgroups: individual subgroup one-stage IPD meta-analyses. (a) All-cause mortality; (b) HF-related mortality; (c) all-cause hospitalisation; and (d) HF-related hospitalisation. a, Although stratified meta-analyses are shown, the interaction *p*-values are calculated based on continuous distribution of age, ejection fraction and baseline exercise capacity. (*continued*)

(b)



(c)

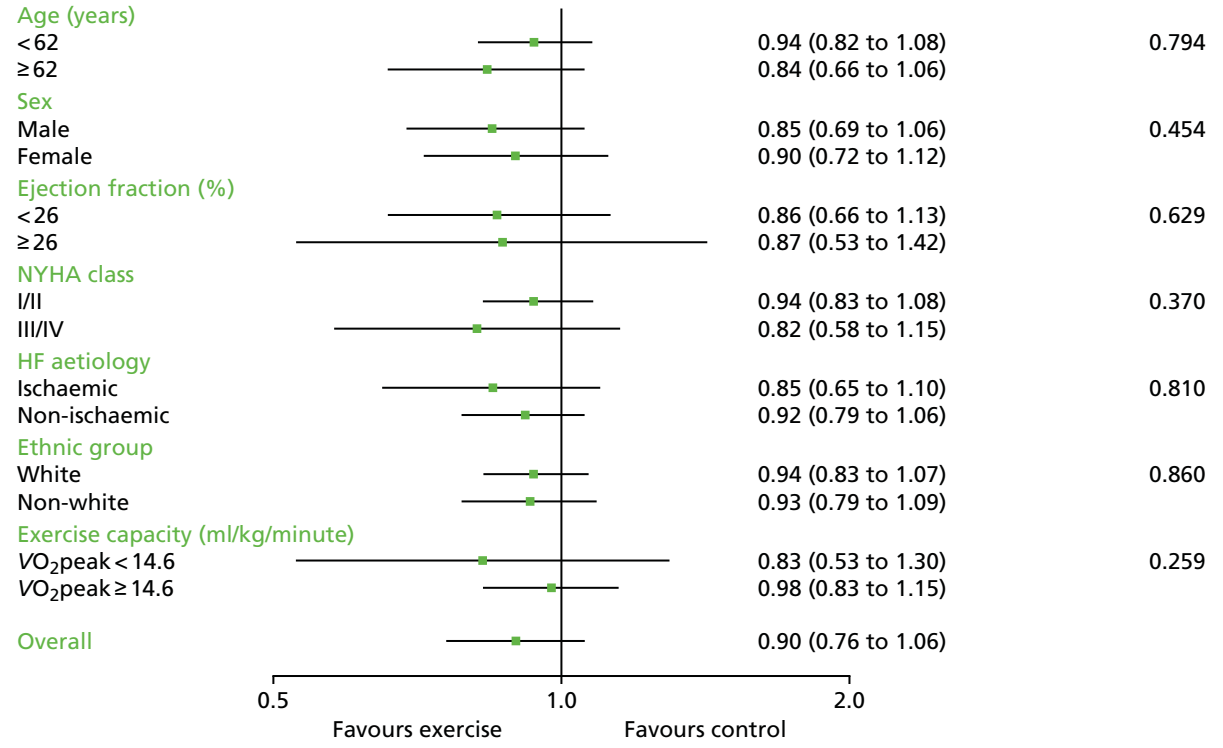
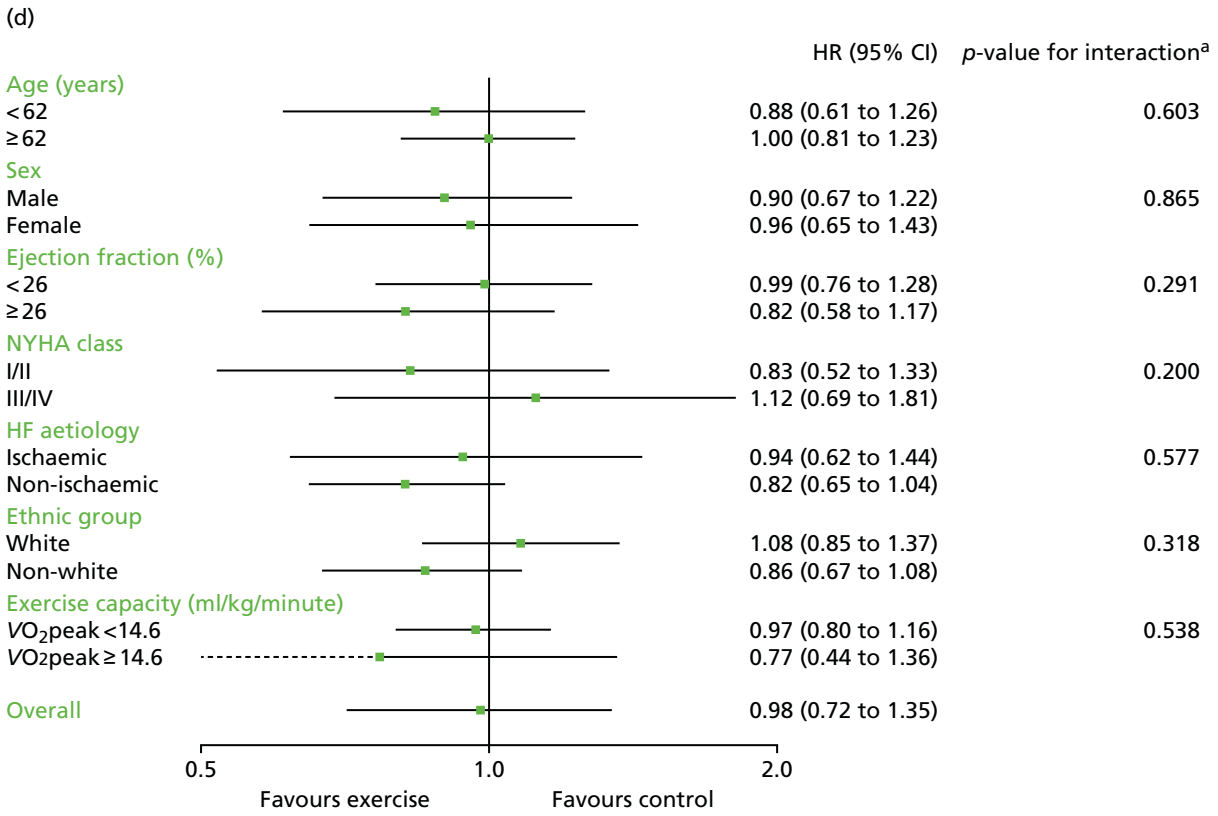


FIGURE 5 Effect of ExCR on mortality and hospitalisation across patient subgroups: individual subgroup one-stage IPD meta-analyses. (a) All-cause mortality; (b) HF-related mortality; (c) all-cause hospitalisation; and (d) HF-related hospitalisation. a, Although stratified meta-analyses are shown, the interaction *p*-values are calculated based on continuous distribution of age, ejection fraction and baseline exercise capacity. (*continued*)



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Secondary analyses

These primary analysis results were broadly consistent across secondary analyses.

Sensitivity analyses

In sensitivity analyses, four weak interaction effects ($p < 0.05$) were seen:

1. Age compared with all-cause mortality ($p = 0.034$) in the two-stage 2-year truncation model (i.e. larger reduction in all-cause mortality with ExCR in older patients).
2. Age compared with HF-related mortality ($p = 0.017$) in the two-stage 2-year truncation model (i.e. larger reduction in HF-related mortality with ExCR in older patients).
3. Ischaemic status compared with HF-related mortality ($p = 0.047$) in the one-stage model (i.e. larger reduction in HF-related mortality with ExCR in ischaemic patients).
4. Standardised baseline exercise capacity compared with all-cause hospitalisation ($p = 0.027$) in the two-stage 1-year truncation model (i.e. larger reduction in all-cause hospitalisation with ExCR in patients with lower than average baseline exercise capacity) (see *Tables 7–10*).

Inferences did not change following the addition of trial-level data from trials that met the study inclusion criteria but did not contribute IPD (data are not shown here, but are available from the authors of this report).

Chapter 6 Impact of exercise-based cardiac rehabilitation on health-related quality of life and exercise capacity

Six trials that provided IPD but had no data on HRQoL or exercise capacity were excluded from analyses in this section.[50,52,54,55,57,73] In addition to comparing usual care with an intervention arm of usual care plus ExCR, Gary *et al.*[59] also compared the effects of cognitive–behavioural therapy to cognitive–behavioural therapy plus ExCR. For the purpose of analysis from this point forward, this will be described as one trial providing two comparisons. For analysis, the data set was split into two and analysed as if the data were provided by two separate trials. For the HRQoL analysis, nine trials[19,58,59,61,63–67] (10 comparisons) provided data for 3000 patients (1496 ExCR patients and 1504 control patients), with a median follow-up of 33 weeks. For the exercise capacity analysis, 13 trials[19,51,56,58–67] (14 comparisons) provided data for 3332 patients (1662 ExCR patients and 1670 control patients), with a median follow-up of 26 weeks. *Figure 6* summarises the study selection process.

Characteristics of included patients and trials

Patient baseline characteristics were well balanced between ExCR patients and control patients (*Table 11*). The majority of patients were male (73%), with a mean age of 61 years. The mean baseline left ventricular ejection fraction was 27%, < 5% of included patients had a HFpEF (defined as an ejection fraction of > 45%), and most patients were in NYHA functional class II (62%) or III (36%). Studies were published between 2000 and 2012 across a number of countries (*Table 12*). Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention; four also included resistance training.[58,61,64,65] Exercise training was most commonly delivered in an exclusively centre-based setting. Four trials were conducted in an exclusively home-based setting.[58,59,61,67] The dose of exercise training ranged across studies, with an average session duration of 15–60 minutes (including warm-up and cool-down), of two to seven sessions per week, exercise intensity equivalent of 40–70% VO_2peak and delivery duration of 4–120 weeks.

Assessment of study quality and risk of bias

There was no evidence of significant small-study bias for the five outcomes studied (*Figure 7*). The overall quality of included trials was judged to be moderate to good, with a median TESTEX[31] score of 11 (range 9–14) out of a maximum score of 15 (*Table 13*). The criteria of allocation concealment and physical activity monitoring in the control groups were met in only two[19,61] and three studies,[19,58,66] respectively. The other TESTEX criteria were each met in ≥ 50% of trials.

Findings

Primary analysis

Compared with control, treatment effects from the one-stage meta-analysis at the 12-month follow-up showed a significant improvement with ExCR in exercise capacity as assessed by the 6MWT (mean difference 21.0 m, 95% CI 1.57 to 40.4 m; $p = 0.034$, $\tau^2 = 491$, $I^2 = 78\%$) and standardised exercise capacity score (mean difference 0.27 SD units, 95% CI 0.11 to 0.43; $p = 0.001$, $\tau^2 = 0.08$, $I^2 = 91\%$). No significant difference in VO_2peak at 12 months was observed (1.01 ml/kg/minute, 95% CI –0.42 to 2.44 ml/kg/minute; $p = 0.168$, $\tau^2 = 2.17$, $I^2 = 94\%$).

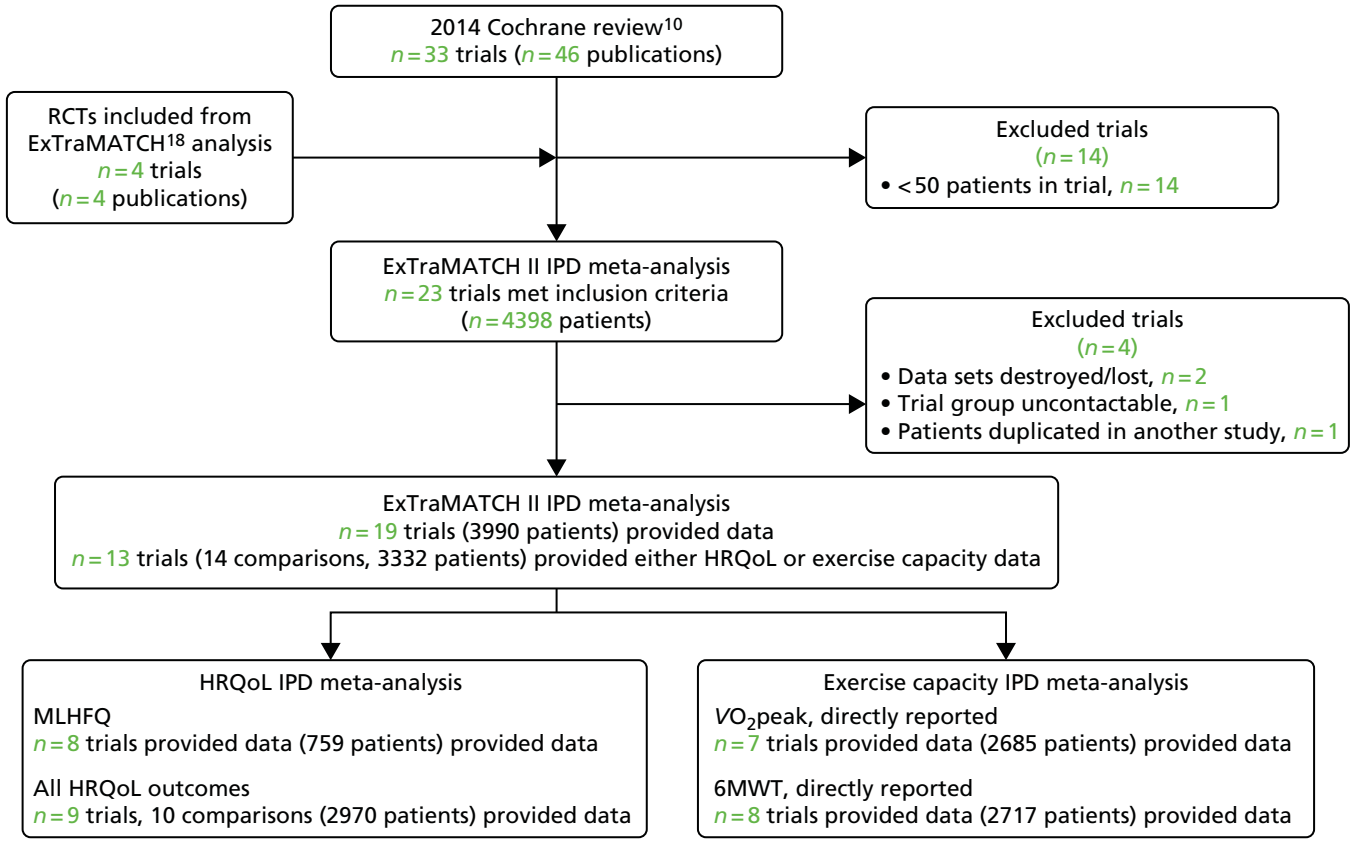


FIGURE 6 The PRISMA flow diagram summarising the selection of studies for HRQoL and exercise capacity analyses.

TABLE 11 Baseline characteristics of patients in the HRQoL and exercise capacity analyses

Characteristic	Intervention		
	ExCR (*N* = 1662)	Control (*N* = 1670)	All (*N* = 3332)
Age (years), mean (SD)	60.9 (13.2)	61.2 (13.5)	61.1 (13.4)
Gender, *n* (%)			
Male	1187 (71.4)	1237 (74.1)	2424 (72.8)
Female	475 (28.6)	433 (25.9)	908 (27.3)
Baseline ejection fraction (%), mean (SD)	27.0 (8.8)	26.9 (8.7)	26.9 (8.8)
Baseline ejection fraction, *n* (%)			
HFrEF (< 45%)	1721 (96.8)	1744 (97.5)	3465 (97.1)
HFpEF (≥ 45%)	57 (3.2)	45 (2.5)	102 (2.9)
NYHA status, *n* (%)			
Class I	20 (1.2)	25 (1.5)	45 (1.4)
Class II	1002 (61)	1032 (63)	2034 (62.0)
Class III	597 (36)	569 (35)	1166 (35.5)
Class IV	19 (1.2)	18 (1.1)	37 (1.1)
Aetiology, *n* (%)			
Ischaemic	892 (54.9)	884 (54.1)	1776 (54.5)
Non-ischaemic	732 (45.1)	750 (45.9)	1482 (45.5)
Ethnicity, *n* (%)			
White	1085 (69.3)	1117 (70.9)	2202 (70.1)
Non-white	480 (30.7)	458 (29.1)	938 (30.0)
VO_2peak (ml/kg/minute), mean (SD)	15.0 (4.5)	15.1 (4.7)	15.0 (4.6)
6MWT (m), mean (SD)	362.6 (109.3)	362.5 (112.1)	362.6 (110.7)

TABLE 12 Characteristics of included trials in the HRQoL and exercise capacity analyses

Study characteristic	*n* (%), unless otherwise stated
Publication year	
1990–9	0 (0)
2000–9	9 (64)
2010–12	5 (36)
Unpublished	0 (0)
Main study location	
Europe	9 (64)
North America[a]	5 (36)

continued

TABLE 12 Characteristics of included trials in the HRQoL and exercise capacity analyses (*continued*)

Study characteristic	*n* (%), unless otherwise stated
Study centre	
Single	10 (71.4)
Multiple	4 (28.6)
Not reported	0 (0)
Sample size	
0–99	8 (57)
100–999	5 (36)
≥ 1000	1 (7)
Duration of latest follow-up (weeks), median (range)	
HRQoL outcomes	33 (26–104)
Exercise capacity outcomes	26 (9–520)
Intervention characteristic	
Intervention type	
Exercise-only programmes	9 (64.3)
Comprehensive programmes	5 (35.7)
Type of exercise	
Aerobic exercise only	10 (71.4)
Aerobic plus resistance training	4 (28.6)
Dose of intervention	
Duration of intervention (weeks), median (range)	24 (4–120)
Frequency (sessions/week), median (range)	3 (2–6.5)
Length of exercise session (minutes), median (range)	30 (15–60)
Exercise intensity (range)	40–70% VO_2peak
	11–15 Borg rating
Setting	
Centre based	9 (64.3)
Home based	5 (35.7)

Borg, Borg Scale of Perceived Exertion.
a HF-ACTION study[19] was categorised as North America, but was also delivered to a small number of patients in France.

