Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation

ExTraMATCH II Collaboration

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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 Draft--

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Abstract:	Aims To undertake an individual patient data (IPD) meta-analysis to assess the impact of exercise-based cardiac rehabilitation (ExCR) in patients with heart failure (HF) on mortality and hospitalisation , and differential effects of ExCR according to patient characteristics: age, sex, ethnicity, New York Heart Association (NYHA) functional class, ischaemic aetiology, ejection fraction, and exercise capacity. Methods Randomised trials of exercise training for at least 3 weeks compared with no exercise control with 6-months' follow up or longer, providing IPD time to event on mortality or hospitalisation (all-cause or HF-specific). IPD were combined into a single dataset. We used Cox proportional hazards models to investigate the effect of ExCR and the interactions between ExCR and participant characteristics. We used both two-stage random effects, and 1-stage fixed effect, models. Results IPD was obtained from 18 trials including 3912 patients with reduced ejection fraction HF. Compared to control, there was no statistically significant difference in pooled time to event estimates in favour of ExCR although confidence intervals were wide: all-cause mortality: hazard ratio (HR): 0.83 (95% confidence interval (CI): 0.67 to 1.04), HF-related mortality: HR 0.84 (95% CI: 0.49 to 1.46), all-cause hospitalisation: HR 0.90 (95% CI: 0.76 to 1.06), and HF-related hospitalisation: HR 0.98 (95% CI: 0.72 to 1.35). No strong evidence was found of differential intervention effects across patient characteristics. Conclusion ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation in reduced ejection fraction HF. However, uncertainty around effect estimates precludes drawing definitive conclusions.

2nd August 2018

Dear Prof Metra

Ms. No.EURJHF-18-404-RTR1

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

Thanks for your follow up email of 23rd July with comments on further Editorial Committee comments and external peer reviewers on our revised manuscript. We have responded in detail to these most recent comments and provided a revised version the manuscript.

Frederica flagged that there were issues with our figures so we uploaded new versions of all the figures that hopefully overcomes her previous concern.

Please do not hesitate to contact me if you should have any further questions.

Best wishes

Prof Rod Taylor & on behalf of co-authors.

Ref: Ms. No. EURJHF-18-404-RT. 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 European Journal of Heart Failure

We thank the reviewers and editor for their additional comments. We provide a point-by-point response below plus a list of manuscript revisions. A tracked edited version of the manuscript has been attached.

	Reviewer comment	Author's response	Revised manuscript
	Reviewer 1		
1	The first two sentences of the 2nd paragraph of the discussion need rewording to help the reviewer follow what is written. I had to read it several time to understand the jump between the discussion of results of Extramatch and the current study	Thank you for pointing this out. It seems that the main confusion appears to be mainly explained by the word "not" being missing from this sentence. This is now added and also shorted the second sentence to avoid duplication. We also changed the word "mortality" to "death".	"Unlike the previous IPD meta-analysis, ExTraMATCH, our analyses did **not** show a definitive benefit of ExCR in terms of either time to all-cause **death** or all-cause hospitalisation. The confidence intervals around the estimates of the effect of ExCR were wide and failed to reach statistical significance."
2	The authors offer several reasons for the neutral results but I wonder whether their existing data could give weight to any of these reasons: A) As time has progressed, HF survival has improved and this might have reduced the effect size in recent trials. I wonder if they could perform a trial level as well as an individual patient level meta-regression on their data according to year of entry to see if this was the case. Something similar was done by Shen et al. N Engl J Med 2017;377:41-51. B) Variation in adherence to ExCr within trials/Variation in composition of best clinical HF care. It is possible that the multicentre trials had external agencies checking compliance to trial protocol. It would be of interest to	We agree with the reviewer. However, most of these points address trial level (as opposed to patient level) explanatory factors underlying our neutral results i.e. date of trial/single vs multicentre/duration or dose of intervention. Given that we did not have individual level data from these variables, they were not analysed within this current IPD meta-analysis. However, we have examined these trial level issues using our meta-regression in our Cochrane review publication which has now been added to the discussion text. We also agree with the reviewer's comment on the importance of ExCR adherence and note that this is already raised in the discussion section of the paper (see last sentence of strengths and limitation sections).	"However, the Cochrane systematic review of ExCR for HF showed that this may not be case. Meta-regression showed no statistical association between trial publication date and the magnitude of ExCR effect on mortality or hospitalisation.[35] This Cochrane analysis also showed no association between the magnitude of ExCR effect and whether trial setting (single or multicentre), type of CR (comprehensive versus exercise only), or ExCR dose."

	show a sensitivity analyses comparing the effect size in just the multicentre trials as compare the single centred ones. Similar sensitivity analyses could be repeated for trial size >250 (arbitrarily chosen) vs <250 C) Clearly there is a lot of variation in the ExCr provided: exercise only vs comprehensive, aerobic vs aerobic + resistance, could sensitivity analyses be performed on these D) Duration of exercise was also variable. I am not sure of the granularity of data available to the authors would allow for a sensitivity analyses into this. E) ExCr dose has been discussed adequately wrt to heterogeneous treatment effects.		
3	The first line of the third paragraph of the discussion is not clearly worded, please can this be amended. It should be noted that subgroup analyses in a meta-analyses have no real statistical grounding when the primary outcome is neutral. With this knowledge the paragraph size and content could be reduced, to provide space to expand on point 2 above in the results and discussion section	We have clarified the first line of the 3rd para of discussion. We are aware that the term "subgroup effect(s)" may be misinterpreted and can include between group differences in observational setting (e.g. difference in mortality between males vs female HF patients). However, what are we referring here to here are differences between group in an intervention setting (e.g. difference in the effect of ExCR on mortality between males vs female HF patients) which are assessed by patient group and treatment group interactions. We have updated the text in the data analysis to clarify this.	"Our finding of a lack of consistent evidence of a beneficial effect of ExCR for any HF patient subgroup agrees with both the previous ExTraMATCH and Cochrane 2014 analyses." "To investigate subgroup effects, specifically interactions between ExCR and patient characteristics, we used the approach recommended by Riley et al."
4	Please modify the conclusions. I agree with the first sentence. I disagree with the 3rd sentence and wonder whether it should be removed. If it cannot be shown in pooled analysis that there is no survival benefit then it is statistically incorrect to move onto subgroup analysis. The second sentence might benefit from rewording to help	Rather than removing this sentence entirely, we have rephrased sentences 2 and 3 in order to emphasise the need for more detailed IPD if these analyses are to be built upon. We believe this an important issue for future trials. We respectfully disagree with the reviewer that a lack of main treatment effect precludes a plausible treatment effect in a	"Although we pooled the IPD from a number of randomised trials, treatment effect estimates remain imprecise which precludes drawing definitive conclusions. In order to be able to definitively assess the effect

	qualify the neutral findings of the first sentence better. We do not want cardiologists to stop offering cardiac rehab to their HF patients yet! Perhaps: 'It is possible that a true benefit of ExCr was missed due to the wide confidence interval for the pooled effects. Future trials should be more uniformly designed to help minimise these wide variations in treatment effects.'	subgroup. Of course, a negative treatment effect in one subgroup and a positive effect in the other subgroup can result in null effect.	of ExCR and to investigate the variation in treatment effects among specific subgroups of HF patients, a consensus needs to be reached which will allow more detailed IPD to be routinely collected in clinical trials in ExCR."
	Reviewer 2		
5	The authors changed the text discussion according to mine and the other reviewer's suggestions. However, they insist with the same positive message about cardiac rehabilitation in heart failure. The sentence in the discussion "Our overall summary estimates were in favor of ..." is not statistically proven, and, I believe, wrong. My feeling is that cardiac rehabilitation is extremely useful in heart failure, but not proven by the present analysis.	We believe the reviewer have misinterpreted our revisions to the last submission because of the use of tracked edit function. We clearly state that last "Compared with no exercise control, ExCR did not have a statistically significant effect on mortality or hospitalisation in patients with reduced ejection fraction HF."	
	Reviewer 3		
6	The authers should be complemented for undertaking a meta-analysis on IPD. This in itself commands an appreciable effort. I think that this format of research method is a great contribution to the existing evidence of cardiac rehabilitation in patients with HF. Despite some convincing data treatments I do miss critical attitudes towards why the results didn't show benefits of ExCR in HF patients. These attitudes should further be investigated in the literature. Such discussions and the preparation to undertake them are still lacking in the current manuscript. I therefore recommend that this research piece should be accepted when further revisions including a more critical attitude towards ExCR and HF patients are included.	Thank you for this positive comment. We have carefully re-reviewed our paper and, as a result, we are confident that we have provided a balanced critique of our finding and our conclusions of the effect of ExCR on mortality and hospitalisation in patients with HF are appropriately cautious.	