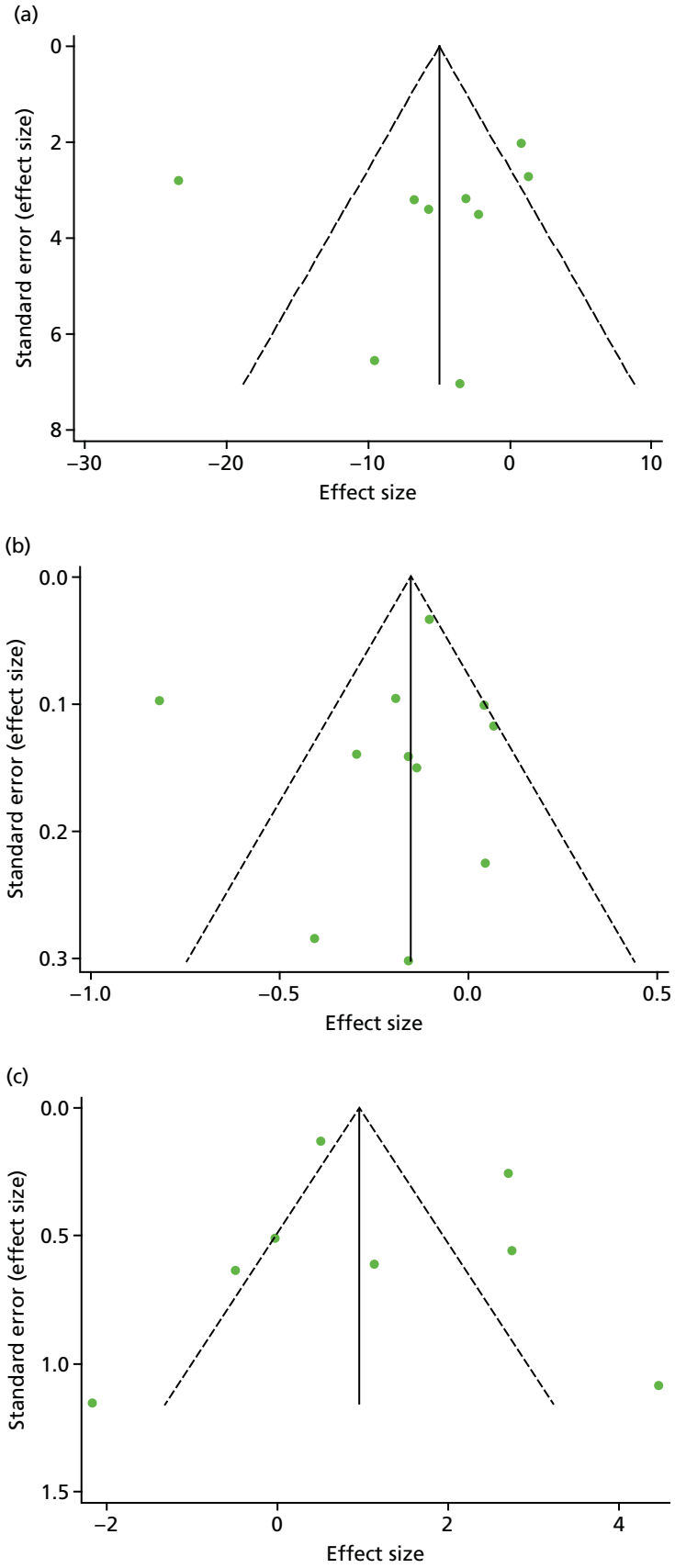
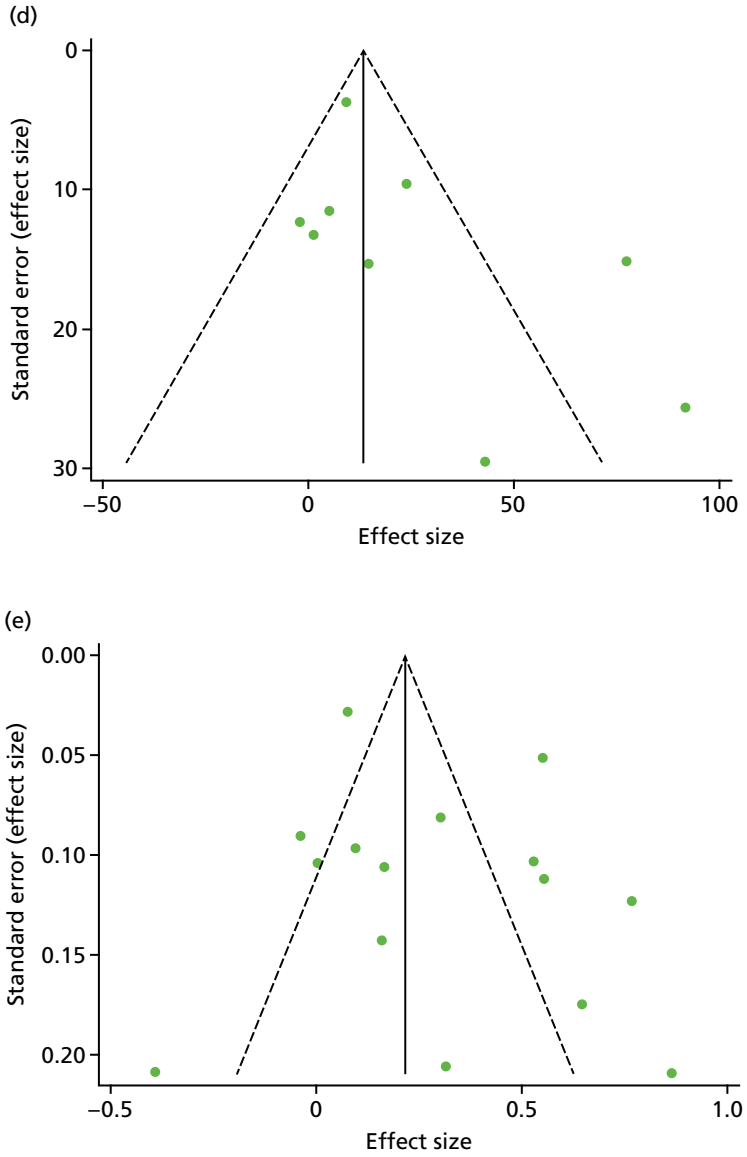


FIGURE 7 Funnel plots for HRQoL and exercise capacity analyses. (a) MLHFQ score (points) (at 12 months), Egger's test –1.40, $p = 0.656$; (b) all HRQoL measures (at 12 months), Egger's test –0.72, $p = 0.577$; (c) VO_2peak directly reported (at 12 months), Egger's test 0.99, $p = 0.665$; (d) 6MWT directly reported (at 12 months), Egger's test 1.71, $p = 0.150$; and (e) all exercise capacity measures (at 12 months), Egger's test 1.85, $p = 0.214$. (*continued*)



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One-stage meta-analysis showed a significant improvement in HRQoL as assessed by the MLHFQ (mean difference –5.94 points, 95% CI –1.0 to –10.9 points; $p = 0.018$, $\tau^2 = 77$, $I^2 = 88\%$) and standardised HRQoL score (mean difference SD 0.20, 95% CI 0.03 to 0.37; $p = 0.020$, $\tau^2 = 0.07$, $I^2 = 85\%$), at the 12-month follow-up. Similar results were seen at the 6-month follow-up (*Figures 8* and *9*). Marked statistical heterogeneity ($I^2 > 70\%$) was seen for all exercise capacity and HRQoL outcomes.

Analyses revealed no consistent interaction between the effect of ExCR and the predefined subgroups (sex, ejection fraction, NYHA class, HF aetiology, ethnicity and baseline exercise capacity), for either exercise or HRQoL.

TABLE 13 Assessment of quality using TESTEX scale[31] of included studies in HRQoL and exercise capacity analysis

First author/study (year)	Eligibility criteria specified	Randomisation specified	Allocation concealed	Groups similar at baseline	Blinding of assessors	Outcome measures in > 85% of participants[a]	Intention-to-treat analysis[b]	Between-group statistical comparisons reported	Point measures and measures of variability reported	Activity monitoring in control group	Relative Exercise intensity reviewed	Exercise volume and energy expended	Overall TESTEX score (maximum score of 15)
Belardinelli *et al.* (2012)[56]	1	0	0	1	0	3	1	1	1	0	0	1	9
Dracup *et al.* (2007)[58]	1	0	0	1	0	3	1	2	1	1	1	1	10
Gary *et al.* (2010)[59]	1	1	0	1	1	3	1	2	1	0	0	0	11
Giannuzzi *et al.* (2003)[60]	1	0	0	1	0	2	1	2	1	0	1	1	10
Hambrecht *et al.* (2000)[51]	1	1	0	1	0	3	0	2	1	0	1	1	11
HF-ACTION (2009)[19]	1	1	1	1	1	3	1	2	1	1	0	1	14
Jolly *et al.* (2009)[61]	1	1	1	1	0	2	1	2	1	0	1	1	12
Mueller *et al.* (2007)[62]	1	0	0	1	0	2	1	2	1	0	1	1	10
Nilsson *et al.* (2008)[63]	1	1	0	1	1	2	1	2	1	0	0	1	11
Passino *et al.* (2006)[67]	1	0	0	1	0	2	1	2	1	0	1	1	10
Witham *et al.* (2005)[64]	1	1	0	1	1	3	1	2	1	0	1	0	12
Witham *et al.* (2012)[65]	1	1	0	1	1	3	1	2	1	0	1	0	12
Yeh *et al.* (2011)[66]	1	1	0	1	1	3	1	2	1	1	0	0	12

a Three points possible.
b If intention to treat was not specifically mentioned, but it was noted that no participants withdrew and all were analysed, then 1 point was awarded.

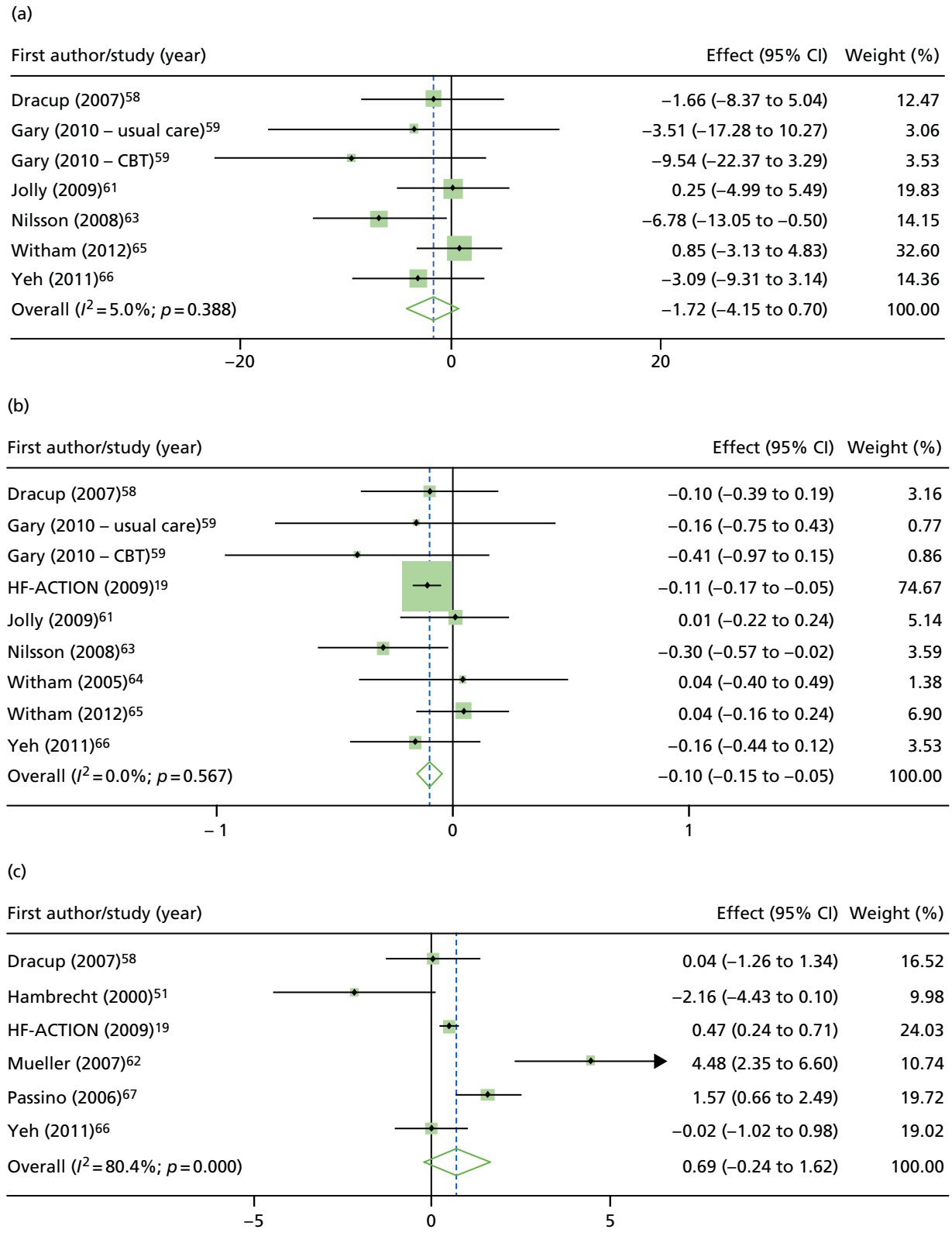
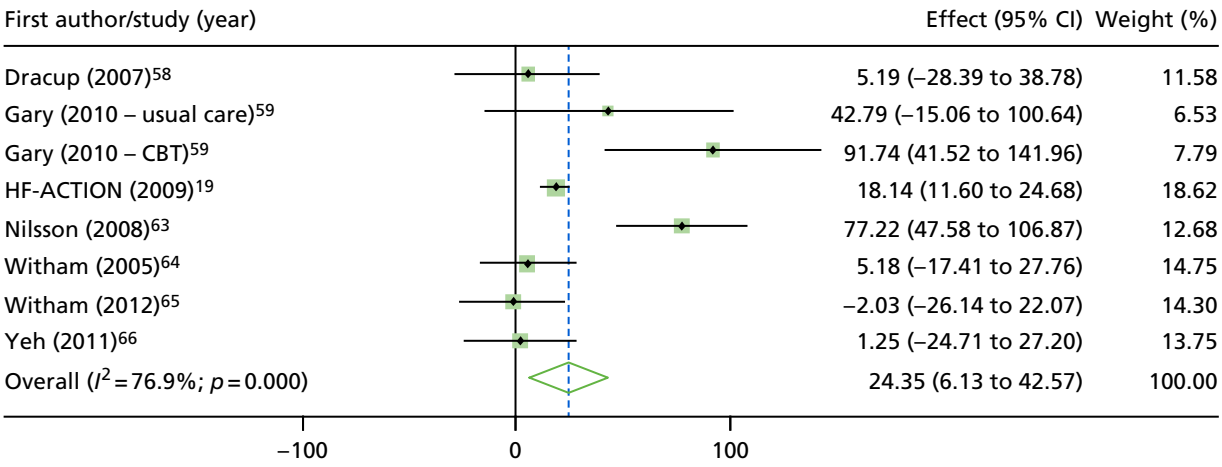
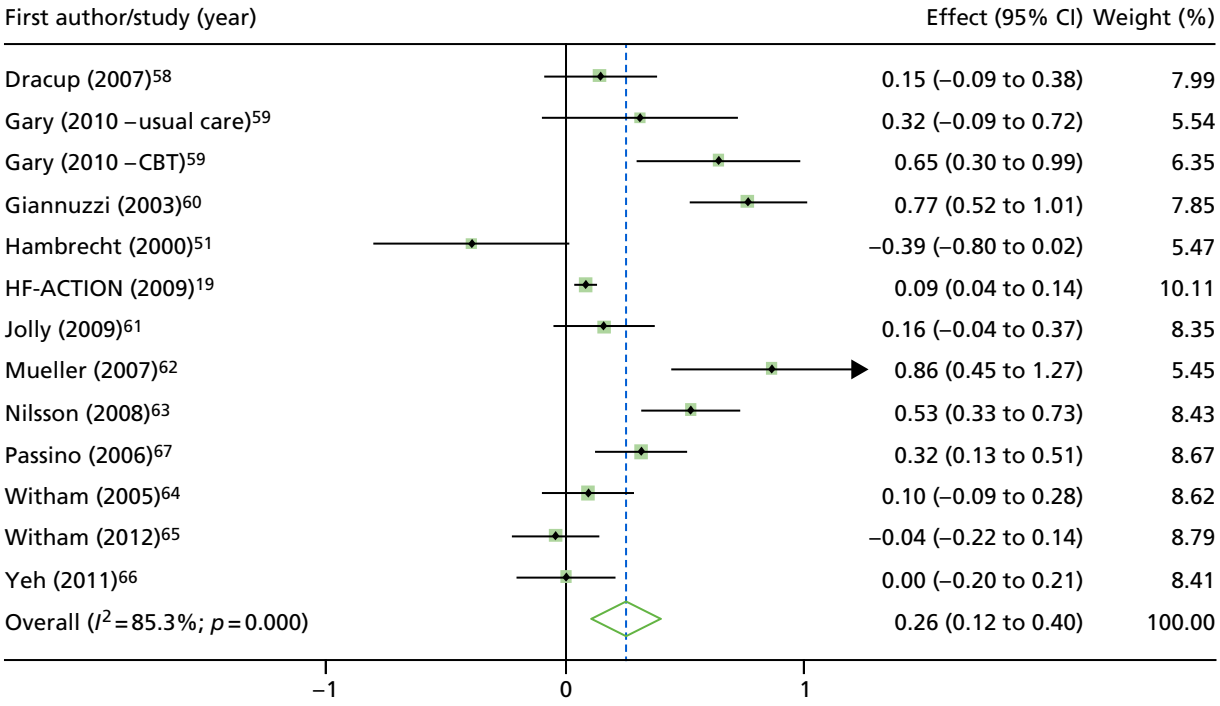


FIGURE 8 Effect of ExCR on HRQoL and exercise capacity at 6 months: two-stage IPD meta-analysis. (a) MLHFQ score (points) (mean difference); (b) all HRQoL measures (standardised mean difference); (c) VO_2peak directly reported (mean difference); (d) 6MWT (m) directly reported (mean difference); and (e) all exercise capacity measures (standardised mean difference). Note that weights are from random effects, DerSimonian–Laird estimator. CBT, cognitive–behavioural therapy. (*continued*)

(d)



(e)



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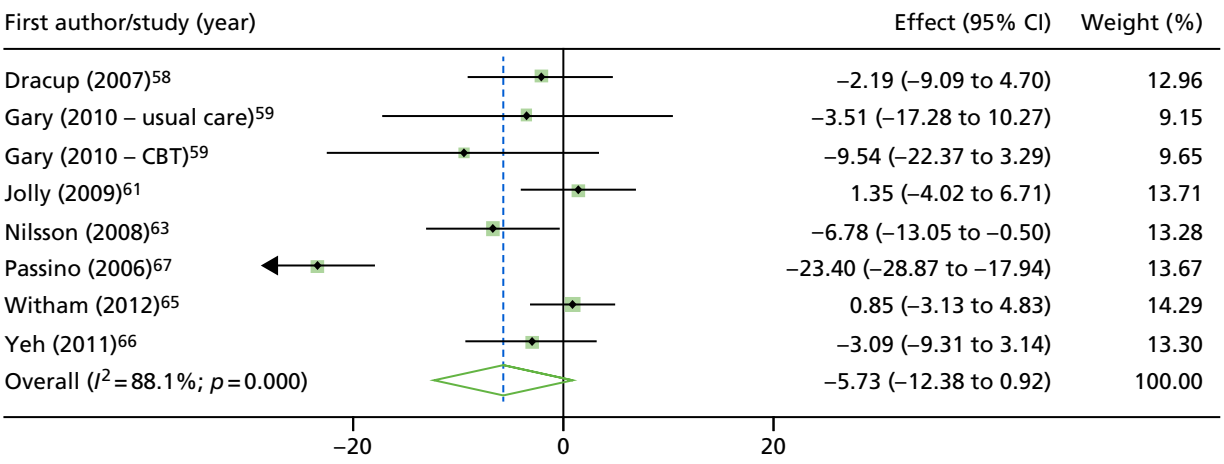
(a)



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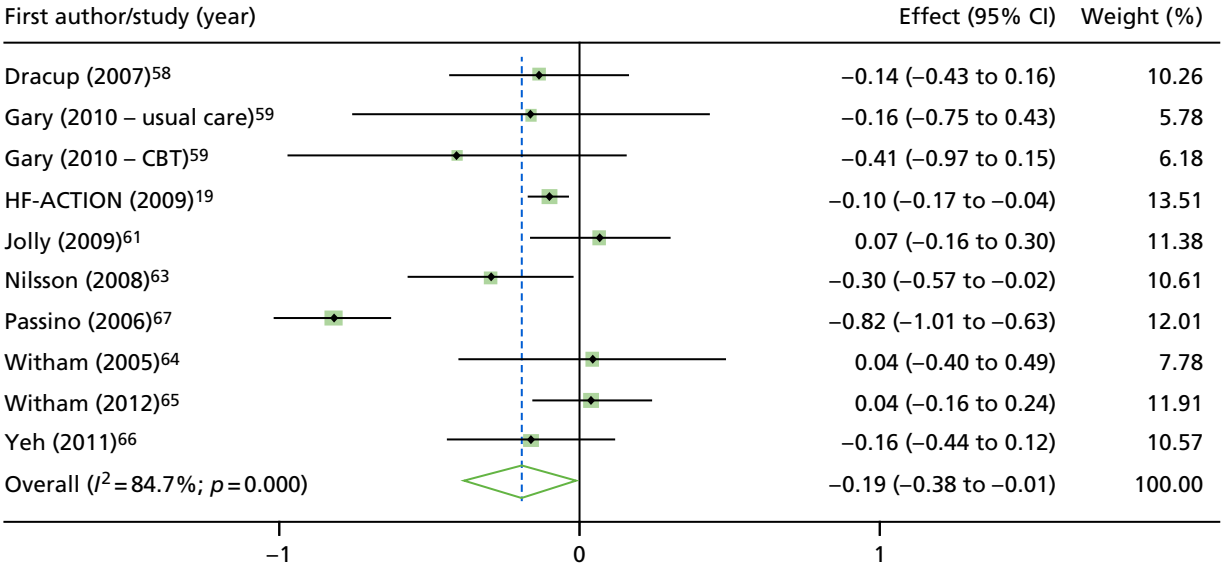

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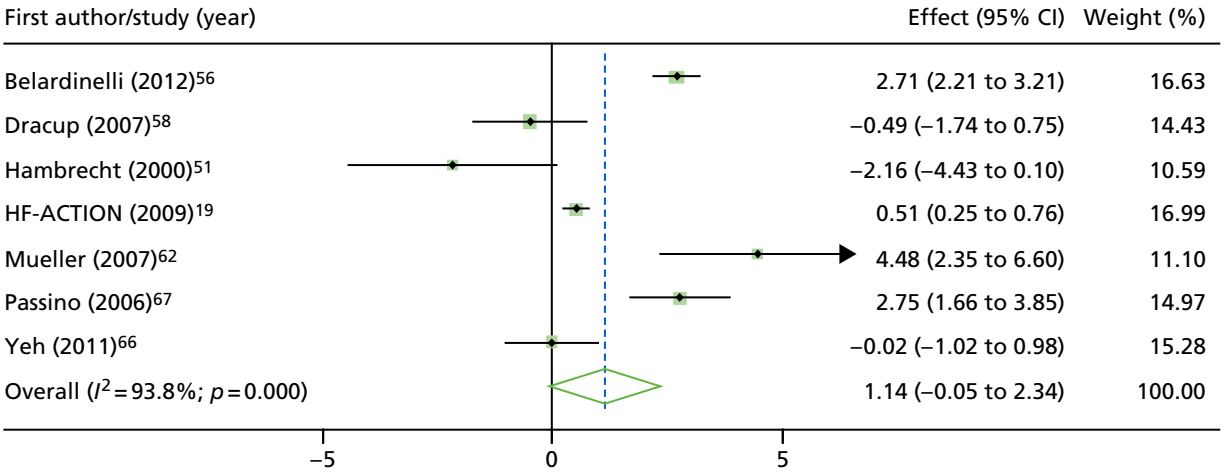
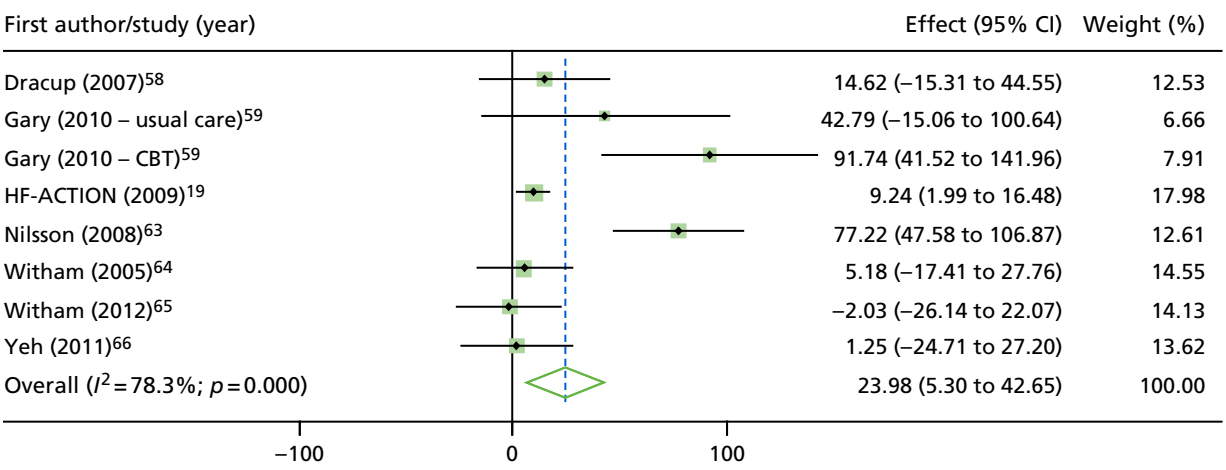


FIGURE 9 Effect of ExCR on HRQoL and exercise capacity at 12 months: two-stage IPD meta-analysis. (a) MLHFQ score (points) (mean difference); (b) all HRQoL measures (standardised mean difference); (c) VO_2peak directly reported (mean difference); (d) 6MWT (m) directly reported (mean difference); and (e) all exercise capacity measures (standardised mean difference). Note that weights are from random effects, DerSimonian–Laird estimator. CBT, cognitive–behavioural therapy. (*continued*)

(d)



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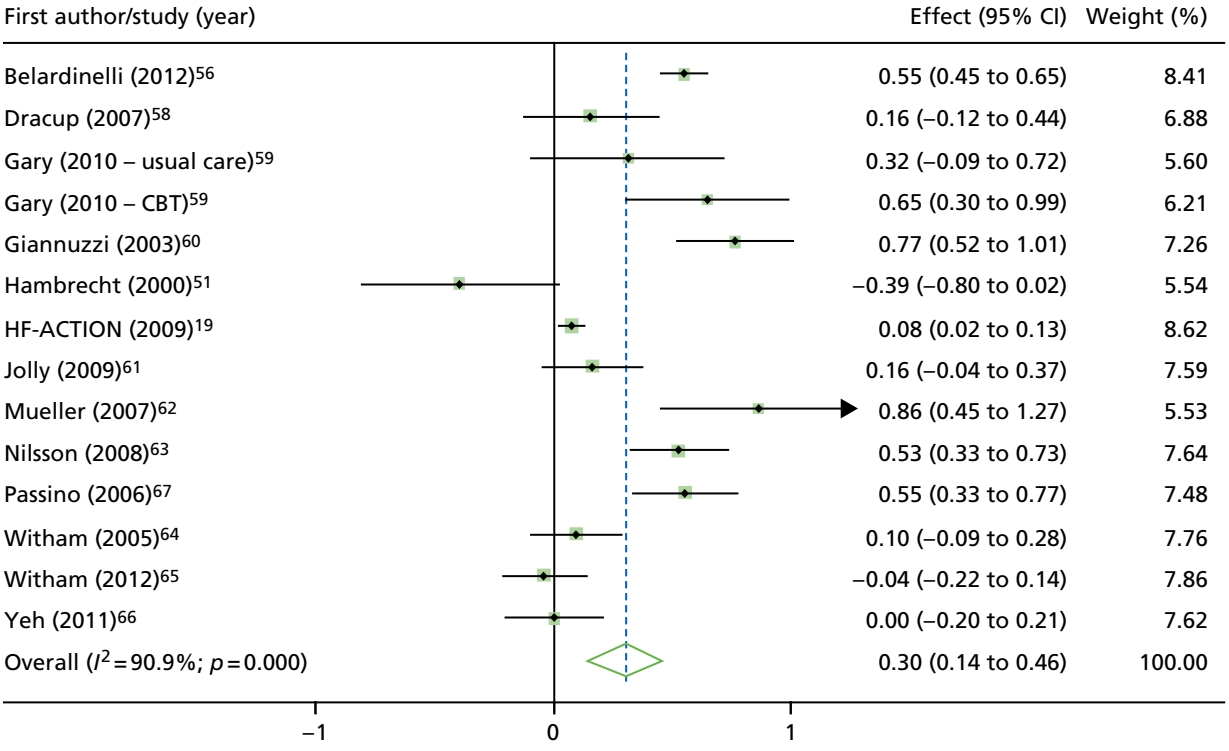

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A differential effect of ExCR across ages was observed in the standardised HRQoL analysis, with a reduction in HRQoL score (i.e. an increase in standardised HRQoL score) as age increased (SD 0.006, 95% 0.002 to 0.011; $p = 0.006$). To put this into context, based on a MLHFQ SD of 24 points, this equates to a decrease of 1.4 points in the treatment effect on the MLHFQ score for every 10-year increase in patient age.

Interaction analyses for the one-stage model at the 12-month follow-up showed differential effects of ExCR by sex, with women showing greater benefit than men for VO_2peak (0.57 ml/kg/minute, 95% CI 0.04 to 1.11 ml/kg/minute; $p = 0.036$) and the 6MWT (14.9 m, 95% CI 1.2 to 28.7 m; $p = 0.034$). Differential effects of ExCR were also seen between ethnic groups, with white patients showing a greater improvement in 6MWT distance than non-white patients (14.2 m, 95% CI 0.40 to 28.0 m; $p = 0.044$).

Secondary analysis

In the repeated measures analyses for each HRQoL and exercise capacity outcome, a significant interaction between ExCR and time was observed (*Figure 10*). To visualise comparisons of changes in HRQoL and exercise capacity in each subgroup, the effect estimates and associated 95% CI from individual subgroup one-stage IPD meta-analyses are shown in *Figure 11*. The *p*-values from the interaction test in the two-stage IPD meta-analyses are presented alongside these estimates.

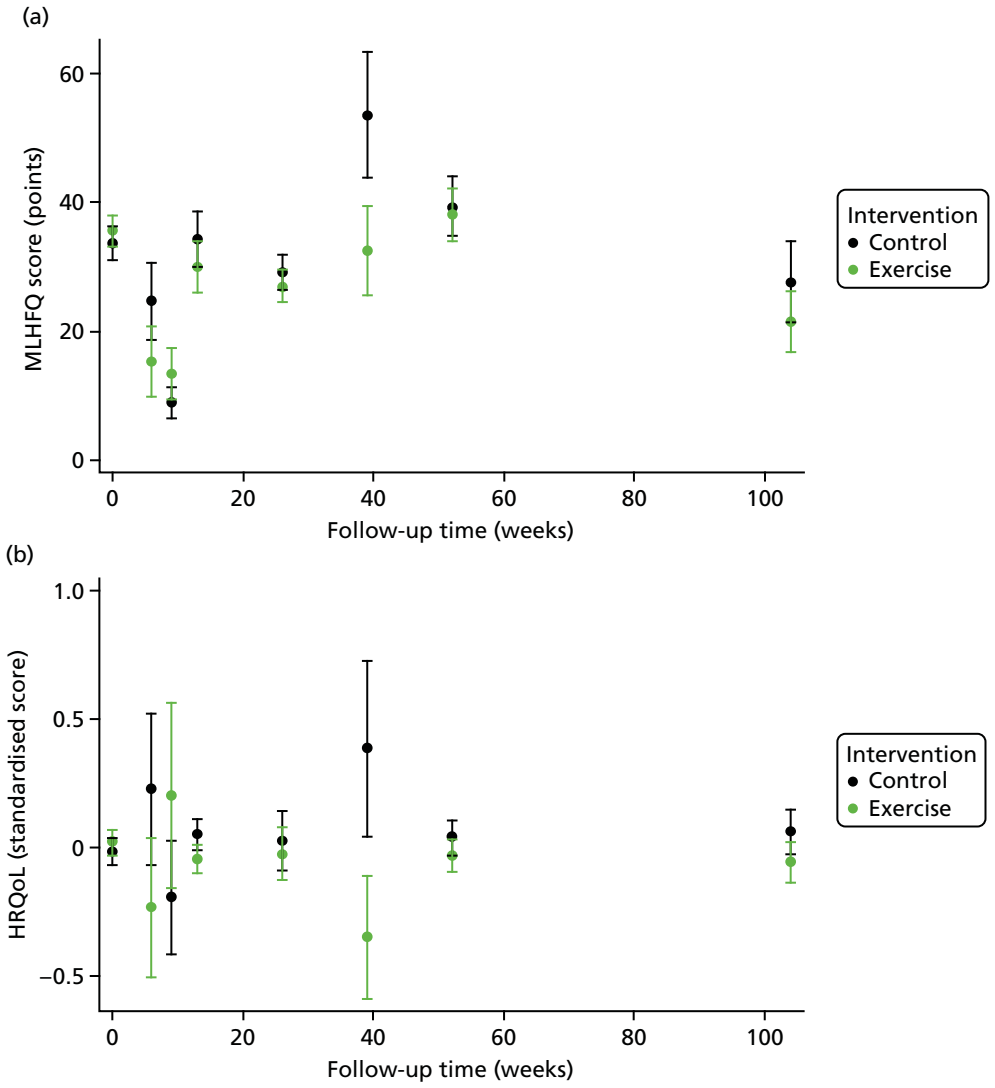

FIGURE 10 Effect of ExCR on HRQoL and exercise capacity. (a) MLHFQ score (points) (mean difference); (b) all HRQoL measures (standardised mean difference); (c) VO_2peak directly reported (mean difference); (d) 6MWT directly reported (mean difference); and (e) all exercise capacity measures (standardised mean difference). (*continued*)

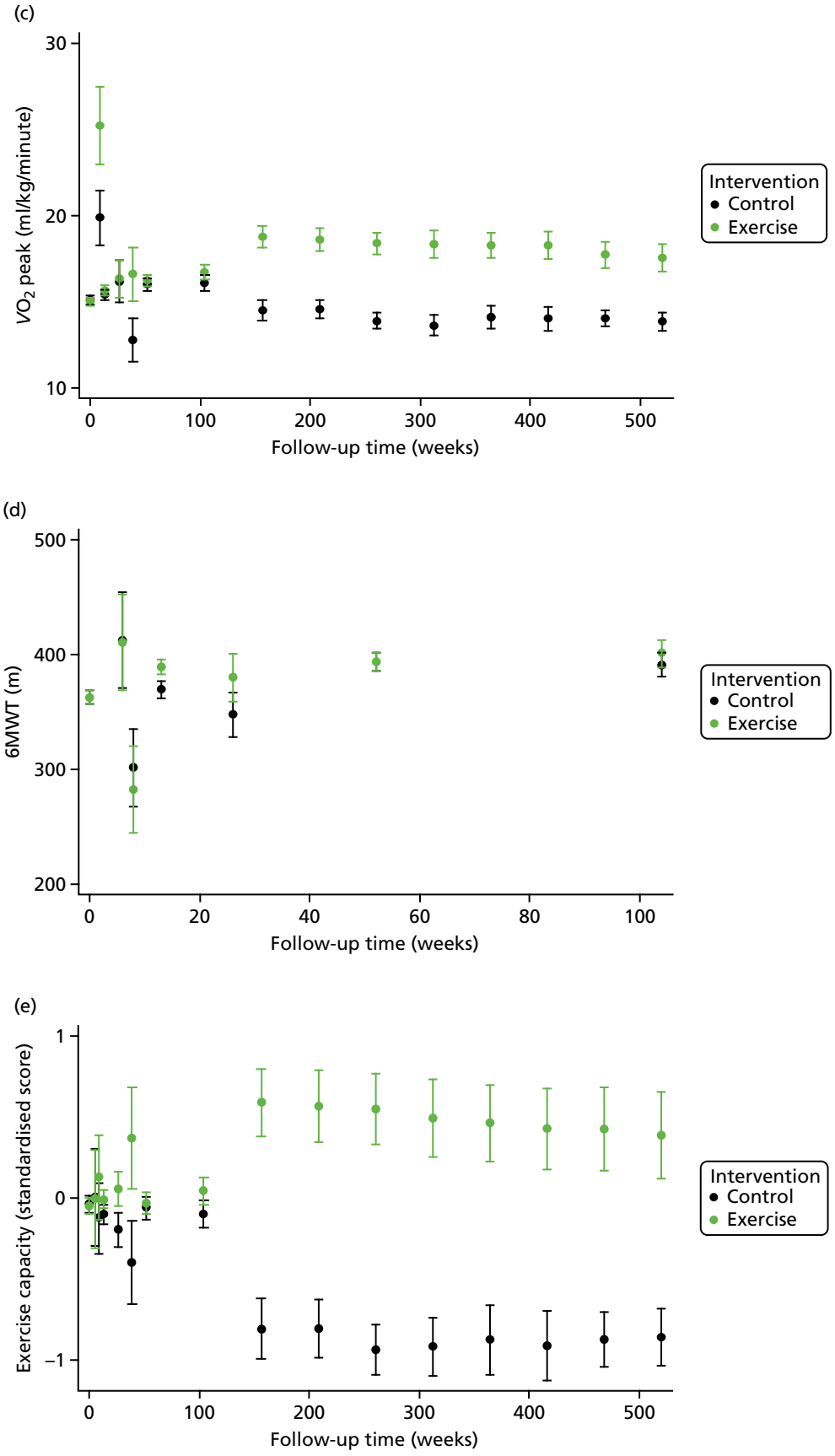

FIGURE 10 Effect of ExCR on HRQoL and exercise capacity. (a) MLHFQ score (points) (mean difference); (b) all HRQoL measures (standardised mean difference); (c) VO_2peak directly reported (mean difference); (d) 6MWT directly reported (mean difference); and (e) all exercise capacity measures (standardised mean difference).