7	there were no page no. on the manuscript	Page numbers have been added	Page numbers have been added
8	**Introduction** You have to define ExCR and what you want to investigate about this intervention. I think you are summarising the previous results of meta-analyses in the past. A single line about the significant results of meta-analysis in the past would be enough for me. Instead underlining the difference between newer trials and the older could be meaningful. For instance patients may become older and are full-titrated with HF medicine/devices nowadays.	We have added definition to introduction. The reviewer's second point has been addressed in comment 2 from reviewer 1 (see above).	"Exercise-based cardiac rehabilitation (ExCR) is recognised as integral to the comprehensive care of HF patients and includes exercise training, education, and psychological support."
9	Mentioning underpowered meta-analysis does only give sense to me if the outcomes were not significant different between groups. This is mostly not the case in the past. However investigating patients characteristics is meaningful in the setting of IPD. This should be stressed out more since patients more > 80 years old a priori could be less likely to benefit from ExCR both because they are not able to achieve the same level of exercise input as younger patients; and maybe also because their likelihood to die or be hospitalised are much larger than patients less than 60 years old.	We agree with the reviewer that the main purpose of IPD meta-analysis is to examine patient subgroup effects. However, we are not clear on what the reviewer is asking us in terms of this paper.	
10	Did you apriori believe that exercise or even type of exercise could be beneficial to differences in type of etiology in HF. For instance did HF patients with underlying tachycardic-, valve-, ischemic- or valve disease differ in the outcomes. Would the overall EF influence the possibility of doing aerobic exercise. EF less than 20% is possibly associated with NYHA 3 and they may not be able to follow an exercise programme.	As stated in the paper, this study was pre-registered and the protocol published in advance of analyses - all the analyses in this analysis were defined apriori. For consistency we also choose the same/similar patient subgrouping as the first ExTraMATCH analysis published in the Brit Med Journal.	
11	**Methods & Results** I wonder how you could include both HF-PEF and HF-REF patients? if you did this according to the NT-proBNP then It would be less confusing but for instance giving a mean EF	Like the reviewer, we are aware of the clinical discussion around the definition of HFrEF vs HFpEF vs HFmEF and that biomarkers including blood and echo can contribute to this. As stated in this paper based on definition of EF of <45%, all	

	when including patients with a normal HF is confusing- however fortunately you did not find any trials with HF-PEF.	patients in this analysis were HFrEF, no trial groups provided us with blood biomarker. The clinical co-authors on this paper including Prof Piepoli and Davos agreed with this clinical rationale.	
12	The methods section is well written.	Thank you	
13	The Results are also well written including tables and figures. However not all the data are exactly below each other in Table 1.	Apologies – we can only assume that the table format must have misaligned when uploaded on the journal website as a pdf. We will carefully check the formatting of table 1 in the pdf version of this resubmission.	
14	The authors should carefully look after typos. For instance in the differential effect "across subgroup section" second last line- "inpatients"	Typos checked for and a full spell check run. “Inpatients” would not have been found in a spell check, so thank you for highlighting that.	
15	**Discussion** I think this part still need some revision. I miss some specific subtitles which would make the discussion more simple and understandable. At the moment the discussion has the form of a long text and it is difficult to follow the independent elements that were discussed. For instance 1) the characteristics of patients 2) the format of the ExCR 3) the quality of the trials 4) the quality of the data. These are by the way divided according to the cluster nature of the data. Therefore I get the impression that authors wants to finish their extensive work in a fast track mode.	We carefully follow the EJHF guidelines to authors for preparation of this paper. If the editorial team advise that subheadings are needed to clarify the discussion, we would be happy to add these. We have put considerable time and effort into the preparation of data, data analysis, preparation of the original paper and revisions – whilst we have sought to be timely in our work, it is certainly not been fast tracked.	
16	I miss some cross references and discussions of the interesting results they found: the older patients were benefitting more than the younger participants in your sensitivity analysis. Why? Are there other results underscoring this? Do you have a theory according to the human physiology? should these results not be mentioned in the summary in the beginning of the discussion? the impact of two year truncation in your	As we discuss in the paper, none of our subgroup findings were consistent and therefore we have sought to be conservative in their interpretation and not ‘talk them up’ e.g. while there was some evidence of age effect in sensitivity analysis, we did not see this main analyses and therefore have considered it inappropriate to speculate on this result in the body of the paper.	

	results may be due to the fact that the impact of ExCR is thinning out over time?		
17	Large heterogeneity of the trials may lead to the wide confidence intervals which is mentioned sparsely, but is this not an essential result?	We agree with the reviewer and added this point to the first paragraph of the discussion.	“The wide confidence intervals may be due to several factors, including: (i) variation in the ExCR intervention across trials;”
18	Do you have some suggestions to avoid the heterogeneity among trials? and what do you believe is the perfect format of the ExCR? maybe underscored about the included trials.	Given the absence of evidence for the differential effect of different formats of CR (e,g. comprehensive vs exercise only/dose of exercise/home vs hospital) we did not consider it possible recommend a ‘perfect’ format of CR.	
	Reviewer 4		
19	The paper by Taylor and co-workers entitled "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" is well written and addresses an issue for which an IPD meta-analysis can be useful. The paper has already been revised after a series of comments from two reviewers and the Editor. The authors have adequately responded to the various points raised in the first review.	Thank you.	

Word count 3584

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

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Keywords: cardiac rehabilitation, exercise training, meta-analysis, systematic review

Total word count: 3584~~201~~

Abstract

Aims To undertake an individual patient data (IPD) meta-analysis to assess the impact of exercise-based cardiac rehabilitation (ExCR) in patients with heart failure (HF) on mortality and hospitalisation, and differential effects of ExCR according to patient characteristics: age, sex, ethnicity, New York Heart Association (NYHA) functional class, ischaemic aetiology, ejection fraction, and exercise capacity.

Methods Randomised trials of exercise training for at least 3 weeks compared with no exercise control with 6-months' follow up or longer, providing IPD time to event on mortality or hospitalisation (all-cause or HF-specific). IPD were combined into a single dataset. We used Cox proportional hazards models to investigate the effect of ExCR and the interactions between ExCR and participant characteristics. We used both two-stage random effects, and 1-stage fixed effect, models.

Results IPD was obtained from 18 trials including 3912 patients with reduced ejection fraction HF. Compared to control, there was no statistically significant difference in pooled time to event estimates in favour of ExCR although confidence intervals were wide: all-cause mortality: hazard ratio (HR): 0.83 (95% confidence interval (CI): 0.67 to 1.04), HF-related mortality: HR 0.84 (95% CI: 0.49 to 1.46), all-cause hospitalisation: HR 0.90 (95% CI: 0.76 to 1.06), and HF-related hospitalisation: HR 0.98 (95% CI: 0.72 to 1.35). No strong evidence was found of differential intervention effects across patient characteristics.

Conclusion ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation in reduced ejection fraction HF. However, uncertainty around effect estimates precludes drawing definitive conclusions.