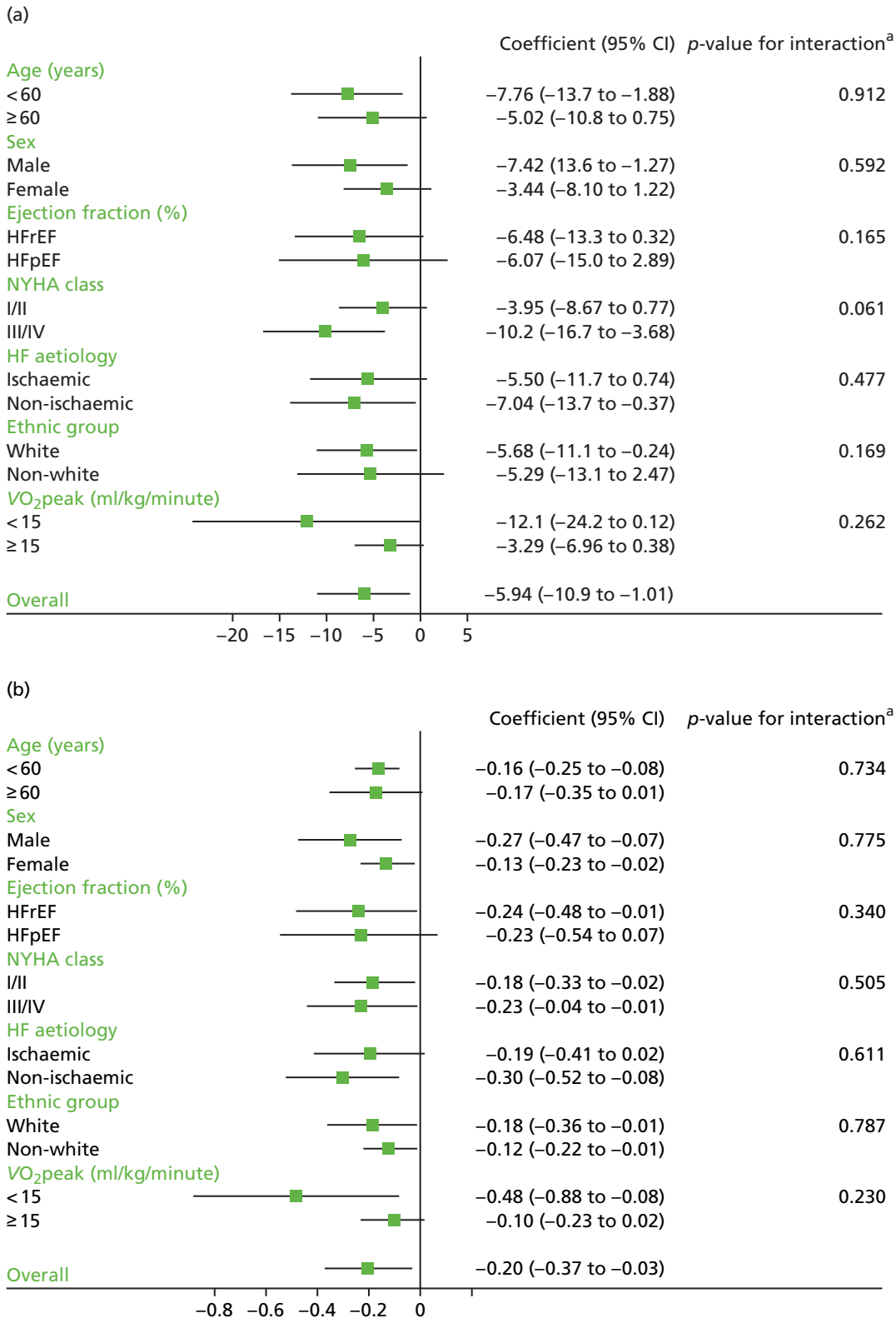

FIGURE 11 Effect of ExCR on HRQoL and exercise capacity across patient subgroups (individual subgroup one-stage IPD meta-analyses). (a) MLHFQ score (points); (b) all HRQoL measures (standardised score); (c) VO_2peak directly reported; (d) 6MWT (m) directly reported; and (e) all exercise capacity measures (standardised score). a, Although stratified meta-analyses are shown, the interaction *p*-values are calculated based on continuous distribution of age, ejection fraction and baseline exercise capacity. (*continued*)

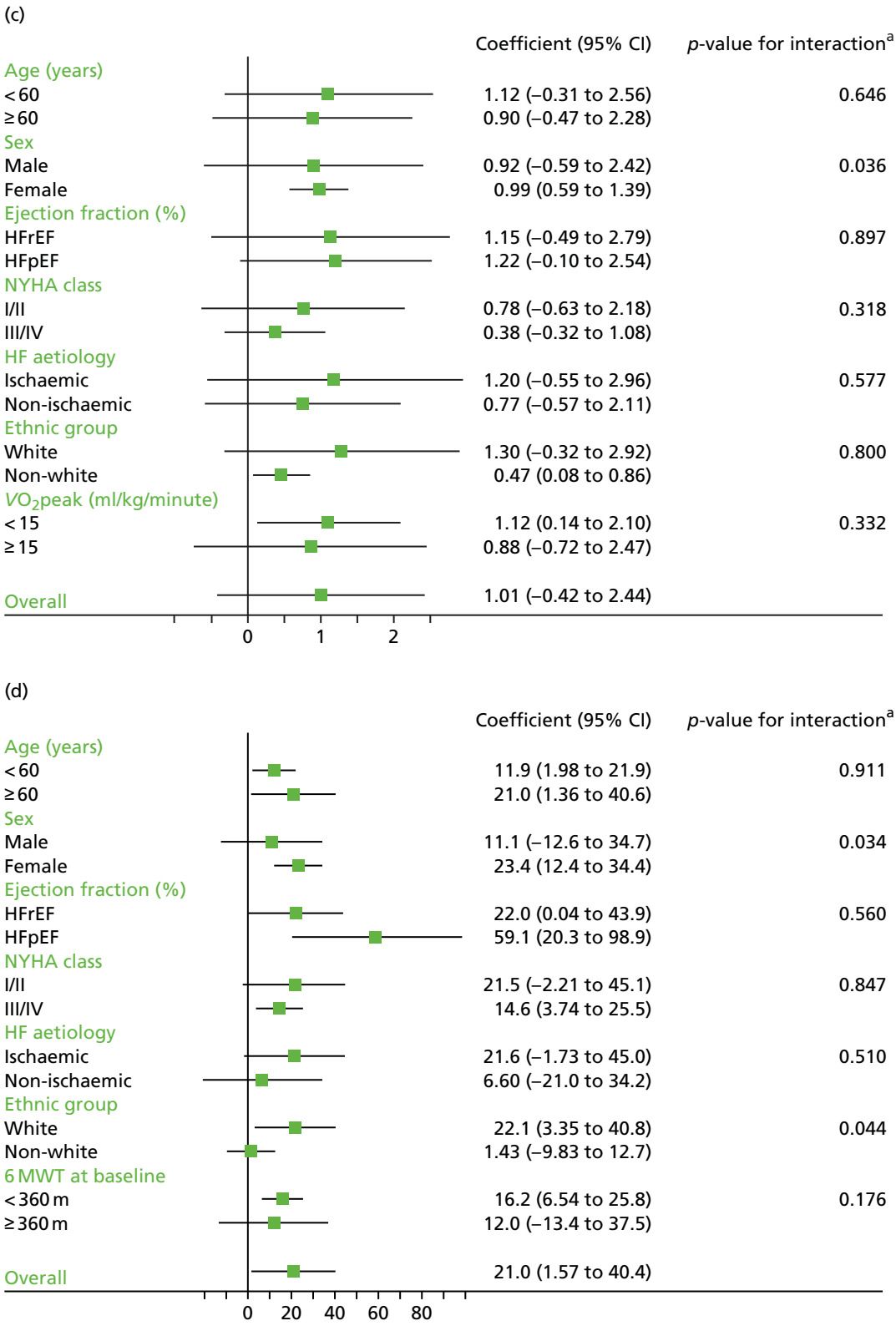

FIGURE 11 Effect of ExCR on HRQoL and exercise capacity across patient subgroups (individual subgroup one-stage IPD meta-analyses). (a) MLHFQ score (points); (b) all HRQoL measures (standardised score); (c) VO_2peak directly reported; (d) 6MWT (m) directly reported; and (e) all exercise capacity measures (standardised score). a, Although stratified meta-analyses are shown, the interaction *p*-values are calculated based on continuous distribution of age, ejection fraction and baseline exercise capacity. (*continued*)

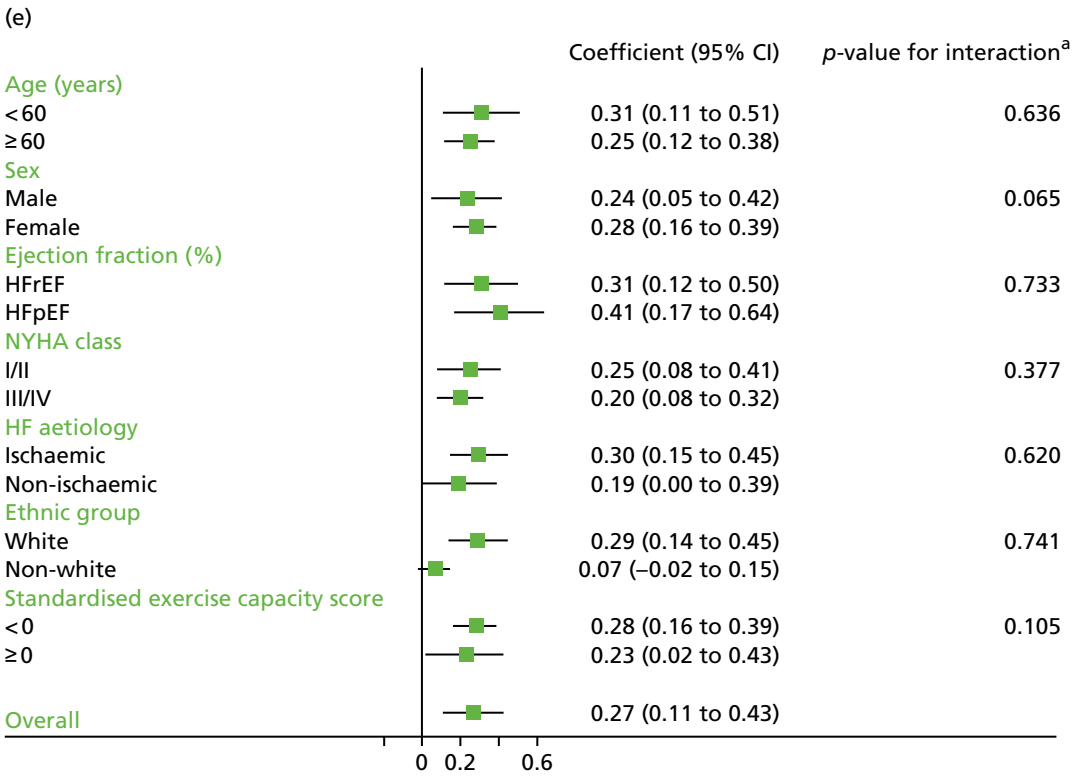

FIGURE 11 Effect of ExCR on HRQoL and exercise capacity across patient subgroups (individual subgroup one-stage IPD meta-analyses). (a) MLHFQ score (points); (b) all HRQoL measures (standardised score); (c) VO_2peak directly reported; (d) 6MWT (m) directly reported; and (e) all exercise capacity measures (standardised score). a, Although stratified meta-analyses are shown, the interaction *p*-values are calculated based on continuous distribution of age, ejection fraction and baseline exercise capacity.

Sensitivity analyses

In sensitivity analyses, the results of the analyses excluding HF-ACTION,[19] were broadly consistent with the overall results (*Tables 14–18*). Similar results were found with the addition of the study-level aggregate data to the two-stage model at 12 months' follow-up.

TABLE 14 Minnesota Living with Heart Failure: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analyses, mean difference (95% CI); *p*-value				Sensitivity analyses excluding HF-ACTION,[19] mean difference (95% CI); *p*-value			
	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect
Overall effect	–2.85 (–5.85 to 0.14); 0.062	–1.73 (–4.15 to 0.70); 0.163	–5.94 (–10.87 to –1.01); 0.018	–5.73 (–12.38 to 0.93); 0.091	Not applicable to MLHFQ analyses as HF-ACTION[19] only supplied KCCQ scores			
Interaction term								
Age (years)	0.12 (–0.10 to 0.35); 0.280		0.01 (–0.20 to 0.22); 0.912					
Gender (male vs. female)	–5.31 (–11.01 to 0.39); 0.068		–1.49 (–6.95 to 3.96); 0.592					
Ejection fraction (%)	0.22 (–0.14 to 0.58); 0.227		0.24 (–0.07 to 0.56); 0.127					
Ejection fraction (HFrEF vs. HFpEF)	4.06 (–11.0 to 19.1); 0.597		8.02 (–3.29 to 19.3); 0.165					
NYHA class (NYHA I/II vs. NYHA III/IV)	–6.38 (–12.31 to –0.45); 0.035		–5.30 (–10.9 to 0.24); 0.061					
HF aetiology (ischaemic vs. non-ischaemic)	4.67 (–1.65 to 11.0); 0.147		2.08 (–3.64 to 7.80); 0.477					
Ethnic group (white vs. non-white)	3.15 (–4.31 to 10.6); 0.408		5.17 (–2.19 to 12.5); 0.169					
Exercise capacity								
Baseline VO_2peak directly measured	0.24 (–0.82 to 1.31); 0.654		0.47 (–0.35 to 1.29); 0.262					
Baseline VO_2peak directly measured and predicted	0.72 (–0.01 to 1.45); 0.053		0.62 (–0.02 to 1.26); 0.058					

KCCQ, Kansas City Cardiomyopathy Questionnaire.

TABLE 15 Standardised HRQoL measure: overall treatment effect and subgroup (interaction) effects

	Primary analyses, mean difference (95% CI); *p*-value				Sensitivity analyses excluding HF-ACTION,[19] mean difference (95% CI); *p*-value			
Baseline variable	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect
Overall effect	–0.11 (–0.16 to –0.06); < 0.001	–0.10 (–0.15 to –0.05); < 0.001	–0.20 (–0.37 to –0.03); 0.020	–0.19 (–0.38 to –0.01); 0.043	–0.11 (–0.24 to 0.01); 0.069	–0.08 (–0.18 to 0.02); 0.131	–0.17 (–0.28 to –0.07); 0.001[a]	–0.21 (–0.45 to 0.04); 0.106
Interaction terms								
Age (years)	0.006 (0.002 to 0.011); 0.006		0.001 (–0.004 to 0.005); 0.734		0.003 (–0.007 to 0.014); 0.536		–0.001 (–0.011 to 0.008); 0.788	
Gender (male vs. female)	0.050 (–0.068 to 0.168); 0.407		0.018 (–0.105 to 0.140); 0.775		–0.223 (–0.469 to 0.024); 0.077		–0.106 (–0.335 to 0.123); 0.365	
Ejection fraction (%)	–0.000 (–0.007 to 0.007); 0.963		–0.004 (–0.011 to 0.004); 0.340		0.010 (–0.006 to 0.025); 0.225		0.010 (–0.003 to 0.023); 0.150	
Ejection fraction (%) (HFrEF vs. HFpEF)	–0.03 (–0.46 to 0.41); 0.902		0.13 (–0.26 to 0.53); 0.505		0.16 (–0.47 to 0.84); 0.581		0.34 (–0.14 to 0.81); 0.163	
NYHA class (NYHA I/II vs. NYHA III/IV)	–0.013 (–0.126 to 0.100); 0.824		0.031 (–0.086 to 0.149); 0.599		–0.126 (–0.380 to 0.129); 0.334		–0.082 (–0.314 to 0.151); 0.491	
HF aetiology (ischaemic vs. non-ischaemic)	0.076 (–0.036 to 0.187); 0.182		0.030 (–0.085 to 0.145); 0.611		0.220 (–0.055 to 0.494); 0.117		0.080 (–0.162 to 0.322); 0.517	
Ethnic group (white vs. non-white)	0.041 (–0.079 to 0.161); 0.506		0.017 (–0.108 to 0.142); 0.787		0.173 (–0.172 to 0.519); 0.325		0.243 (–0.086 to 0.573); 0.147	
Exercise capacity								
Baseline VO_2peak directly measured	–0.002 (–0.014 to –0.011); 0.775		0.008 (–0.005 to 0.021); 0.230		0.012 (–0.035 to 0.059); 0.612		0.021 (–0.012 to 0.055); 0.216	
Baseline VO_2peak directly measured and predicted	0.000 (–0.012 to 0.013); 0.956		0.008 (–0.004 to 0.021); 0.208		0.023 (–0.010 to 0.056); 0.171		0.020 (–0.008 to 0.048); 0.172	

a Fixed effect on treatment with a random effect on study, due to non-convergence of the random treatment effect model.

TABLE 16 Peak oxygen uptake directly measured: overall treatment effect and subgroup (interaction) effects

	Primary analyses, mean difference (95% CI); *p*-value				Sensitivity analyses excluding HF-ACTION,[19] mean difference (95% CI); *p*-value			
Baseline variable	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect
Overall effect	0.62 (–0.82 to 2.07); 0.397	0.69 (–0.24 to 1.62); 0.145	1.01 (–0.42 to 2.44); 0.168	1.14 (–0.05 to 2.34); 0.061	0.71 (–1.10 to 2.52); 0.444	0.77 (–0.73 to 2.28); 0.315	1.15 (–0.60 to 2.90); 0.196	1.26 (–0.31 to 2.82); 0.115
Interactions term								
Age (years)	0.00 (–0.02 to 0.02); 0.980		–0.00 (–0.02 to 0.14); 0.646		–0.01 (–0.07 to 0.04); 0.628		–0.02 (–0.06 to 0.03); 0.415	
Gender (male vs. female)	–0.25 (–0.78 to 0.27); 0.345		–0.57 (–1.11 to –0.04); 0.036		–0.67 (–2.47 to 1.14); 0.468		–0.42 (–1.80 to 0.95); 0.549	
Ejection fraction (%)	0.03 (0.00 to 0.06); 0.034		0.02 (–0.01 to 0.05); 0.157		0.05 (–0.04 to 0.13); 0.280		0.03 (–0.04 to 0.11); 0.349	
Ejection fraction (%) (HFrEF vs. HFpEF)	0.07 (–1.88 to 2.01); 0.947		–0.13 (–2.07 to 1.81); 0.897		–1.34 (–2.42 to 5.09); 0.485		–0.19 (–3.34 to 2.97); 0.907	
NYHA class (NYHA I/II vs. NYHA III/IV)	–0.10 (–0.58 to 0.38); 0.687		–0.25 (–0.75 to 0.24); 0.318		–0.50 (–2.13 to 1.13); 0.549		–0.75 (–1.95 to 0.46); 0.224	
HF aetiology (ischaemic vs. non-ischaemic)	0.02 (–0.44 to 0.47); 0.945		–0.13 (–0.60 to 0.34); 0.577		–0.63 (–2.04 to 0.79); 0.386		–0.24 (–1.39 to 0.91); 0.683	
Ethnic group (white vs. non-white)	–0.19 (–0.66 to 0.29); 0.447		–0.07 (–0.58 to 0.45); 0.800		–0.47 (–2.36 to 1.43); 0.628		0.16 (–1.71 to 2.03); 0.870	
Exercise capacity								
Baseline VO_2peak directly measured	0.01 (–0.04 to 0.06); 0.719		0.03 (–0.03 to 0.08); 0.332		–0.06 (–0.21 to 0.09); 0.435		–0.04 (–0.17 to 0.10); 0.602	
Baseline VO_2peak directly measured and predicted	0.01 (–0.04 to 0.06); 0.702		0.03 (–0.02 to 0.08); 0.299		–0.06 (–0.21 to 0.09); 0.452		–0.03 (–0.16 to 0.10); 0.660	

TABLE 17 Six-minute walk test directly measured: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analyses, mean difference (95% CI); *p*-value				Sensitivity analyses excluding HF-ACTION,[19] mean difference (95% CI); *p*-value			
	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect
Overall effect	22.1 (1.87 to 42.3); 0.032	24.4 (6.13 to 42.6); 0.009	21.0 (1.57 to 40.4); 0.034	24.0 (5.30 to 42.7); 0.012	22.1 (–1.64 to 45.8); 0.068	27.9 (1.25 to 54.6); 0.040	24.0 (1.25 to 46.7); 0.039	29.0 (3.05 to 55.0); 0.029
Interaction terms								
Age (years)	0.01 (–0.49 to 0.50); 0.973		–0.03 (–0.56 to 0.50); 0.911		0.45 (–0.81 to 1.72); 0.482		0.97 (–0.23 to 2.17); 0.115	
Gender (male vs. female)	–10.7 (–23.6 to 2.26); 0.106		–14.9 (–28.7 to –1.16); 0.034		–19.7 (–47.3 to 7.92); 0.162		–13.5 (–39.9 to 12.9); 0.317	
Ejection fraction (%)	0.34 (–0.46 to 1.14); 0.399		0.21 (–0.64 to 1.06); 0.634		1.05 (–0.78 to 2.88); 0.262		0.04 (–1.69 to 1.77); 0.963	
Ejection fraction (%) (HFrEF vs. HFpEF)	0.68 (–47.8 to 49.2); 0.978		15.4 (–36.3 to 67.0); 0.560		13.8 (–6.09 to 88.6); 0.717		14.7 (–56.1 to 85.4); 0.685	
NYHA class (NYHA I/II vs. NYHA III/IV)	–1.81 (–14.3 to 10.6); 0.776		1.31 (–12.0 to 14.6); 0.847		–5.90 (–34.6 to 22.8); 0.687		–8.14 (–35.7 to 19.4); 0.563	
HF aetiology (ischaemic vs. non-ischaemic)	3.73 (–8.26 to 15.7); 0.542		–4.30 (–17.1 to 8.51); 0.510		37.9 (9.34 to 66.4); 0.009		26.9 (–0.13 to 54.0); 0.051	
Ethnic group (white vs. non-white)	10.46 (–2.55 to 23.5); 0.115		14.2 (0.40 to 28.0); 0.044		–20.7 (–60.5 to 19.0); 0.307		8.34 (–29.5 to 46.1); 0.665	
Exercise capacity								
Baseline 6MWT directly measured	–0.05 (–0.11 to 0.01); 0.079		0.19 (–0.08 to 0.46); 0.176		–0.06 (–0.18 to 0.06); 0.321		–0.05 (–0.16 to 0.07); 0.421	

TABLE 18 Standardised exercise capacity score: overall treatment effect and subgroup (interaction) effects

Baseline variable	Primary analyses, mean difference (95% CI); *p*-value				Sensitivity analyses excluding HF-ACTION,[19] mean difference (95% CI); *p*-value			
	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect	One-stage model, 6-month follow-up, with random treatment effect	Two-stage model, 6-month follow-up, with random treatment effect	One-stage model, 12-month follow-up, with random treatment effect	Two-stage model, 12-month follow-up, with random treatment effect
Overall effect	0.230 (0.067 to 0.392); 0.006	0.256 (0.116 to 0.396); < 0.001	0.268 (0.110 to 0.426); 0.001	0.302 (0.142 to 0.462); < 0.001	0.256 (0.079 to 0.433); 0.005	0.278 (0.105 to 0.451); 0.002	0.298 (0.125 to 0.471); 0.001	0.324 (0.150 to 0.497); < 0.001
Interaction terms								
Age (years)	0.001 (–0.003 to 0.004); 0.758		–0.001 (–0.005 to 0.003); 0.636		0.003 (–0.008 to 0.014); 0.565		–0.000 (–0.010 to 0.009); 0.948	
Gender (male vs. female)	–0.063 (–0.157 to 0.319); 0.194		–0.096 (–0.197 to 0.006); 0.065		–0.066 (–0.250 to 0.118); 0.484		–0.065 (–0.240 to 0.110); 0.464	
Ejection fraction (%)	0.007 (0.001 to 0.012); 0.021		0.005 (–0.001 to 0.011); 0.108		0.008 (–0.003 to 0.019); 0.131		0.008 (–0.003 to 0.018); 0.169	
Ejection fraction (HFrEF vs. HFpEF)	0.11 (–0.20 to 0.43); 0.487		0.06 (–0.28 to 0.40); 0.733		0.21 (–0.23 to 0.65); 0.348		0.06 (–0.36 to 0.49); 0.766	
NYHA class (NYHA I/II vs. NYHA III/IV)	–0.010 (–0.098 to 0.079); 0.826		–0.043 (–0.138 to 0.052); 0.377		–0.011 (–0.184 to 0.162); 0.900		–0.061 (–0.224 to 0.101); 0.459	
HF aetiology (ischaemic vs. non-ischaemic)	0.012 (–0.074 to 0.098); 0.783		0.024 (–0.070 to 0.117); 0.620		0.035 (–0.143 to 0.213); 0.701		0.049 (–0.121 to 0.219); 0.573	
Ethnic group (white vs. non-white)	–0.064 (–0.159 to 0.031); 0.187		0.018 (–0.088 to 0.124); 0.741		–0.096 (–0.352 to 0.160); 0.461		0.078 (–0.195 to 0.351); 0.577	
Exercise capacity								
Standardised scores using baseline VO_2peak, 6MWT, ISWT units and watts score	–0.025 (–0.066 to 0.017); 0.240		–0.017 (–0.048 to 0.508); 0.105		–0.070 (–0.147 to 0.007); 0.077		–0.052 (–0.129 to 0.026); 0.191	

Chapter 7 Results from the surrogate analyses

Inclusion of trials in the ExTraMATCH II surrogate analyses

All 19 trials from the ExTraMATCH II study were eligible for inclusion in the surrogate analyses, if they provided the required data (as detailed in *Chapter 3*). Only 10 trials[19,51,58,61–67] provided data for the surrogate analyses. *Figure 12* summarises the availability of studies and patient data for exercise capacity and the patient-relevant outcomes of mortality, hospitalisation and HRQoL.

Characteristics of included patients and trials

Patient baseline characteristics were well balanced across the ExCR and control groups (*Table 19*). Patients had a mean age of 62 years and the majority were male (73%). The mean baseline left ventricular ejection fraction was 26% and most patients were in NYHA functional class II (63%) or III (34%). Studies were published between 2000 and 2012 from a range of geographical locations (*Table 20*). Sample size was typically small and ranged from 50 to 2130 patients. All trials included ExCR based on an aerobic exercise intervention. The dose of ExCR ranged widely across studies, with an average session duration of 15–60 minutes, of two to seven sessions per week, exercise intensity equivalent of 40–70% VO_2peak and delivery duration of 4–120 weeks. The change in exercise capacity and final patient-relevant outcomes for each included study are shown in *Table 21*.

Assessment of study quality and risk of bias

The overall quality of included trials was judged to be moderate to good, with a median TESTEX[31] score of 11 (range 10–14) out of a maximum score of 15 (*Table 22*).

Findings

Mediation analysis

The four criteria that must be satisfied to establish that change in exercise capacity is a mediator of mortality, hospitalisation and change in HRQoL are listed in *Table 23*. First, mean improvements were seen in all exercise capacity metrics of ExCR compared with control, although none reached statistical significance at $p < 0.05$. Second, greater differences in exercise capacity significantly reduced the risk of mortality and hospitalisation and were associated with a larger gain in HRQoL. Third, although ExCR decreased both the risk of mortality and hospitalisation, and was also associated with a larger gain in HRQoL, there was no statistically significant difference compared with the control. Finally, the effect of ExCR compared with control on final patient-relevant outcomes was attenuated by adding Δ6MWT and ΔVO_2peak (directly and indirectly measured) to the model. No attenuation was seen with the addition of ΔVO_2peak when measured directly.

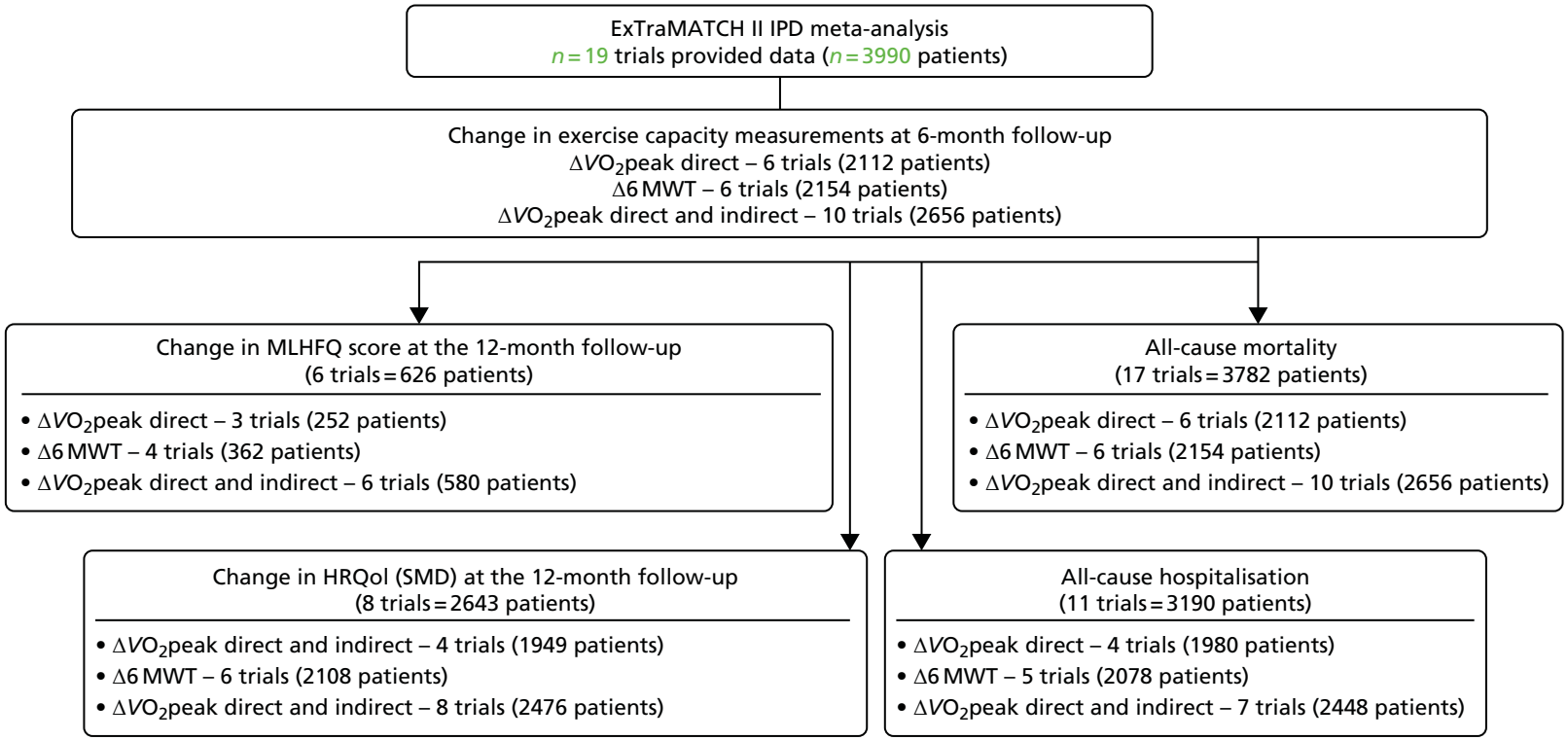

FIGURE 12 The PRISMA flow diagram summarising the selection of studies for the ExTraMATCH II surrogate analyses. Δ6MWT, change in 6-minute walk test; ΔVO_2peak, change in VO_2peak.

TABLE 19 Baseline characteristics of patients in surrogate analyses

Baseline variable	ExCR group (*n* = 1345)	Control group (*n* = 1311)	All patients (*n* = 2656)
Age (years), mean (SD)	61.2 (13.0)	61.6 (13.4)	61.39 (13.19)
Gender (male), *n* (%)	970 (72.1)	973 (74.2)	1943 (73.2)
Baseline ejection fraction, mean (SD)	26.0 (7.9)	26.2 (7.6)	26.1 (7.8)
NYHA class, *n* (%)			
Class I	13 (1)	27 (2)	27 (2)
Class II	834 (62)	861 (64)	848 (63)
Class III	485 (36)	444 (33)	457 (34)
Class IV	13 (1)	13 (1)	13 (1)
Aetiology (ischaemic), *n* (%)	713 (53)	708 (54)	1421 (54)
Ethnicity (white), *n* (%)	914 (70)	908 (71)	1822 (70)
VO_2peak (ml/kg/minute), mean (SD)	15.1 (4.6)	15.2 (4.8)	15.1 (4.7)
6MWT (m), mean (SD)	368 (108)	366 (110)	367 (109)

TABLE 20 Characteristics of included studies and interventions in surrogate analyses

Study characteristic	*n* (%), unless otherwise stated
Publication year	
2000–9	8 (80)
2010–12	2 (20)
Main study location	
Europe	6 (60)
North America[a]	4 (40)
Study centre	
Single	7 (70)
Multiple	3 (30)
Sample size	
0–99	5 (50)
100–999	4 (40)
≥ 1000	1 (10)
Duration of latest follow-up (weeks), median (range)	10.5 (6–30)
Intervention characteristic	
Type of exercise	
Aerobic exercise only	6 (60)
Aerobic plus resistance training	4 (40)
Dose of intervention	
Duration of intervention (weeks), median (range)	24 (4–120)
Frequency (sessions/week), median (range)	2.75 (2.5–6.5)
Length of exercise session (minutes), median (range)	30 (15–60)
Exercise intensity (range)	40–70% VO_2peak
	11–15 Borg rating
Setting	
Centre based	3 (30)
Home based	2 (20)
Both home and centre based	5 (50)

Borg, Borg Scale of Perceived Exertion.
a HF-ACTION study[19] was categorised as North America, but was also delivered to a small number of patients in France.