Introduction

With increasing numbers of people living longer with symptomatic heart failure (HF), the effectiveness and accessibility of health services for HF patients have never been more important. Exercise-based cardiac rehabilitation (ExCR) is recognised as integral to the comprehensive care of HF patients.[1,2] Cardiac rehabilitation is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health.[2] Exercise training is at the centre of rehabilitation provision for HF. In addition, it is now accepted that programmes should be comprehensive in nature and also include education and psychological care, as well as focus on health and life-style behaviour change and psychosocial wellbeing.[2,3]

Systematic reviews have shown ExCR offers important health benefits for HF patients.[4-7] The 2014 Cochrane review, based on aggregate trial data up to 12-months follow up, reported a reduction in the risk of overall hospitalisation (relative risk (RR) 0.75; 95% CI 0.62 to 0.92), HF-specific hospitalisation (RR 0.61; 95% CI 0.46 to 0.80) compared with no exercise control.[7] However, there is uncertainty as to whether there are differential effects of ExCR across HF patient subgroups. In 2004, the Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH) Collaborative Group published an individual patient data (IPD) meta-analysis based on 9 randomised trials in 801 HF patients.[8] ExTraMATCH reported a reduction in all-cause mortality (hazard ratio (HR): 0.65, 95% CI 0.46 to 0.92) and in the composite of mortality and hospital admission (HR 0.72, 95% CI 0.56 to 0.93) with ExCR compared to no exercise control. There were no statistically significant treatment effects across subgroups. ~~However,~~ Given the small number of trials, patients, and events, those subgroup analyses are likely to be underpowered. As the ExTraMATCH analysis did not take into account the cluster (or trial-level) nature of the data, it is likely to have underestimated the precision of the treatment effect. Since the ExTraMATCH analysis, there have been publications of trials of ExCR in HF, including HF-ACTION, a large US National Institute of Health funded trial with 2331 HF patients recruited from 82 centres.[9]

The ExTraMATCH II collaboration brings together the most comprehensive IPD meta-analysis of randomised trial data for ExCR in HF to date. Using contemporary IPD meta-analysis statistical methods, this study aimed to assess the impact of ExCR on the time to event outcomes (all-cause mortality, HF-specific mortality, all-cause hospital admission, and HF-specific hospital admission), and to identify subgroups of patients with HF that may respond differently to ExCR.

Methods

This study was conducted and reported in accordance with current IPD guidance and Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA IPD) statement.[10,11] The study was registered with the PROSPERO (CRD42014007170) and our full study protocol has been published elsewhere.[12,13]

Search strategy and selection criteria

Trials for inclusion were identified from the original ExTraMATCH IPD meta-analysis and the current Cochrane systematic review of ExCR for HF.[7,8] The Cochrane review searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE, MEDLINE, CINAHL, PsycINFO, and the NHS Centre for Reviews and Dissemination. 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 searched. No language limitations were imposed. Details of the search strategy used are reported in the study protocol.[12]

Trials which met the following criteria were eligible for inclusion in this analysis: (i) randomised trials of adult patients (aged 18 years and older) with a diagnosis of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) based on objective assessment of left ventricular ejection fraction and on clinical findings; (ii) trial intervention (ExCR) that included an aerobic exercise training component performed by the lower limbs, lasting a minimum of 3 weeks,[7] either alone or as part of a comprehensive cardiac rehabilitation programme which may also include health education and/or a psychological intervention; (iii) a control arm which did not prescribe an exercise intervention; (iv) a minimum follow-up of 6 months; and (v) a sample size of at least 50 (to ensure that the logistical effort in obtaining, cleaning and organising the data was commensurate with the contribution of the dataset to the analysis).[14,15]

Data management

The principal investigators of included trials were invited by email to participate in this IPD meta-analysis and share their anonymised trial data. Included datasets had ethical approval and consent from their sponsors. The complete list of all requested variables and details regarding collaboration with principal investigators are reported in the study protocol.[12] Each dataset was saved in its original format and then converted and combined into one overall master dataset with standardised variables. All files are stored on a secure password protected computer server managed in accordance with the data management standard operating procedures of the nationally registered Exeter Clinical Trials Unit. Data from each trial were checked on range, extreme values, internal consistency, missing values, and consistency with published reports. Data discrepancies or missing information were discussed with trial investigators. Access to data at all stages of cleaning and analysis was restricted to core members of the research team (OC, RST, FCW, and SW).

Specification of outcomes, subgroups, and risk of bias assessment

We sought patient level time to event data from investigators for the following outcomes: time to all-cause and HF-specific mortality, and time to first all-cause and HF-specific hospitalisation. We also sought IPD on the following pre-defined patient characteristics: age, gender, ejection fraction, New York Heart Association (NYHA) functional class, HF aetiology (ischaemic or. non-ischaemic), ethnicity (white or other), and baseline (pre-randomisation) exercise capacity (e.g. peak oxygen uptake (VO_2)). Study quality/risk of bias was assessed using the TESTEX quality assessment tool.[16]

Statistical analysis

A detailed statistical analysis plan was prepared (available from authors). All analyses were carried out according to the principle of intention to treat (i.e. patients included according to their randomised trial arm) and included only patients with observed baseline data (where required) and outcome data at follow-up. Where missing data was 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. We checked for potential small study bias by assessing funnel plot asymmetry and using the Egger test.[22]

In the primary analysis, a two-stage approach was taken, with each trial first analysed using a Cox proportional hazards regression model and then trial-specific estimates of treatment effect (hazard ratio (HR)) or treatment–covariate interactions (HR of the interaction effect) were combined across trials using a random effects model. A random effects model was preferred due to the high degree of clinical heterogeneity across the individual trials, which included different patient populations, types of ExCR intervention, and comparators.[17] The 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% confidence interval (CI). Additionally, the I^2 and τ^2 statistics were reported alongside the associated p-value for the results of the main analyses.

Secondary analyses were based on a one-stage meta-analysis approach. Due to failure of convergence of one-stage random effects models, which was likely to be due to the low level of statistical heterogeneity between trials (indicated by the τ^2 statistic), a fixed effect approach was used: Cox regression models, stratified by trial. Stratification allowed the baseline hazard to vary between trials, rather than forcing the baseline hazards in individual trials to be proportionate to each other.[19] To investigate subgroup effects, specifically interactions between ExCR effect and patient characteristics, we used the approach recommended by Riley et al.[20] Continuous covariates were centred around the mean value within each trial; binary covariates were centred around the proportion within each trial. To present the results graphically, we performed individual subgroup one-stage fixed-effect IPD meta-analyses.

To test the robustness of primary and secondary analyses, we undertook a number of pre-specified sensitivity analyses: (i) exclusion of the largest trial (HF-ACTION[9]); (ii) truncation of outcomes at 1-, 2- and 5-year follow-up. Small study effects were assessed for each outcome by funnel plot asymmetry

and using the Egger test.[22] Results are reported as estimated HRs with 95% CIs. All analyses were undertaken using Stata 14.2 StataCorp LP, College Station, Texas, USA.

Results

Study selection

A total of 23 trials were deemed eligible for this IPD meta-analysis. Data from six trials have been analysed previously and were available from the ExTraMATCH database.[23-28] We were unable to include data from three trials (355 patients); for two trials data were no longer available [29,30] and the investigators of the other trial could not be contacted.[31] Of the remaining 17 trials, 14 investigators responded positively and shared their trial data. After obtaining IPD, one trial[32] was excluded as it was determined that it included patient data that overlapped with another trial.[33] A further trial was not included as insufficient data was provided to allow calculation of survival time or time to hospitalisation.[34] This resulted in the inclusion of 18 trials comprising 3912 patients (1948 ExCR, 1964 control) with a median follow-up of 19 months for mortality outcomes and 11 months for hospitalisation outcomes. Figure 1 summarises the study selection process. Full citations of included trials are included in eAppendix.[e1-e18]

Characteristics of included trials and participants

Patient baseline characteristics were well balanced between ExCR and control patients (see Table 1). The majority of patients were male (75%), with a mean age of 61 years (standard deviation (SD) 13). The mean baseline left-ventricular ejection fraction was 26.7% (SD 8.1%); no included trials recruited patients with preserved ejection fraction heart failure (ejection fraction >45%), and most patients were in NYHA functional class II (59%) or III (37%). Trials from Europe and North America were published between 1990 and 2012 (see Table 2). Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention; six also included resistance training.[e3,e4,e8,e9,e14,e15] 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. Three trials were conducted in an exclusively home-based setting.[e4,e9,e13] The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 12 to 90 weeks, with between 2 and 7 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 to 85% peak VO_2.

Quality of included trials

The overall quality of included trials was judged to be moderate to good, with a median TESTEX score of 11 (range 9 to 14) out of a maximum score of 15 (eTable1). The criteria of allocation concealment and physical activity monitoring in the control groups were met in only three trials;[e4,e7,e17] the other TESTEX criteria were met in 50% or more of trials.

Effects of intervention on event outcomes

Compared with control, ExCR did not have a statistically significant effect on mortality or hospitalisation. However, all time to event pooled treatment effects from random effects two-stage IPD meta-analysis were in favour of ExCR but with wide confidence intervals; all-cause mortality: HR 0.83 (95% CI 0.67 to 1.04), p=0.107, 17 trials, 3782 patients, I^2 =26%, τ^2=0.04; HF-specific mortality: HR 0.84 (95% CI 0.49 to 1.46), p=0.527, 9 trials, 915 patients, I^2 =0%, τ^2=0.00; all-cause hospitalisation: HR 0.90 (95% CI 0.76 to 1.06), p=0.210, 11 trials, 3190 patients, I^2 =12.4%, τ^2=0.01; and HF-specific hospitalisation: HR 0.98 (95% CI 0.72 to 1.35), p=0.902, 13 trials, 3494 patients, I^2 =45%, τ^2=0.10 (Figure 2a-d). These primary analysis results were broadly consistent across secondary and sensitivity analyses (eTables 2, 3, 4, and 5). Inferences did not change following the addition of trial level data from trials that met our study inclusion criteria but were not able to contribute IPD (data not shown here, available from authors). There was no evidence of significant small study bias for the four outcomes (eFigure 1).

***Differential treatment effects* across *patient characteristics* (*subgroups*)**

Interaction analyses for the two-stage model revealed no consistent interactions between the effect of ExCR and any of the predefined subgroups (age, gender, ejection fraction, NYHA class, HF

aetiology, ethnicity and baseline peak VO_2) for all-cause mortality, HF-related mortality, all-cause hospitalisation, or HF-related hospitalisation. For comparison 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 ~~(~~Figures 3a-d~~,)~~ along with the p-value from the interaction test in the two-stage IPD meta-analyses. Some evidence of an interaction effect between ExCR and a patient characteristic~~ -~~($p<0.05$) was seen in four sensitivity analyses (eTables 2, 3, 4, and 5): (i) ExCR was associated with a larger reduction in all-cause mortality in older patients (p=0.034) in the two-stage model with 2-year truncation; (ii) ExCR was associated with a larger reduction in HF-mortality older patients (p=0.017) in the two-stage model with 2-year truncation; (iii) ExCR was associated with a larger reduction in HF-mortality in ischemic patients (p=0.047) in the one-stage model without truncation; and (iv) ExCR was associated with a larger reduction in all-cause hospitalisation~~–~~ in patients with lower baseline peak VO_2 (p=0.027) in the two-stage model with 1-year truncation.

Discussion

Compared with no exercise control, ExCR did not have a statistically significant effect on mortality or hospitalisation ~~–~~in patients with reduced ejection fraction HF. Although we pooled IPD from 18 trials including 3912 patients, treatment effect estimates were imprecise. We found no strong evidence for a differential effect of ExCR according to patient characteristics. ~~.~~

Unlike the previous IPD meta-analysis, ExTraMATCH[8], our analyses did not show a definitive benefit of ExCR in terms of either time to all-cause death or all-cause hospitalisation. ~~In contrast to this previous analysis, our~~The confidence intervals around the effect of ExCR were wide and failed to reach statistical significance. The wide confidence intervals may be due to several factors, including: (i) variation in the ExCR intervention across trials; (ii) variation in adherence to ExCR within trials; (iii) variation in treatment effect of ExCR among adherent patients; and (iv~~ii~~) variation in the composition/effectiveness of usual care within and across trials. A potential explanation for this reduction in strength of effect of ExCR on clinical events could be due to improvements in rates of mortality and hospitalisation with time as a ~~is~~ result of the inclusion of more recent trials in this updated IPD analysis. More recent trials are more likely to ~~that~~ have utilised prognostic innovations in usual care treatments for HF, ~~which include~~ including devices (resynchronisation and defibrillator therapy) and disease modifying drugs (beta-blockers, ACE inhibitors, angiotensin II receptor antagonists, and mineralocorticoid receptor antagonists). ~~A similar reduction in mortality benefits of ExCR over time has been seen in trials where ExCR was provided to post-myocardial infarction and revascularisation patients.[35]~~ However, the Cochrane systematic review of ExCR for HF showed that this may not be case. Meta-regression showed no statistical association between trial publication date and the magnitude of ExCR effect on mortality or hospitalisation.[11,35] This Cochrane analysis also showed no association between the magnitude of ExCR effect and trial setting (single or multicentre), type of CR (comprehensive versus exercise only), or ExCR dose.

Our finding of a lack of consistent evidence of a beneficial effect of ExCR for any HF patient subgroup agrees with both the previous ExTraMATCH and Cochrane 2014 analyses.~~Our finding of a lack of consistent evidence for HF patient subgroup effects of ExCR~~ This lack of consistent evidence to ~~support differential effects of ExCR in patients with different characteristics~~ agrees ~~with both the previous ExTraMATCH and Cochrane 2014 analyses~~.[7,8] However, these two previous studies had major limitations that are likely to have limited their ability to detect subgroup effects. ExTraMATCH included data on only 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 found no association between trial level patient characteristics (age, gender, ejection fraction) and ExCR. However, meta-regression analysis is highly prone to study level confounding (ecological fallacy) and should be interpreted with great caution.[36] Nevertheless, our findings are also consistent with the IPD subgroup interaction analyses from the multicentre HF-ACTION trial. The HF-ACTION investigators reported no significant interaction effect on their composite primary outcome (all-cause mortality or hospitalisation) between~~of~~ exercise training intervention ~~on their composite primary outcome (all-cause mortality or hospitalisation)~~ and the subgroups of age (≤70 vs. > 70 years), gender, race (white vs. non-white), HF aetiology (ischaemic vs. non ischaemic), ejection fraction (≤25% vs. >25%), and~~or~~ NHYA class (II vs. III/IV).[9,37]

Strengths and limitations

Our ExTraMATCH II study has a number of strengths. We believe this to be the first IPD meta-analysis including sufficiently large numbers of HF patients (3912) and events (701 all-cause deaths, 1642 first all-cause hospitalisations) to be able to identify differential effects of ExCR in patients with different characteristics. We were able to standardise the handling and analysis of time to event outcomes across trials. Our findings were broadly consistent across analytic approaches that included one-- and two-stage IPD meta-analysis models and a range of sensitivity analyses. Finally, we found no evidence of publication bias. Whilst systematic reviews and meta-analyses of IPD from

randomised trials are recognised as the gold standard for assessing intervention effects,[39] our study has a number of limitations. First and foremost, there was a lack consistency in how included trials with IPD in our analyses defined and collected clinical event outcome data. As noted in recent commentaries on clinical events in HF trials, with the exception of all-cause mortality, the collection and reporting the other outcomes including cause-specific mortality and hospitalisation can be prone to confounding and bias.[39] We made considerable efforts to contact study authors in order to clarify issues around the definition of hospitalisations and HF-specific deaths. 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 our conclusions for these outcomes. Second, overall, IPD was available to ExTraMATCH II for 3912/4267 patients in 18/23 trials identified as eligible, equating to an omission of only 8% of all participants across all eligible trials. However, not all included trials collected IPD for the time to event outcomes or patient characteristics assessed in this study. The large multicentre HF-ACTION trial did not collect HF-specific hospitalisation, thus reducing our statistical power for this outcome. Although, across the trials that provided outcome data, the proportion of patients with missing clinical event or baseline covariate data was low, this may have introduced bias in our results. Finally, we did not have patient level data on 'ExCR dose', i.e. adherence to duration, frequency and intensity of ExCR undertaken by an individual patient. Using IPD from HF-ACTION, Keteyian et al found exercise volume (defined as metabolic equivalent of task (MET)-hour per week) to be a predictor for the composite outcome of all-cause mortality or hospitalisation (p=0.03).[40] Whilst this analysis ~~was~~ indicates that patient level ExCR 'dose' is a key potential explanatory variable ~~and one that~~, this data was not available across the trials in our analyses.

Implications for practice and further research

In spite of the comprehensiveness of this IPD meta-analysis, 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 reduced ejection fraction HF; in particular, to increase the power to examine whether 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 ~~triallists~~ trial investigators to more consistently collect, report, and share patient-level data in the future. Two central aspects of future data collection include a consensus on the definition, collection, and reporting of clinical event data, especially hospitalisation, plus the capture of data on patient~~--~~level adherence to the amount of exercise training during the ExCR intervention period. Our forthcoming IPD meta-analysis will examine the impact of ExCR exercise capacity on health-related quality of life and explore how this treatment effect may vary across according to HF patient characteristics.[12,13]

Conclusion

ExCR did not significantly reduce the risk of mortality and hospitalisation in patients with reduced ejection fraction HF. Although we pooled the IPD from a number of randomised trials, treatment effect estimates remain imprecise which precludes drawing definitive conclusions. ~~Further evidence is needed to~~ To allow definitive~~ly~~ assessment of the effect of ExCR for patients with HF~~,~~, and to investigate ~~the potential for variation in~~ differential treatment effects across specific patient characteristics, ~~among HF patients with different characteristics,~~ a consensus in trial methodology needs to be reached that will allow more detailed and consistently recorded IPD to be routinely collected from clinical trials in ExCR.