TABLE 21 Change in exercise capacity and final patient-relevant outcomes for each included study

Study (year)	ΔVO_2peak direct (ml/kg/minute), mean difference (95% CI)	Δ6MWT (m), mean difference (95% CI)	ΔVO_2peak direct and indirect (ml/kg/minute), mean difference (95% CI)	ΔMLHFQ, mean score (points) difference (95% CI)	ΔHRQoL any validated measure, mean difference (95% CI)	All-cause mortality, HR (95% CI)	All-cause hospital admission, HR (95% CI)
Dracup *et al.* (2007)[58]	0.04 (–1.26 to 1.34)	5.19 (–28.39 to 38.78)	0.15 (–0.91 to 1.21)	–2.19 (–9.09 to 4.70)	–0.15 (–0.44 to 0.15)	1.16 (0.51 to 2.64)	1.31 (0.84 to 2.05
Hambrecht *et al.* (2000)[51]	–2.16 (–4.43 to 0.10)		–2.16 (–4.43 to 0.10)			0.93 (0.13 to 6.65)	0.97 (0.14 to 6.88)
HF-ACTION (2009)[19]	0.47 (0.24 to 0.71)	18.14 (11.60 to 24.68)	0.43 (0.20 to 0.66)		–0.10 (–0.17 to –0.04)	0.92 (0.75 to 1.13)	0.93 (0.83 to 1.03)
Jolly *et al.* (2009)[61]			0.57 (–0.15 to 1.29)	1.35 (–4.02 to 6.71)	0.07 (–0.16 to 0.30)	1.62 (0.45 to 5.78)	0.72 (0.36 to 1.42)
Mueller *et al.* (2007)[62]	4.47 (2.35 to 6.60)		4.48 (2.35 to 6.60)			0.78 (0.33 to 1.85)	
Nilsson *et al.* (2008)[63]		77.22 (47.58 to 106.87)	1.78 (1.09 to 2.46)	–6.78 (–13.05 to –0.50)	–0.30 (–0.57 to –0.02)		
Passino *et al.* (2006)[67]	1.57 (0.66 to 2.49)		1.57 (0.66 to 2.49)	–23.41 (–28.87 to –17.94)	–0.82 (–1.01 to –0.63)	0.48 (0.23 to 0.97)	
Witham *et al.* (2005)[64]		5.18 (–17.41 to 27.76)	0.12 (–0.40 to 0.64)		0.04 (–0.40 to 0.49)	0.29 (0.03 to 2.84)	1.03 (0.41 to 2.60)
Witham *et al.* (2012)[65]		–2.03 (–26.14 to 22.08)	–0.05 (–0.60 to 0.51)	0.86 (–3.13 to 4.84)	0.04 (–0.16 to 0.24)	2.09 (0.19 to 23.03)	0.94 (0.39 to 2.28)
Yeh *et al.* (2011)[66]	–0.02 (–1.02 to 0.98)	1.25 (–24.71 to 27.20)	–0.17 (–1.16 to 0.82)	–3.09 (–9.31 to 3.14)	–0.16 (–0.43 to 0.12)		0.57 (0.14 to 2.38)
Pooled results	0.69 (–0.24 to 1.62); $p = 0.145$, $I^2 = 80.4\%$	16.69 (–1.08 to 34.36); $p = 0.066$, $I^2 = 76.5\%$	0.61 (0.10 to 1.11); $p = 0.019$, $I^2 = 80.3\%$	–5.53 (–13.27 to 2.21); $p = 0.162$, $I^2 = 91.5\%$	–0.18 (–0.39 to 0.02); $p = 0.084$, $I^2 = 87.9\%$	0.83 (0.67 to 1.04); $p = 0.107$, $I^2 = 25.7\%$	0.90 (0.76 to 1.06); $p = 0.210$, $I^2 = 12.4\%$

Δ6MWT, change in 6MWT; ΔHRQoL, change in HRQoL score; ΔMLHFQ, change in MLHFQ score; ΔVO_2peak: change in VO_2peak.

TABLE 22 Assessment of quality of included studies in surrogate analyses using TESTEX scale

Study (year)	Eligibility criteria specified	Randomisation specified	Allocation concealed	Groups similar at baseline	Blinding of assessors	Outcome measures in > 85% of participants[a]	Intention-to-treat analysis[b]	Between-group statistical comparisons reported	Point measures and measures of variability reported	Activity monitoring in control group	Relative Exercise intensity reviewed	Exercise volume and energy expended	Overall TESTEX score (maximum score of 15)
Dracup *et al.* (2007)[58]	1	0	0	1	0	3	1	2	1	1	1	1	10
Hambrecht *et al.* (2000)[51]	1	1	0	1	0	3	0	2	1	0	1	1	11
HF-ACTION (2009)[19]	1	1	1	1	1	3	1	2	1	1	0	1	14
Jolly *et al.* (2009)[61]	1	1	1	1	0	2	1	2	1	0	1	1	12
Mueller *et al.* (2007)[62]	1	0	0	1	0	2	1	2	1	0	1	1	10
Nilsson *et al.* (2008)[63]	1	1	0	1	1	2	1	2	1	0	0	1	11
Passino *et al.* (2006)[67]	1	0	0	1	0	2	1	2	1	0	1	1	10
Witham *et al.* (2005)[64]	1	1	0	1	1	3	1	2	1	0	1	0	12
Witham *et al.* (2012)[65]	1	1	0	1	1	3	1	2	1	0	1	0	12
Yeh *et al.* (2011)[66]	1	1	0	1	1	3	1	2	1	1	0	0	12

a Three points possible.
b If intention to treat was not specifically mentioned, but it was noted that no participants withdrew and all were analysed, then 1 point was awarded.

TABLE 23 Criteria to establish change in exercise capacity as a mediator in the relationship between treatment effect and patient-relevant final outcomes

Criteria	ΔVO_2peak direct (ml/kg/minute)	Δ6MWT (m)	ΔVO_2peak direct and indirect (ml/kg/minute)
Criterion 1			
Treatment assignment has a significant effect on exercise capacity	0.61 (95% CI –0.89 to 2.11)	14.61 (95% CI –6.16 to 35.37)	0.58 (95% CI –0.35 to 1.51)
Criterion 2			
Exercise capacity has a significant effect on ΔMLHFQ score	–1.64 (95% CI –2.57 to –0.71)	–0.06 (95% CI –0.08 to –0.03)	–1.80 (95% CI –2.77 to –0.83)
Exercise capacity has a significant effect on ΔHRQoL all measures (SD units)	–0.06 (95% CI –0.08 to –0.04)	–0.002 (95% CI –0.003 to –0.001)	–0.07 (95% CI –0.08 to –0.05)
Exercise capacity has a significant effect on all-cause mortality (HR)	0.88 (95% CI 0.84 to 0.92)	0.997 (95% CI 0.995 to 0.998)	0.88 (95% CI 0.84 to 0.92)
Exercise capacity has a significant effect on all-cause hospital admission (HR)	0.93 (95% CI 0.91 to 0.96)	0.998 (95% CI 0.997 to 0.999)	0.94 (95% CI 0.92 to 0.96)
Criterion 3			
Treatment assignment has a significant effect on patient-relevant final outcomes: • ΔMLHFQ score: –5.84 points (95% CI –11.96 to 0.77 points) • ΔHRQoL all outcomes (SD units): –0.22 (95% CI –0.38 to –0.07) • All-cause mortality HR: 0.85 (95% CI 0.73 to 0.99) • All-cause hospital admission HR: 0.91 (95% CI 0.83 to 1.00)			
Criterion 4[a]			
The effect of treatment assignment on ΔMLHFQ score is attenuated when the change in exercise capacity is added to the model	–8.28 (95% CI –18.56 to 2.01)	–1.77 (95% CI –4.76 to 1.23)	–4.70 (95% CI –10.81 to 1.40)
The effect of treatment assignment on ΔHRQoL all outcomes is attenuated when the change in exercise capacity is added to the model	–0.28 (95% CI –0.56 to –0.01)	–0.05 (95% CI –0.12 to 0.01)	–0.17 (95% CI –0.31 to –0.02)
The effect of treatment assignment on all-cause mortality HR is attenuated when the change in exercise capacity is added to the model	0.99 (95% CI 0.79 to 1.24)	1.00 (95% CI 0.81 to 1.24)	1.01 (95% CI 0.83 to 1.22)
The effect of treatment assignment on all-cause hospital admission HR is attenuated when the change exercise capacity is added to the model	0.93 (95% CI 0.82 to 1.04)	0.97 (95% CI 0.86 to 1.09)	0.95 (95% CI 0.85 to 1.06)

Δ6MWT, change in 6MWT; ΔHRQoL, change in HRQoL; ΔMLHFQ, change in MLHFQ score; ΔVO_2peak, change in VO_2peak.
a Mediator-adjusted coefficient.

Meta-analytic regression: R^2 and surrogate threshold effect

Regression coefficients of determination (R^2) and correlation coefficients (p-value) between the change in exercise capacity and hospitalisation were poor ($R^2_{trial} < 50\%$ and $p < 0.50$). Moderate to good levels of correlation ($R^2_{trial} > 50\%$ and $p > 0.50$) between exercise capacity VO_2peak and 6MWT with mortality and HRQoL were seen (*Table 24*). The STE for MLHFQ score ranged from an increase of 1.6 to 4.6 ml/kg/minute for VO_2peak. The STE was not estimable for the 6MWT. Negative correlation coefficients indicate that larger ExCR effects on exercise capacity are associated with larger ExCR effects on mortality and HRQoL. *Figures 13–15* illustrate the results of the meta-regression and STE analyses.

TABLE 24 Surrogacy metrics for change in exercise capacity and final outcomes

Surrogate metric	ΔVO_2peak direct (ml/kg/minute)	Δ6MWT (m)	ΔVO_2peak direct and indirect (ml/kg/minute)
ΔMLHFQ score	R^2_{trial} = 94%	R^2_{trial} = 65%	R^2_{trial} = 54%
	p = –0.80	p = –0.90**	p = –0.64
	STE 2 ml/kg/minute	STE not estimable	STE 3.2 ml/kg/minute
ΔHRQoL all outcomes (SD)	R^2_{trial} = 81%	R^2_{tria} = 54%	R^2_{trial} = 62%
	p = –0.60	p = –0.57	p = –0.53
	STE 1.6 ml/kg/minute	STE not estimable	STE 2 ml/kg/minute
All-cause mortality (HR)	R^2_{trial} = 21%	R^2_{trial} = 1%	R^2_{trial} = 7%
	p = –0.89**	p = –0.20	p = –0.31
	STE 4.6 ml/kg/minute	STE not estimable	STE not estimable
All-cause hospital admission (HR)	R^2_{trial} = 26%	R^2_{trial} = 9%	R^2_{trial} = 14%
	p = –0.20	p = –0.03	p = –0.21
	STE 1.8 ml/kg/minute	STE 38 ml/kg/minute	STE 1.8 ml/kg/minute

**$p < 0.05$.
Δ6MWT, change in 6MWT; ΔHRQoL, change in HRQoL; ΔMLHFQ, change in MLHFQ score; ΔVO_2peak, change in VO_2peak.

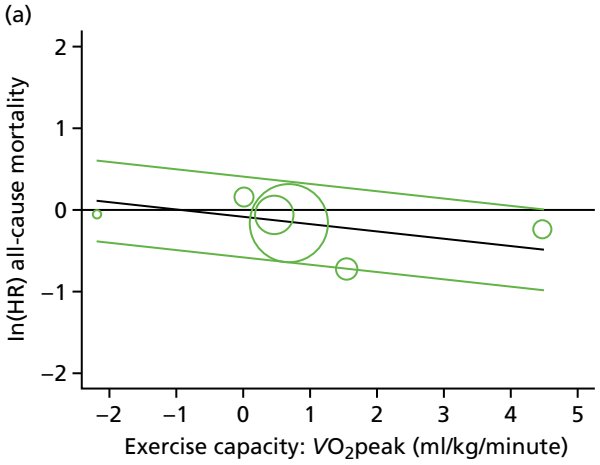

FIGURE 13 Regression analyses: relationship at the 6-month follow-up between ΔVO_2peak direct and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference. (*continued*)

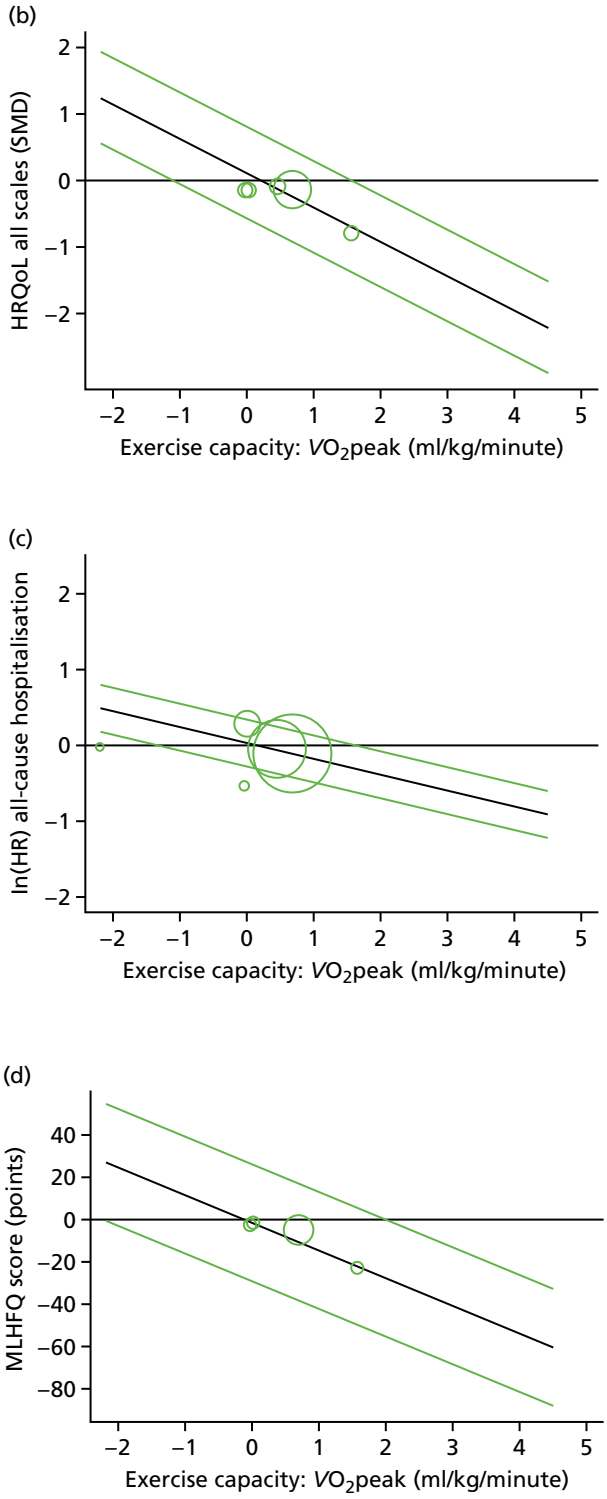

FIGURE 13 Regression analyses: relationship at the 6-month follow-up between ΔVO_2peak direct and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference.

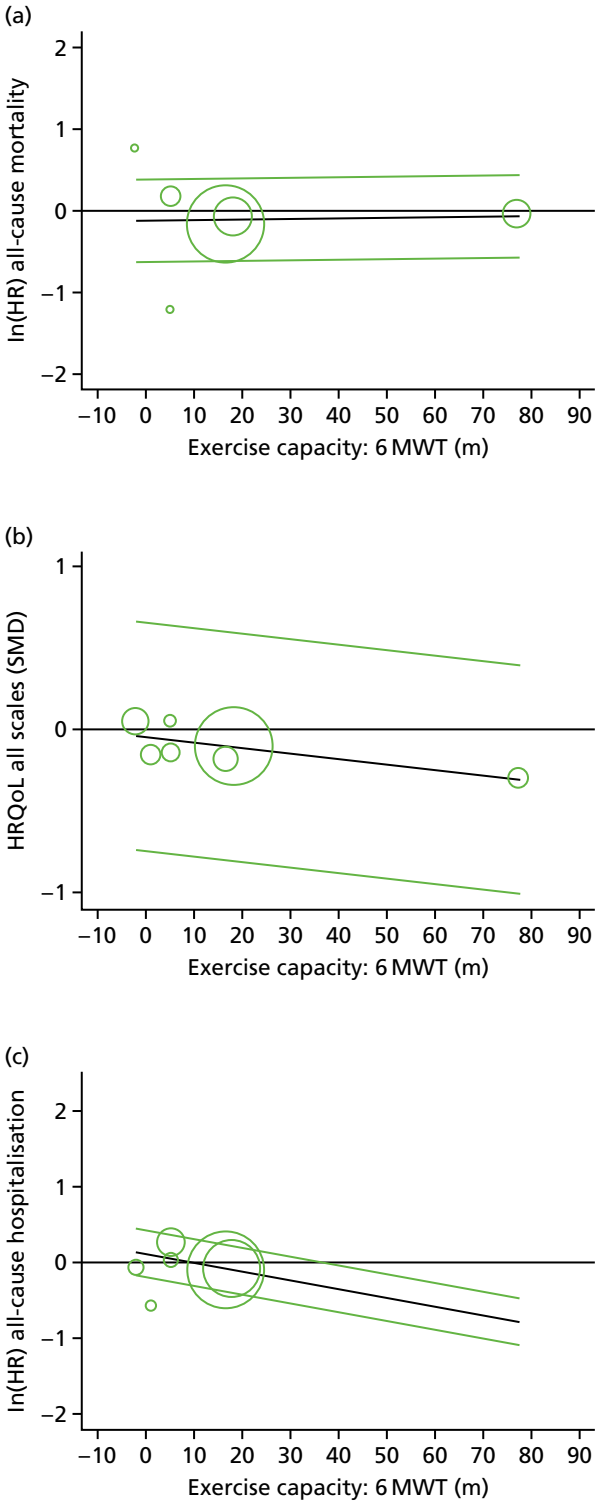

FIGURE 14 Regression analyses: relationship at the 6-month follow-up between Δ6MWT and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference. (*continued*)

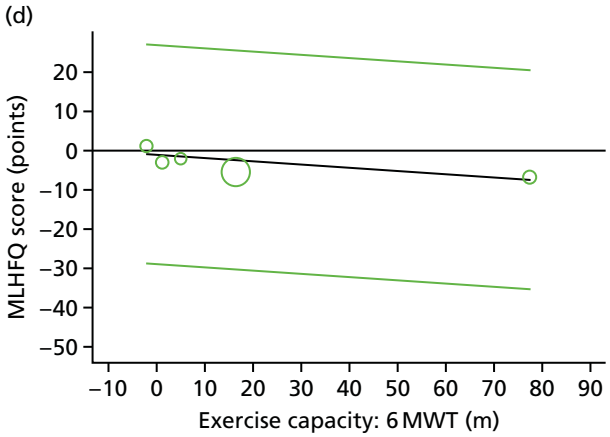

FIGURE 14 Regression analyses: relationship at the 6-month follow-up between Δ6MWT and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference.

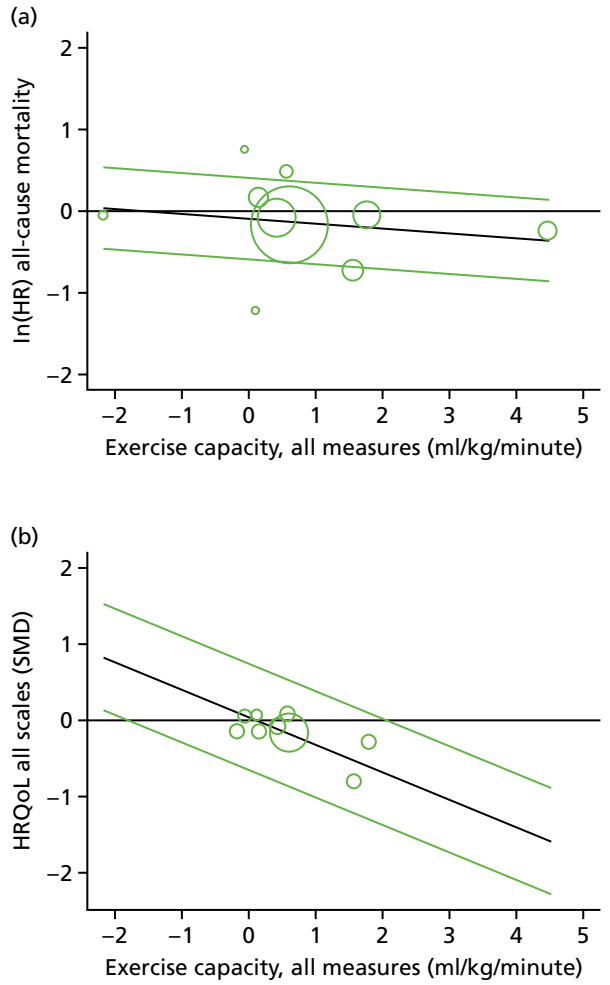

FIGURE 15 Regression analyses: relationship between ΔVO_2peak direct and indirect and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference. (*continued*)

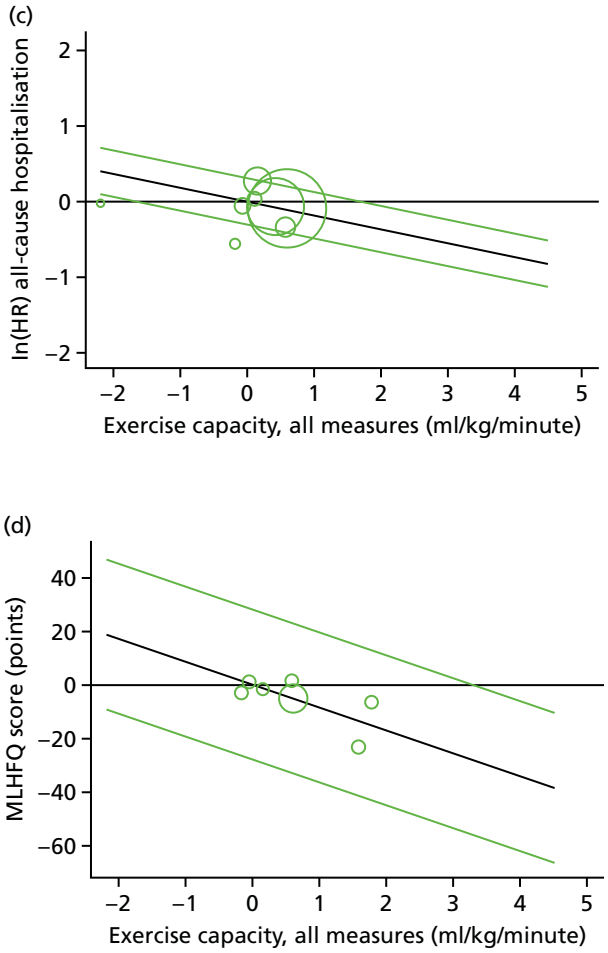

FIGURE 15 Regression analyses: relationship between ΔVO_2peak direct and indirect and (a) log(HR) of all-cause mortality; (b) ΔHRQoL all outcomes; (c) log(HR) of all-cause hospitalisation; and (d) ΔMLHFQ score. Circles represent trial-level treatment effects, with sizes proportionate to study weights (based on inverse variance weighting). Solid green lines correspond to the bounds of the 95% prediction interval for the true effect on the final outcomes in a new study. SMD, standardised mean difference.

Small-study bias

There was no evidence of significant small-study bias, as shown by the funnel plots (*Figure 16*) or Egger's test *p*-values, for any of the exercise capacity outcomes (ΔVO_2peak direct, $p = 0.699$; Δ6MWT, $p = 0.93$; ΔVO_2peak direct and indirect, $p = 0.553$), or for the four patient-relevant final outcomes (ΔMLHFQ score, $p = 0.607$; ΔHRQoL outcomes, $p = 0.659$; mortality, $p = 0.745$; hospitalisation, $p = 0.733$).

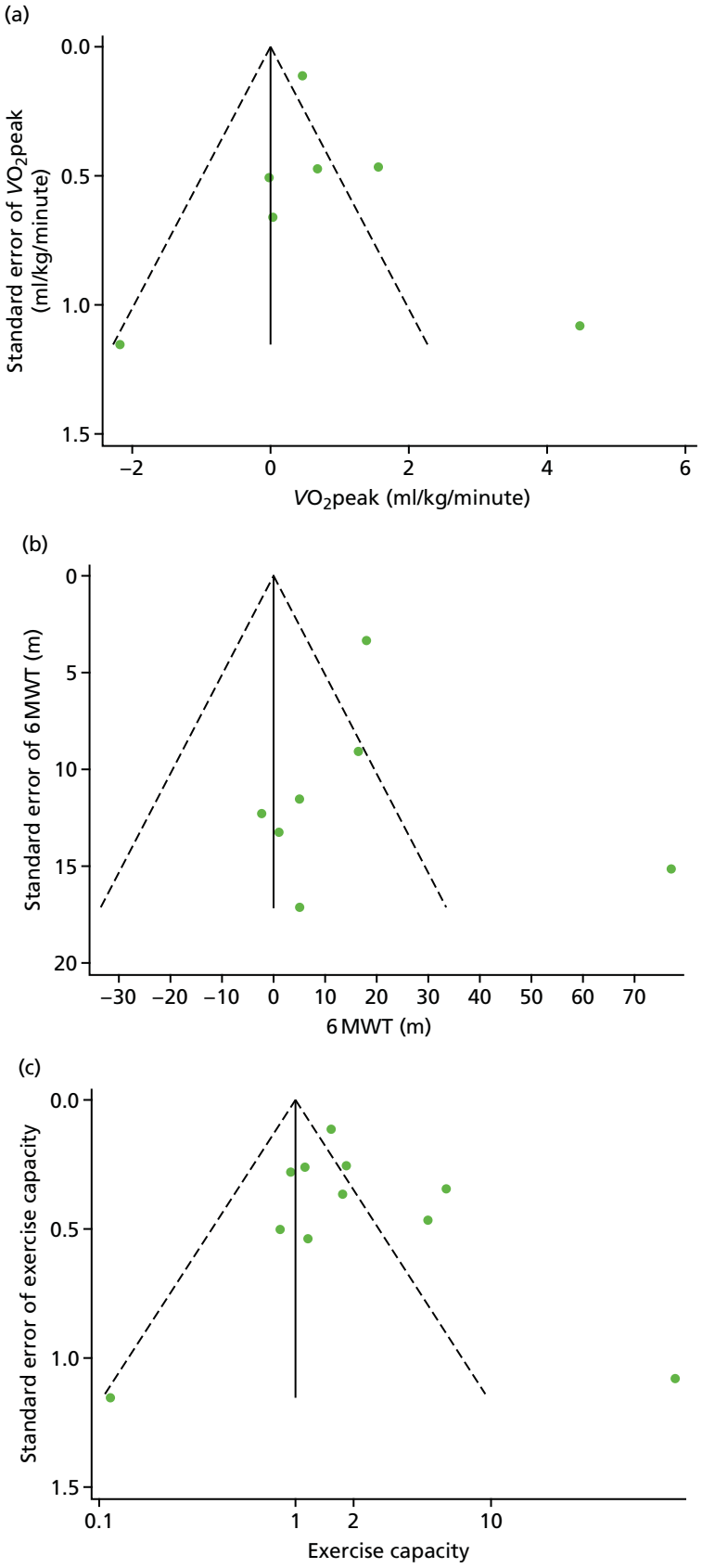

FIGURE 16 Funnel plots for the surrogate analyses. (a) VO_2peak; (b) 6MWT; (c) converted exercise capacity score; (d) HRQoL; (e) MLHFQ score; (f) mortality; and (g) hospitalisation. (*continued*)

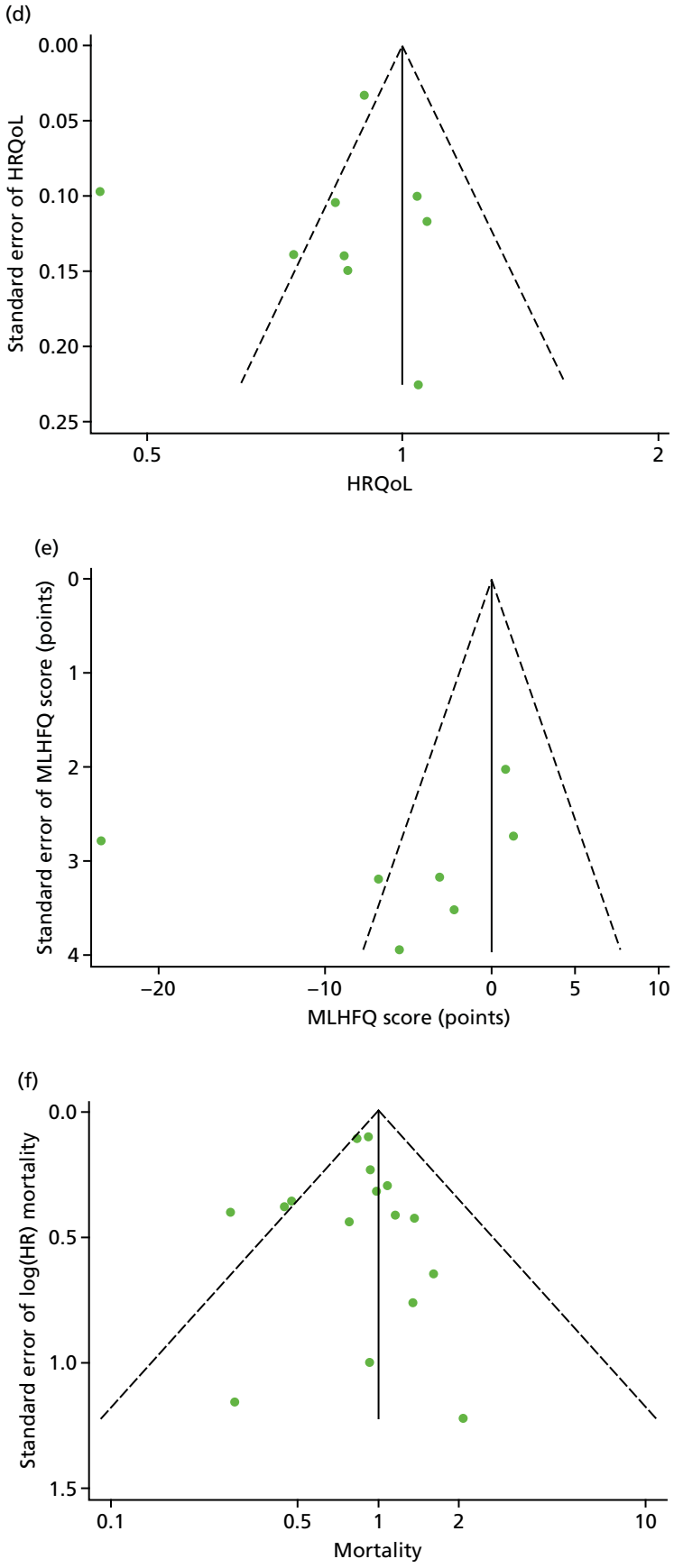

FIGURE 16 Funnel plots for the surrogate analyses. (a) VO_2peak; (b) 6MWT; (c) converted exercise capacity score; (d) HRQoL; (e) MLHFQ score; (f) mortality; and (g) hospitalisation. (*continued*)

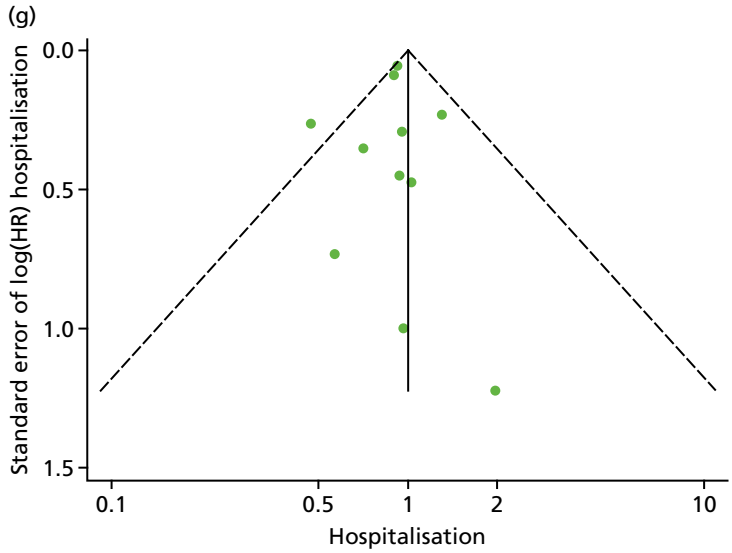

FIGURE 16 Funnel plots for the surrogate analyses. (a) VO_2peak; (b) 6MWT; (c) converted exercise capacity score; (d) HRQoL; (e) MLHFQ score; (f) mortality; and (g) hospitalisation.

Chapter 8 Discussion

The ExTraMATCH II project is a meta-analysis of IPD from HF patients recruited to RCTs conducted worldwide, which sought to determine which HF patient subgroups benefit most from ExCR and assess the suitability of exercise capacity as a surrogate end point.

Summary of findings

Of the 37 eligible trials, 19 contributed data to the IPD meta-analysis: 18 trials (3912 patients) to the clinical events (mortality and hospitalisation) analysis; 13 trials (3332 patients) to the exercise capacity and HRQoL analysis; and 10 trials (2656 patients) to the exercise capacity mediational/surrogate end-point analysis.

Patient characteristics at baseline were well balanced between patients in the ExCR and control groups. The majority of patients were male (74%), had a mean age of 61 years, had experienced HFrEF (mean left ventricular ejection fraction of 26.9%) and were in NYHA functional class II (59%) or III (38%). Trials from Europe and North America were published between 1990 and 2012. Sample sizes ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention, which was most commonly delivered in either an exclusively centre-based setting or a centre-based setting in combination with some home exercise sessions. The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 15–90 weeks, with between two and seven sessions per week (median session duration was between 4 and 120 minutes, including warm-up and cool-down). The intensity of exercise ranged between 50% and 85% VO_2peak. The overall quality of included trials was judged to be moderate to good, with a median TESTEX score[31] of 11 (range 9–14) out of a maximum score of 15.

Compared with no exercise control, ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation. However, uncertainty around effect estimates precludes drawing definitive conclusions for these event outcomes. In contrast, ExCR was found to significantly improve both exercise capacity and HRQoL, the improvement in MLHFQ score being also clinically important (i.e. a mean reduction of ≥ 5 points).[74] We found no consistent differences in ExCR effects across patient subgroups (i.e. age, sex, ethnicity, NYHA functional class, ischaemic aetiology, ejection fraction and baseline exercise capacity) on mortality, hospitalisation, exercise capacity or HRQoL. The validation of exercise capacity as a putative surrogate end point for patient-relevant outcomes (i.e. mortality, hospitalisation and HRQoL) was limited by access to only a small number of trials that were able to contribute suitable patient-level data. Although subject to considerable statistical uncertainty, the results provide indicative evidence that VO_2peak and 6MWT may be suitable surrogate end points for the treatment effect of ExCR on final outcomes in patients with HF.

Comparison to existing evidence

The finding of a lack of consistent evidence for HF patient subgroup effects of ExCR agrees with both the previous ExTraMATCH[18] and Cochrane analyses.[10] However, these two previous studies had major limitations that are likely to have limited their ability to detect subgroup effects. ExTraMATCH[18] included data on 801 HF patients and observed 88 deaths and 300 patients with a composite outcome of death or hospitalisation and, therefore, lacked statistical power. Using meta-regression analysis, the 2014 Cochrane review[10] found no association between trial-level patient characteristics and ExCR. However, meta-regression analysis is highly prone to study-level confounding (ecological fallacy) and should be interpreted with great caution.[75]

The findings are also consistent with the IPD subgroup analyses from the multicentre HF-ACTION study.[19] The HF-ACTION[19] investigators reported no significant interaction effect of exercise training intervention on their composite primary outcome (i.e all-cause mortality or hospitalisation) and subgroups of age (≤ 70 vs. > 70 years), sex, race (white vs. non-white), HF aetiology (ischaemic vs. non ischaemic), ejection fraction (≤ 25% vs. > 25%) or NHYA class (II vs. III/IV).[19] A post hoc analysis by HF-ACTION[19] investigators found a significant (adjusted $p = 0.02$) interaction between ExCR and the change in 6MWT with ExCR and ethnicity (+26 m in black patients vs. +11 m in white patients), consistent with the current study.[76]

The validation study results of the suitability of exercise as surrogate outcome, albeit uncertain, are broadly in agreement with this research team's recent study based on a trial-level meta-analysis.[77]

Strengths and limitations

The ExTraMATCH II project has a number of strengths. The IPD meta-analysis is the largest to date and has greater power to detect any differential treatment effect across groups than single trials or aggregate meta-analysis. We were able to standardise the handling and analysis of time-to-event outcomes and continuous outcomes across trials. We found no evidence of publication bias. The project was conducted and reported in accordance with current IPD guidance and the PRISMA IPD statement.[21,78]

Although systematic reviews and meta-analyses of IPD from randomised trials are recognised as the gold standard for assessing intervention effects,[79] the study has a number of limitations. First, there was a lack of consistency in how included trials with IPD in the analyses defined and collected the outcomes of interest (i.e. time to event for death and hospitalisation, exercise capacity and HRQoL). We made considerable efforts to contact study authors to clarify issues around the definition of outcomes, especially HF-related mortality and hospitalisations. Although we were able to resolve data issues in many cases, we recognise that a lack of consistency in outcome definition across included trials may exist, weakening the strength of these conclusions. Second, we were not able to obtain IPD from all includable trials for all outcomes; not all investigators for the trials that met the inclusion criteria were able to provide IPD and, of the trials that did provide IPD, not all collected the outcomes of interest. For example, the large NIH-funded US multicentre HF-ACTION study[19] did not collect HF-specific hospitalisation data,[19] thus reducing the statistical power for this outcome. Third, we did not seek patient-level data on 'ExCR dose' (i.e. adherence according to exercise training duration, frequency and intensity undertaken by an individual patient). Using IPD from HF-ACTION,[19] Keteyian *et al.*[80] found exercise volume (defined as metabolic equivalent of task hours per week) to be a predictor for the composite outcome of all-cause mortality or hospitalisation ($p = 0.03$). Fourth, there were high levels of statistical heterogeneity for both exercise capacity and HRQoL outcomes. This heterogeneity may well have reflected the variation in ExCR interventions across the included trials. Fifth, the analysis is based on randomised trials identified by literature searches up to 2013 and, therefore, did not include IPD from more recent trials that may have met the inclusion criteria of this study.