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Conflict of Interest: RST and HMD are currently co-chief investigators and KJ a co-investigator on a National Institute for Health Research (NIHR) funded programme grant designing and evaluating the clinical and cost-effectiveness of a home-based cardiac rehabilitation intervention for heart failure patients (RP-PG-1210-12004). All other authors declare no conflicts.

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Figure legends

Figure 1. PRISMA flow diagram

Figure 2. Effect of ExCR on mortality and hospitalisation across patient subgroups

Figure 3. Effect of ExCR on mortality and hospitalisation across patient subgroups

Table

Table 1. Baseline characteristics of patients

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			
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			
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			
Ischaemic	1094 (57)	1080 (56)	2174 (57)
Non-ischemic	809 (43)	838 (44)	1647 (43)
Ethnicity			
White	1100 (70)	1140 (72)	2240 (71)
Non-white	472 (30)	445 (28)	917 (29)
VO_2 peak (ml/kg/min); mean (SD)	14.9 (4.4)	15.0 (4.6)	14.9 (4.5)

Data are n (%) unless otherwise indicated; percentages may not sum to 100 because of rounding;

NHYA: New York Heart Association; SD: standard deviation; VO_2 peak: peak oxygen uptake.

Table 2. Characteristics of included trials

Study characteristics	
Publication year	
1990 to 1999	2 (11)
2000 to 2009	12 (67)
2010 to 2012	3 (17)
Unpublished	1 (6)
Main study location	
Europe	14 (78)
North America*	4 (22)
Single study centre	
Single	12 (67)
Multiple	5 (28)
Not reported	1 (6)
Sample size	
0 to 99	10 (56)
100 to 999	7 (39)
1000 and over	1 (6)
Duration of follow-up in dataset (months), median (range)	

Mortality	18.6 (11.8 to 419)
Hospitalisation	11.2 (2.6 to 98)
Intervention characteristics	
Intervention type	
Exercise only programs	5 (28)
Comprehensive programs	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 to 90)
Frequency (sessions per week), median (range)	2.8 (2 to 7)
Length of exercise session (mins), median (range)	24 (15 to 120)
Exercise intensity, range	40-80% maximum heart rate 50-85% peak VO_2 12-18 Borg rating
Setting	

Centre-based only	6 (33)
Home-based only	3 (17)
Centre- and home-based	8 (44)
Not reported	1 (6)

Data are n (%) unless otherwise indicated; percentages may not sum to 100 because of rounding;

*****O'Connor study was categorised as North America but was also delivered to a small number of patients in France

Figure

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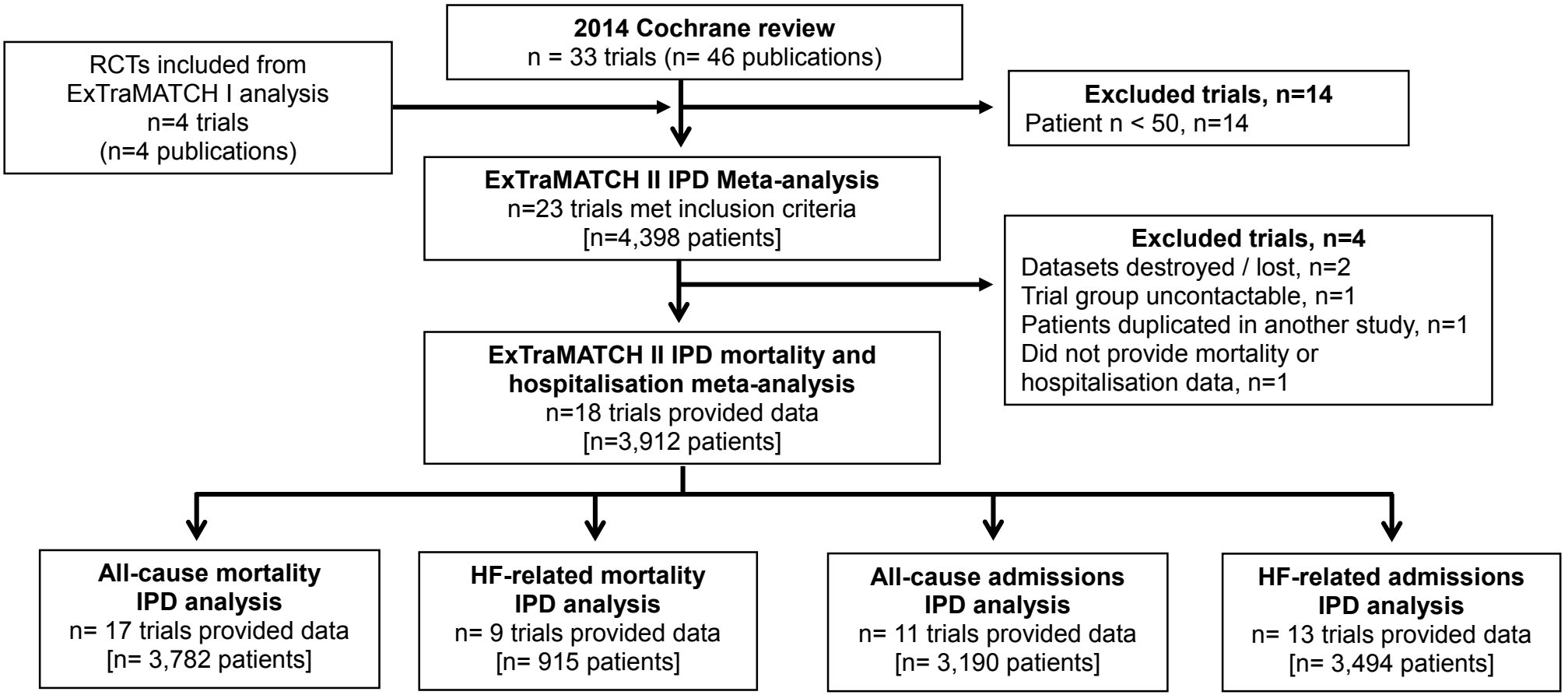

Figure

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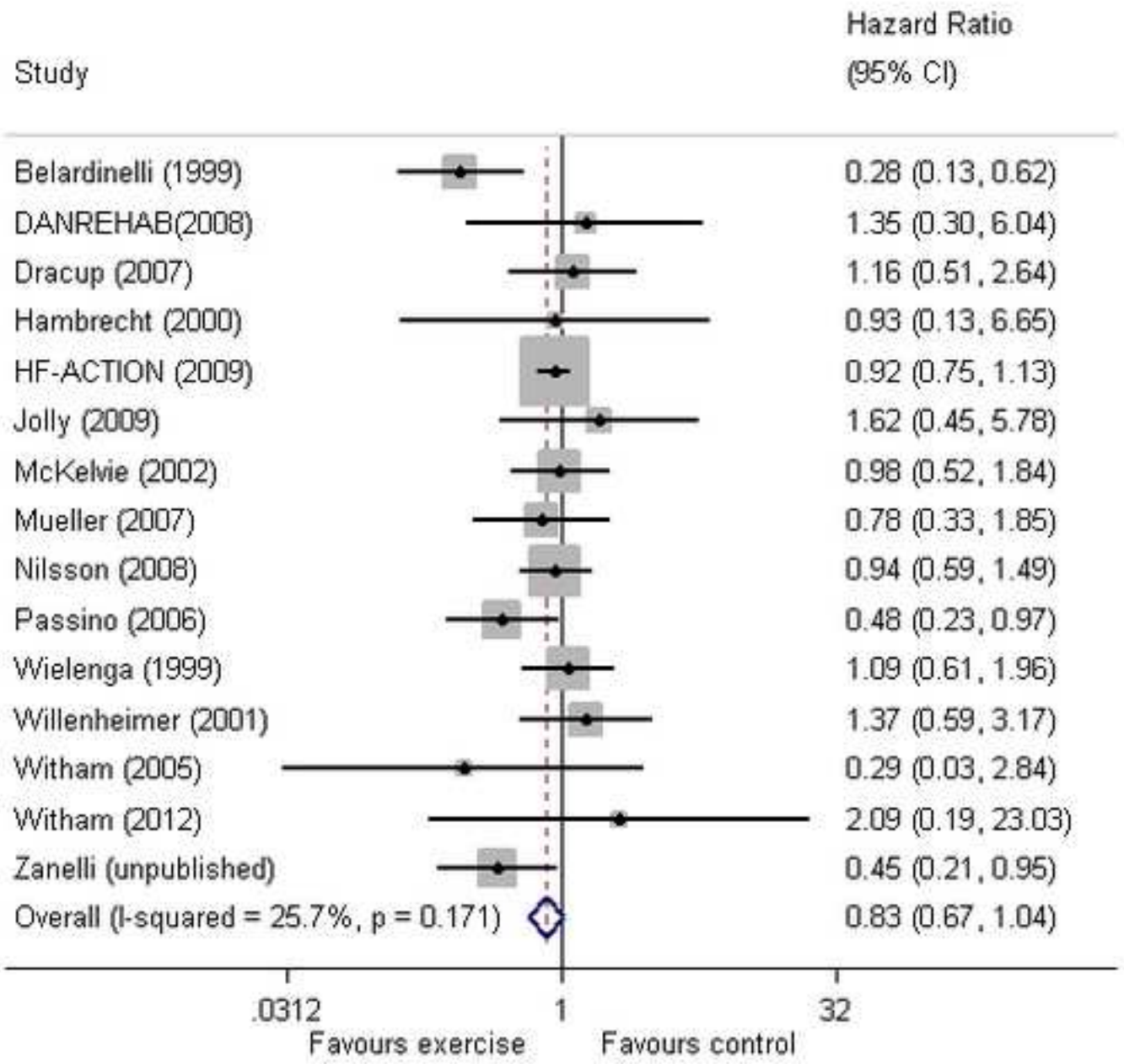