Finally, in terms of the surrogate validation analysis, a particular limitation was the proportion of included trials that provided patient-level data on both exercise capacity and patient-relevant outcomes. Of the 19 trials (3990 patients) that met the inclusion criteria, only 10 trials (2656 patients) provided paired data on exercise capacity and mortality, hospitalisation or HRQoL. This has a number of implications for the interpretation of the findings. First, the statistical power of the analysis was low, evidenced by the wide CIs in pooled analysis and, although all outcomes were in direction of benefit of ExCR, none reached a level of formal statistical significance at the 5% level. Second, and relatedly, we had limited statistical power to detect an association between changes in exercise capacity and the final patient-related outcomes. Last, the results are likely to be subject to selection bias and, therefore, may not be representative of all RCT evidence.

Relevance to clinical practice

The observed improvements in patient exercise capacity and HRQoL with ExCR participation support the class I recommendation of current international clinical guidelines that ExCR should be offered to HF patients.[3,13,15] The findings do not endorse limiting ExCR interventions to subgroups of HF patients.

Research recommendations

In spite of the comprehensiveness of this IPD meta-analysis, the findings of this study demonstrate that further evidence is still required to definitively assess the impact of ExCR on mortality and hospitalisation in patients with HFrEF; in particular, to increase the power to examine whether or not the effect of ExCR varies according to patient characteristics. To more reliably quantify the impact of ExCR on clinical outcomes and examine how these effects may vary across HF patients, there is an urgent need for trial investigators to more consistently collect, report and share patient-level data in the future.

Two central aspects of future data collection are a consensus on the definition, collection and reporting of clinical event data, especially hospitalisation, and the capture of data on patient-level adherence to the amount of exercise training during the ExCR intervention period. More generally, the research community should continue to implement policies that encourage primary study authors to make their data sets available, either by depositing in publicly available repositories or by sharing with IPD meta-analysis collaborations when directly requested.[81]

Given that the vast majority of IPD in this study was from HFrEF patients, future trials including HFpEF patients are needed to assess the effectiveness of ExCR and whether or not there are differential effects of ExCR in this patient group.

Future IPD meta-analyses of RCTs for interventions in HF are needed to confirm the tentative conclusion that VO_2peak and 6MWT may be suitable surrogate end points for the final patient-related outcomes. Such future IPD meta-analyses also need to consider individual patient adherence to exercise training.

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Contributions of authors

Rod S Taylor (Professor of Health Services Research) was project chief investigator with overall responsibility for the project and guarantor, designed the project, obtained the data, contributed to the design of the data analysis, led the report write-up and edited the final report.

Sarah Walker (Research Fellow in Medical Statistics) performed the data checking and cleaning process, undertook the statistical analysis for the impact of ExCR on clinical events and exercise capacity/HRQoL outcomes, and contributed to drafting of the paper.

Oriana Ciani (Postdoctoral Research Fellow) designed the project, undertook the statistical analysis for the mediation and surrogate validation of exercise capacity, and contributed to drafting of the paper.

Fiona Warren (Senior Lecturer in Medical Statistics) designed the project, advised on the statistical analysis and contributed to the report write-up.

Neil A Smart (Professor in Exercise and Sports Science) designed the project, provided advice and content-specific expertise, contributed to the data checking and cleaning, and contributed to the report write-up.

Massimo Piepoli (Professor of Cardiology) designed the project, provided advice and content-specific expertise and contributed to obtaining the data and report write-up.

Constantinos H Davos (Associate Professor of Cardiovascular Diseases) contributed to obtaining the data, provided advice and content-specific expertise, and contributed to the report write up.

Publications

Taylor RS, Piepoli MF, Smart N, Coats AJS, Ellis S, Dalal H, *et al.* Exercise training for chronic heart failure (ExTraMATCH II): protocol for an individual participant data meta-analysis. *Int J Cardiol* 2014;**174**:683–7.

Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren F, *et al.* Validation of exercise capacity as a surrogate endpoint in exercise-based rehabilitation for chronic heart failure: a meta-analysis of randomised controlled trials. *JACC Heart Fail* 2018;**6**:596–604.

Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, *et al.* Impact of exercise-based rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual-patient data meta-analysis of randomised trials – manuscript submitted for publication. *Eur J Heart Failure* 2018;**20**:1735–43.

Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, *et al.* Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure. individual participant meta-analysis. *J Am Coll Cardio* 2019;**73**:1430–43.

Data–sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Project management committees

Project Management Group

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International Steering Committee

All members of the Project Management Group, plus:

Professor Andrew Coats (chairperson), Istituto di Ricovero e Cura a Carattere Scientifico, San Raffaele, Pisana, Italy; and University of Warwick, Coventry, UK.

Professor Stephen Ellis, Duke Clinical Research Institute, Durham, NC, USA.

Associate Professor Hasnain M Dalal, University of Exeter Medical School, Exeter, UK; and Research, Development & Innovation, Royal Cornwall Hospital, Truro, UK.

Professor Steven Keteyian, Department of Medicine, Henry Ford Hospital, Detroit, MI, USA.

Professor Christopher O'Connor, Duke Clinical Research Institute, Durham, NC, USA.

Professor David Whellan, Department of Medicine, Sidney Kimmel Medical College, Philadelphia, PA, USA.

Appendix 2 Example database search strategy from the Cochrane 2014 review

MEDLINE(R) Ovid

Date range searched: 1946 to January week 4 2013.

Date searched: January 2013.

Search strategy

1. xp Myocardial Ischemia/
2. myocard$4 adj5 (ischaemi$2 or ischemi$2)).ti,ab.
3. (ischaemi$2 or ischemi$2) adj5 heart).ti,ab.
4. xp Coronary Artery Bypass/
5. oronary.ti,ab.
6. xp Coronary Disease/
7. xp Myocardial Revascularization/
8. Myocardial Infarction/
9. myocard$5 adj5 infarct$5).ti,ab.
10. (heart adj5 infarct$5).ti,ab.
11. exp Angina Pectoris/
12. angina.ti,ab.
13. exp Heart Failure/
14. (heart adj5 failure).ti,ab.
15. (HFNEF or HFPEF or HFREF or 'HF NEF' or 'HF PEF' or 'HF REF').ti,ab.
16. or/1-15
17. exp Heart Diseases/
18. (heart adj5 disease$2).ti,ab.
19. myocard$5.ti,ab.
20. cardiac$2.ti,ab.
21. CABG.ti,ab.
22. PTCA.ti,ab.
23. (stent$4 and (heart or cardiac$4)).ti,ab.
24. Heart Bypass, Left/or exp Heart Bypass, Right/
25. or/17-24
26. *Rehabilitation Centers/
27. exp Exercise Therapy/
28. *Rehabilitation/
29. exp Sports/
30. Physical Exertion/or exertion.ti,ab.
31. exp Exercise/
32. rehabilitat$5.ti,ab.
33. (physical$4 adj5 (fit or fitness or train$5 or therap$5 or activit$5)).ti,ab.
34. (train$5 adj5 (strength$3 or aerobic or exercise$4)).ti,ab.
35. ((exercise$4 or fitness) adj5 (treatment or intervent$4 or programs$2 or therapy)).ti,ab.
36. Patient Education as Topic/
37. (patient$2 adj5 educat$4).ti,ab.
38. ((lifestyle or life-style) adj5 (intervent$5 or program$2 or treatment$2)).ti,ab.
39. *Self Care/

40. (self adj5 (manage$5 or care or motivate$5)).ti,ab.
41. *Ambulatory Care/
42. exp Psychotherapy/
43. psychotherap$2.ti,ab.
44. (psycholog$5 adj5 intervent$5).ti,ab.
45. relax$6.ti,ab.
46. exp Relaxation Therapy/or exp Mind-Body Therapies/
47. exp Counseling/
48. (counselling or counseling).ti,ab.
49. exp Cognitive Therapy/
50. exp Behavior Therapy/
51. ((behavior$4 or behaviour$4) adj5 (modify or modificat$4 or therap$2 or change)).ti,ab.
52. *Stress, Psychological/
53. (stress adj5 management).ti,ab.
54. (cognitive adj5 therap$2).ti,ab.
55. meditat$4.ti,ab.
56. *Meditation/
57. exp Anxiety/
58. (manage$5 adj5 (anxiety or depress$5)).ti,ab.
59. CBT.ti,ab.
60. hypnotherap$5.ti,ab.
61. (goal adj5 setting).ti,ab.
62. (goal$2 adj5 setting).ti,ab.
63. (psycho-educat$5 or psychoeducat$5).ti,ab.
64. (motivat$5 adj5 (intervention or interv$3)).ti,ab.
65. Psychopathology/
66. psychopathol$4.ti,ab.
67. psychosocial$4.ti,ab.
68. distress$4.ti,ab.
69. exp Health Education/
70. (health adj5 education).ti,ab.
71. (heart adj5 manual).ti,ab.
72. Autogenic Training/
73. autogenic$5.ti,ab.
74. or/26-39
75. or/40-73
76. 16 or 25
77. 74 or 75
78. 76 and 77
79. randomized controlled trial/
80. randomized controlled trial.pt.
81. controlled clinical trial.pt.
82. controlled clinical trial/
83. Random Allocation/
84. Double-Blind Method/
85. single-blind method/
86. (random$ or placebo$).ti,ab.
87. ((singl$3 or doubl$3 or tripl$3 or trebl$3) adj5 (blind$3 or mask$3)).ti,ab.
88. exp Research Design/
89. Clinical Trial.pt.
90. exp clinical trial/

91. (clinic$3 adj trial$2).ti,ab.
92. or/79-91
93. 78 and 92
94. (Animals not Humans).sh.
95. 93 not 94
96. limit 95 to yr=‘2008 -Current’

Appendix 3 Identified randomised controlled trials meeting inclusion criteria

First author/ study (year)	Total patients (*n*)[a]	Trial setting (single or multicentre)	NYHA class	Mean ejection fraction (%)	Mean age (years)	Male (%)	Exercise type[b]	Overall exercise duration (minutes)	Exercise frequency (sessions/ week)	Mean programme duration (weeks)	Exercise setting[c]	Longest follow-up (months)
Cochrane 2014 review												
Austin *et al.* (2005)[70]	200	Single	II/III	NR	72	43	Mix	120	2.5	24	Both	60
Belardinelli *et al.* (1999)[50]	99	Single	II/IV	28	55	89	Aerobic	40	2.5	56	Centre	26
Belardinelli *et al.* (2012)[56]	123	Single	II/III	37	59	78	Aerobic	40	2.5	56	Centre	120
Davidson *et al.* (2010)[69]	105	Single	I/II/III/IV	NR	72.3	67	Mix	40	1	12	Centre	12
Dracup *et al.* (2007)[58]	173	Single	II/IV	26	54	72	Mix	28	4	52	Home	12
DANREHAB (2008)[57]	91	Single	I/II/III	NR	66	90	Mix	90	3	12	Both	12
Gary *et al.* (2010)[59]	65	Single	II/III	NR	65.8	42	Aerobic	37.5	3	12	Home	6
Giannuzzi *et al.* (2003)[60]	90	Multi	II/III	25	60.5	88	Aerobic	30	4	24	Both	6
Hambrecht *et al.* (2000)[51]	73	Single	I/II/III	29	54	100	Aerobic	15	6.5	24	Both	6
HF-ACTION (2009)[19]	2331	Multi	II/III/IV	25	59	72	Aerobic	30	2.5	120	Both	48
Jolly *et al.* (2009)[61]	169	Multi	I/II/IV	NR	66	75	Mix	25	5	48	Home	12
Klecha *et al.* (2007)[71]	50	Single	II/III	28	61	100	Aerobic	20	3	24	Centre	6
McKelvie *et al.* (2002)[52]	181	Multi	I/II/III	NR	65.5	81	Mix	30	2	36	Both	12
Mueller *et al.* (2007)[62]	50	Single	NR	NR	55	100	Aerobic	120	5	4	Centre	74
Nilsson *et al.* (2008)[63]	80	Single	II/III	31	70	79	Aerobic	50	2	16	Centre	12
Passino *et al.* (2006)[67]	95	Single	I/II/III	34	60.5	87	Aerobic	30	3	36	Home	9
Willenheimer (2001)[54]	54	Single	NR	36.5	64	71.5	Aerobic	30	2.5	16	Centre	10
Witham *et al.* (2005)[64]	82	Single	II/III	NR	80.5	55	Mix	20	2.5	24	Both	6
Witham *et al.* (2012)[65]	107	Single	II/III	NR	81	100	Mix	60	2	24	Both	6
Yeh *et al.* (2011)[66]	100	Multi	I/II/III	29	67.5	64	Aerobic	30	2.5	12	Both	6

First author/ study (year)	Total patients (*n*)[a]	Trial setting (single or multicentre)	NYHA class	Mean ejection fraction (%)	Mean age (years)	Male (%)	Exercise type[b]	Overall exercise duration (minutes)	Exercise frequency (sessions/ week)	Mean programme duration (weeks)	Exercise setting[c]	Longest follow-up (months)
ExTraMATCH I (2004)												
Dubach *et al.* (1997);[72] Myers (2002)[82]	51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	8.5
Zanelli *et al.* (1997)[55]	155	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10
Wielenga *et al.* (1999)[53]	80	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	47.3

DANREHAB, DANish Cardiac ReHABilitation trial; NR, not reported.
a Total number of patients randomised.
b 'Mix' includes aerobic and resistance training.
c Exercise settings comprise home, centre or both.
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Appendix 4 ExTraMATCH II core data fields

Variable	Description
Study-level data	
Centre ID	Centre name
Randomised control patients (*n*)	
Randomised exercise patients (*n*)	
Patient-level data: descriptive	
Patient ID	
Date of randomisation	dd/mm/yyyy
Allocated treatment	1. Exercise
	2. Control
Date of birth	dd/mm/yyyy
Gender	1. Male
	2. Female
	9. Data unavailable
Race	1. White/Caucasian
	2. African/African-American
	3. Asian
	4. Other
	9. Data unavailable
Aetiology of HF	1. Ischaemic heart disease
	2. Idiopathic dilated cardiomyopathy
	3. Other/unknown
	9. Data unavailable
Year of HF diagnosis	yyyy
NYHA class at entry/baseline	1. NYHA class I
	2. NYHA class II
	3. NYHA class III
	4. NYHA class IV
	9. Unknown/unavailable
Ejection fraction at entry/baseline (%)	

Variable	Description
Patient level data: outcomes	
Method of exercise capacity assessment	1. 6MWT
	2. Bicycle ergometer test
	3. Treadmill test
	4. Other (state)
Exercise capacity score at entry (units)	
Follow-up 1 exercise capacity score	Follow-up time (months)
Follow-up 2 exercise capacity score	Follow-up time (months)
Follow-up 3 exercise capacity score	Follow-up time (months)
HRQoL	1. MLHFQ
	2. Other measure (state)
HRQoL at entry	Total and subscores
Follow-up 1 HRQoL score	Total and subscores
	Follow-up time (months)
Follow-up 2 HRQoL score	Total and subscores
	Follow-up time (months)
Follow-up 3 HRQoL score	Total and subscores
	Follow-up time (months)
Date of death	dd/mm/yyyy
Cause of death	1. Acute myocardial infarction
	2. Sudden death
	3. Heart failure
	4. Other cardiac
	5. Stroke
	6. Other vascular/thromboembolic
	7. Non-cardiovascular
	8. Unknown
	(1–4, cardiac; 1–6, cardiovascular)
Date of first all-cause hospital admission	dd/mm/yyyy
	1. De novo hospitalisation
	2. Rehospitalisation
Date of first HF hospital admission	dd/mm/yyyy
	1. De novo hospitalisation
	2. Rehospitalisation
Number of all-cause hospitalisations	
Number of all HF hospitalisations	

Variable	Description
Dropout	
Date of study discontinuation	dd/mm/yyyy
Reason for study discontinuation	
Exercise training (applies only to exercise group patients)	
Study-level data	
Prescribed exercise training	
Overall duration	— weeks (ranges if appropriate)
Session duration	— minutes (range if appropriate)
Frequency of sessions	— sessions/week (range if appropriate)
Intensity	— % units (range if appropriate)
Setting	1. Centre only
	2. Home only
	3. Both centre and home (define proportion of sessions at each location)
	4. Other (state)
Patient-level data	
Attended first exercise training	1. Yes
	2. No
	3. Not reported
Are details available at patient level on exercise dose received?	1. Yes
	2. No

dd, date; ID, identification; mm, month; yyyy, year.

Appendix 5 Prediction of VO_2peak in heart failure from submaximal exercise tests

6-minute walk test

A number of studies have examined the relationship between 6MWT and VO_2peak in HF patients and reported variable levels of association/correlation. Many studies failed to report a prediction equation or reported a multivariate equation that incorporated clinical parameters not available in the ExTraMATCH II IPD set. A recent discussion paper on the use of the 6MWT in HF has questioned the reliability of prediction of VO_2peak.[42] However, a review in 2010, by Ross *et al.*,[39] of 11 studies in 1083 patients with cardiopulmonary disease (many with HF) found generally high levels of association of VO_2peak and 6MWT (average correlation coefficient of 0.59). Using a study-level random-effects linear regression approach, the authors derived the following overall prediction model, with a standard error of estimate of 1.1 ml/kg/minute:

$$VO_2\text{peak (ml/kg/minute)} = 4.948 + 0.023 \times \text{6MWT (m)}. \quad (1)$$

Incremental shuttle walk test

Keell *et al.*[40] tested the safety and acceptability of the ISWT in patients with chronic HF and examined the relationship between ISWT performance and VO_2peak:

$$VO_2\text{peak (ml/kg/minute)} = (0.27 \times \text{number of 10-m shuttles}) + 7.77. \quad (2)$$

Similarly, Fowler *et al.*[41] proposed the following formula in patients following coronary artery bypass surgery:

$$VO_2\text{peak (ml/kg/minute)} = 7.81 + [0.03 \times \text{ISWT distance (m)}]. \quad (3)$$

EME
HS&DR
HTA
PGfAR
PHR

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