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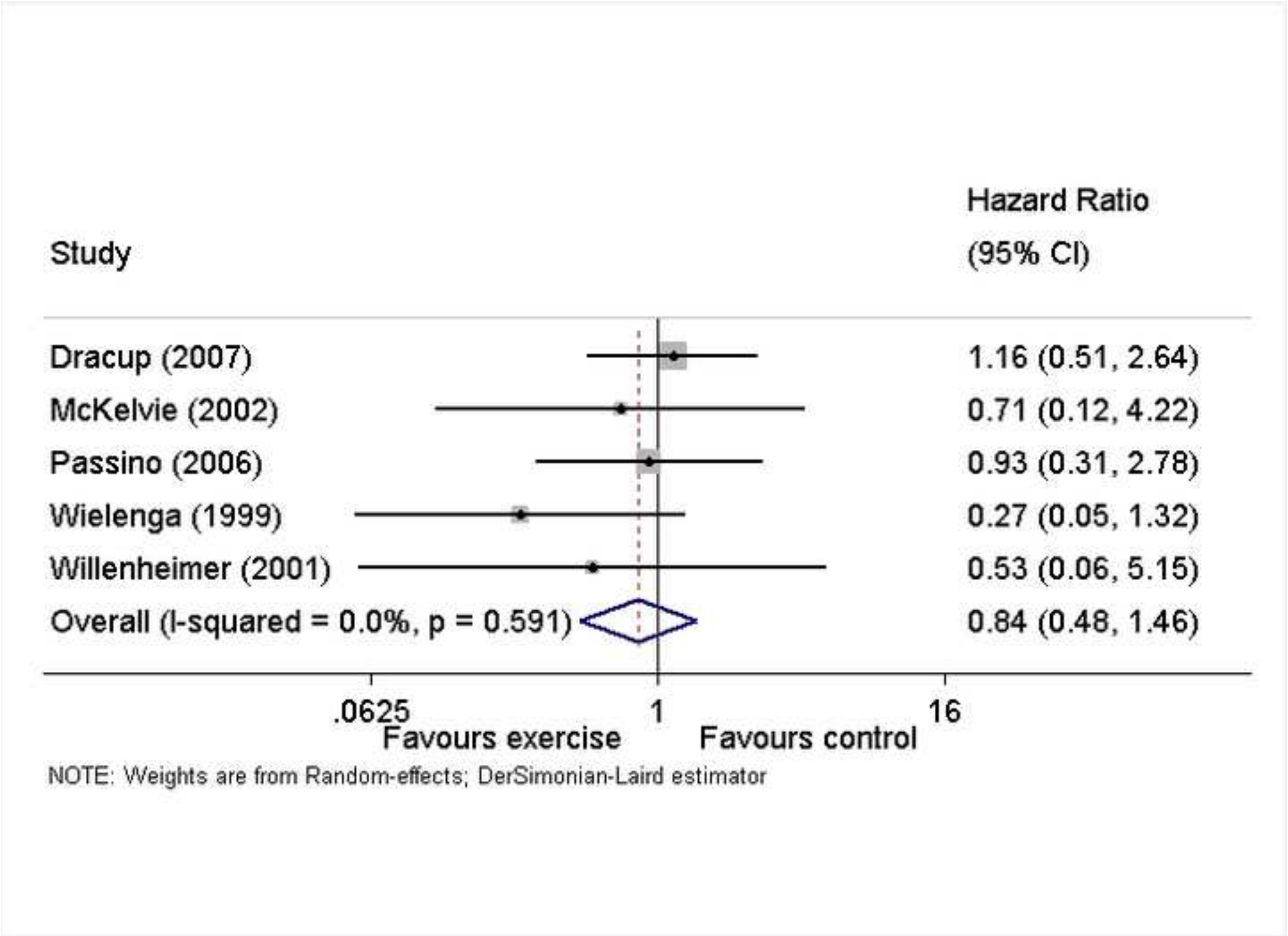

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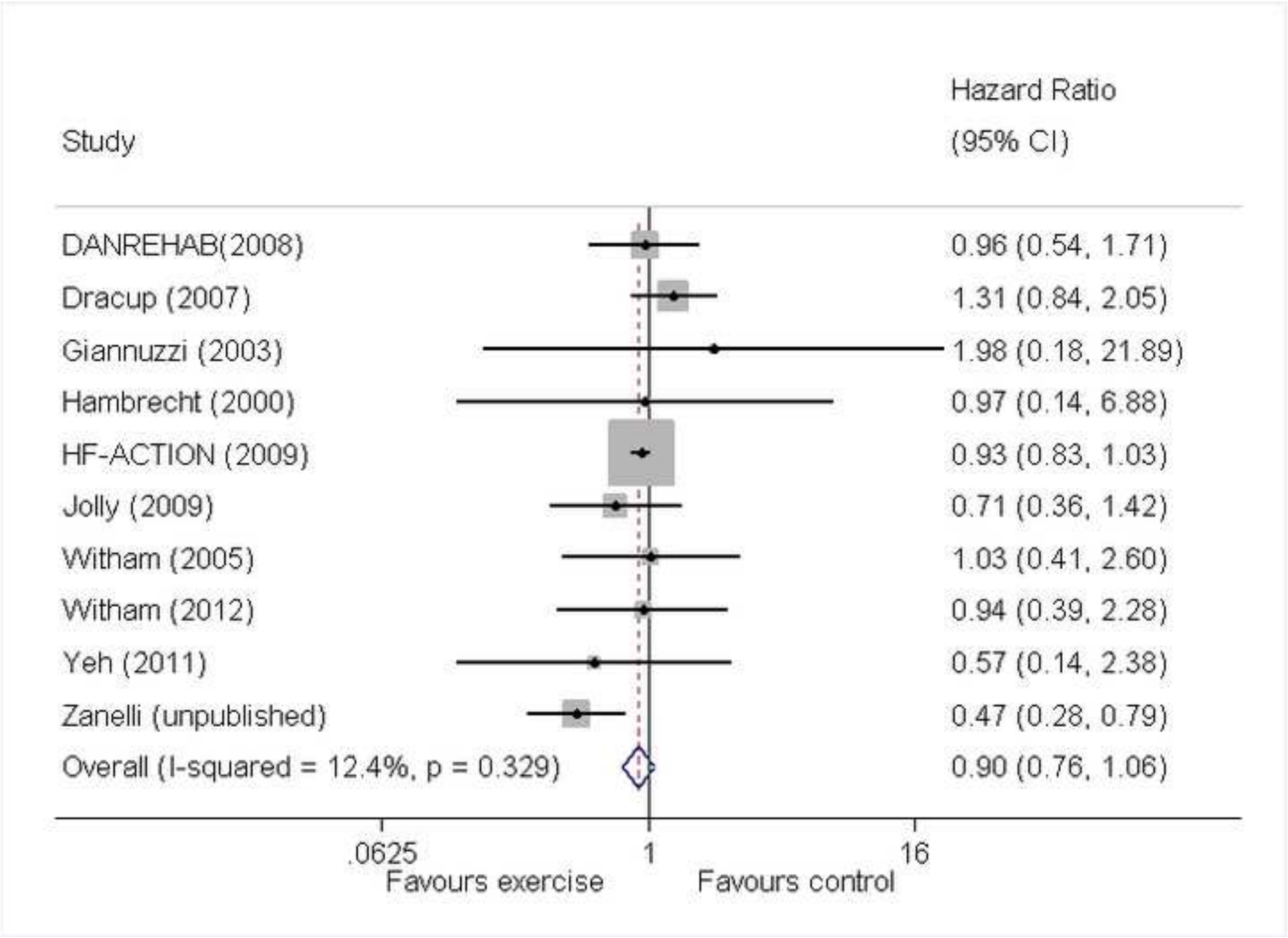

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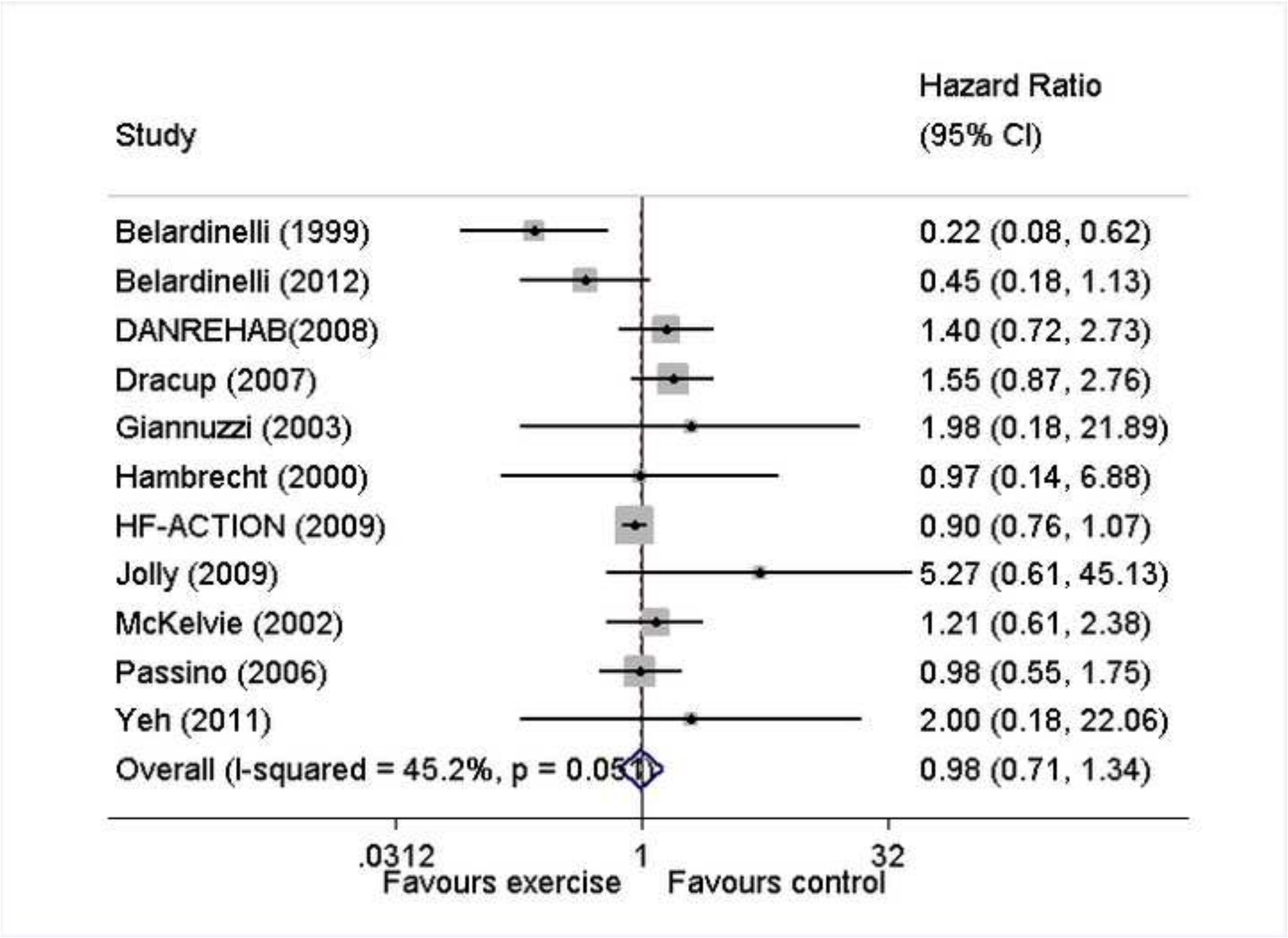

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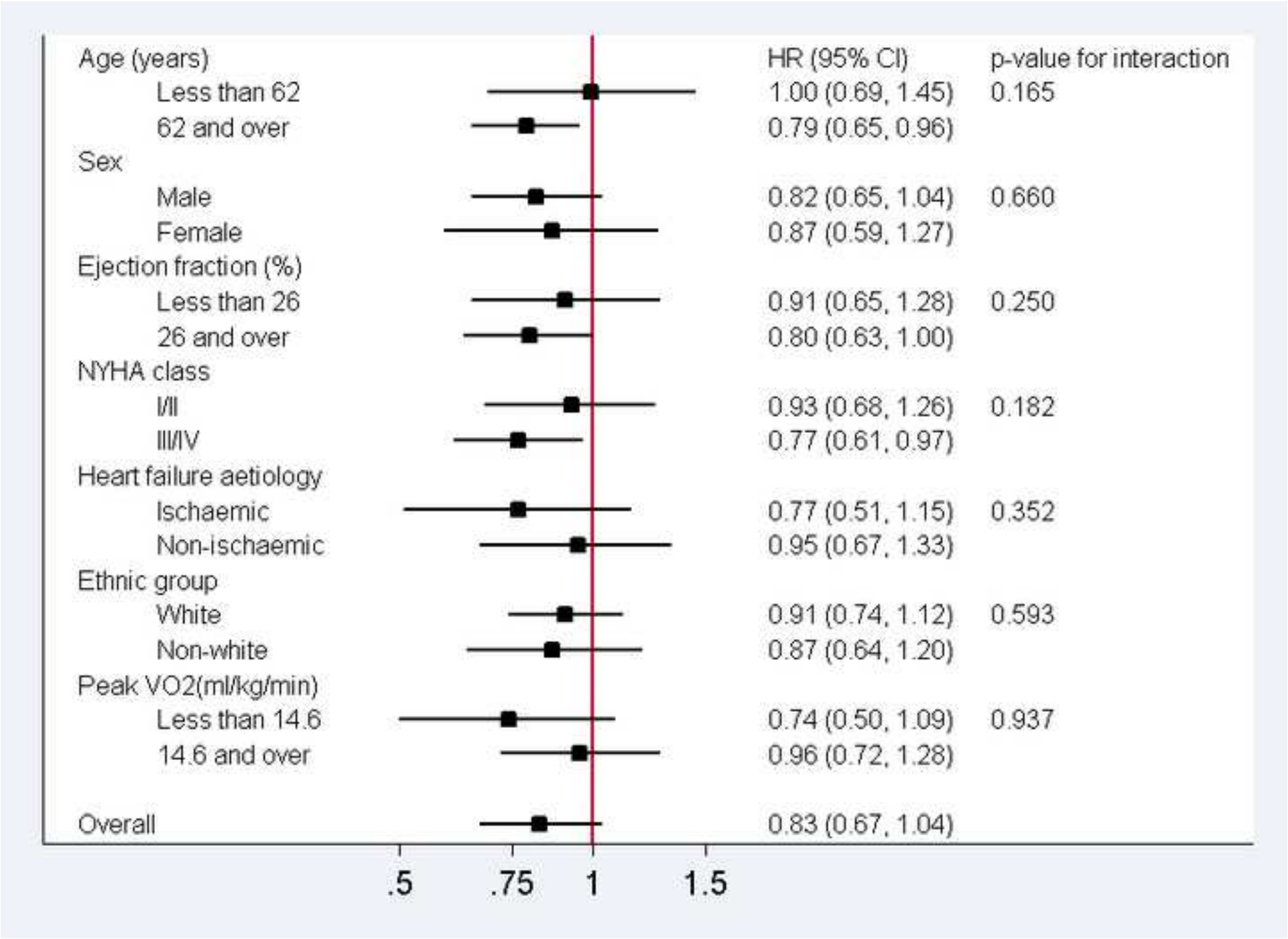

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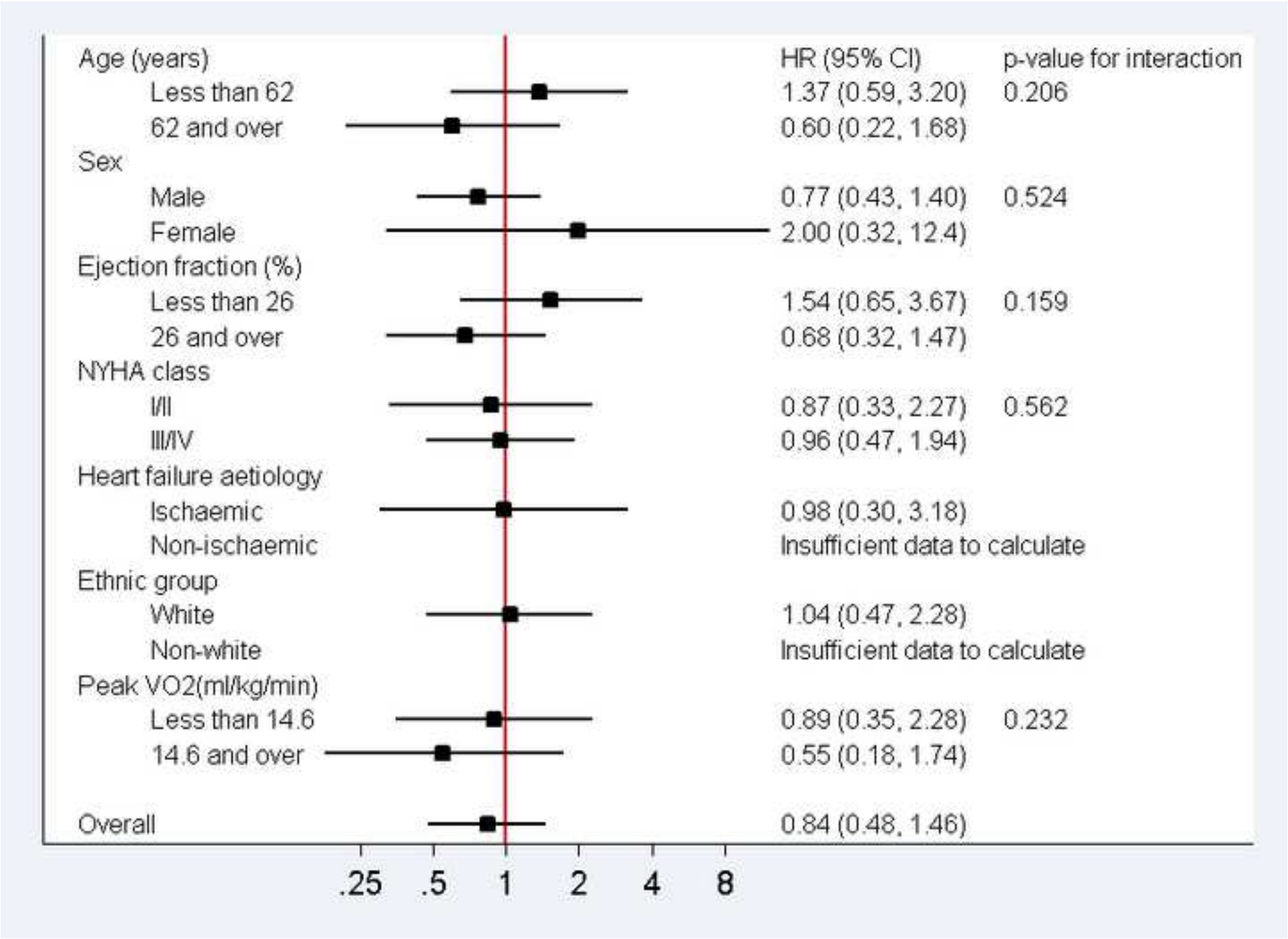

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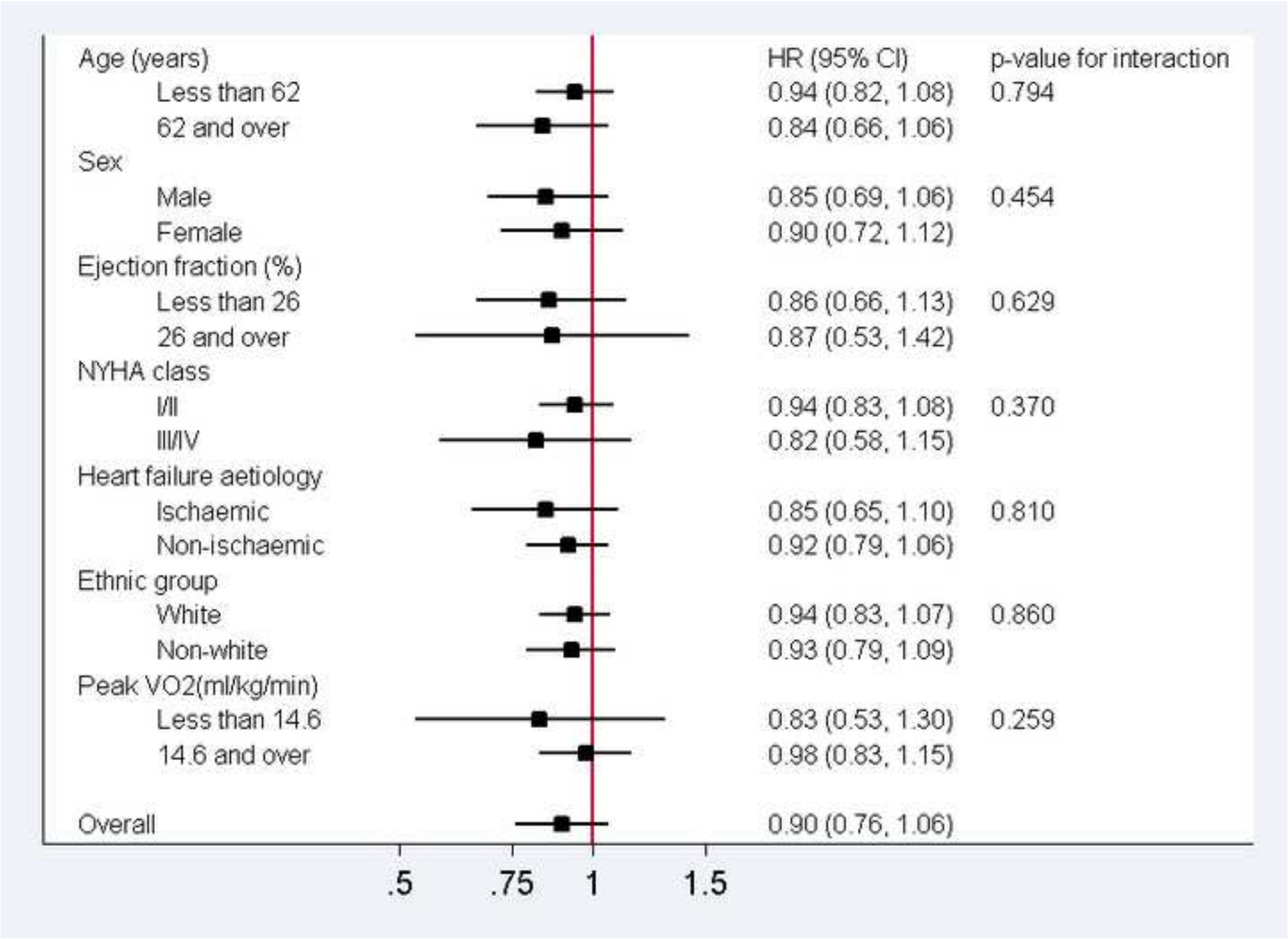

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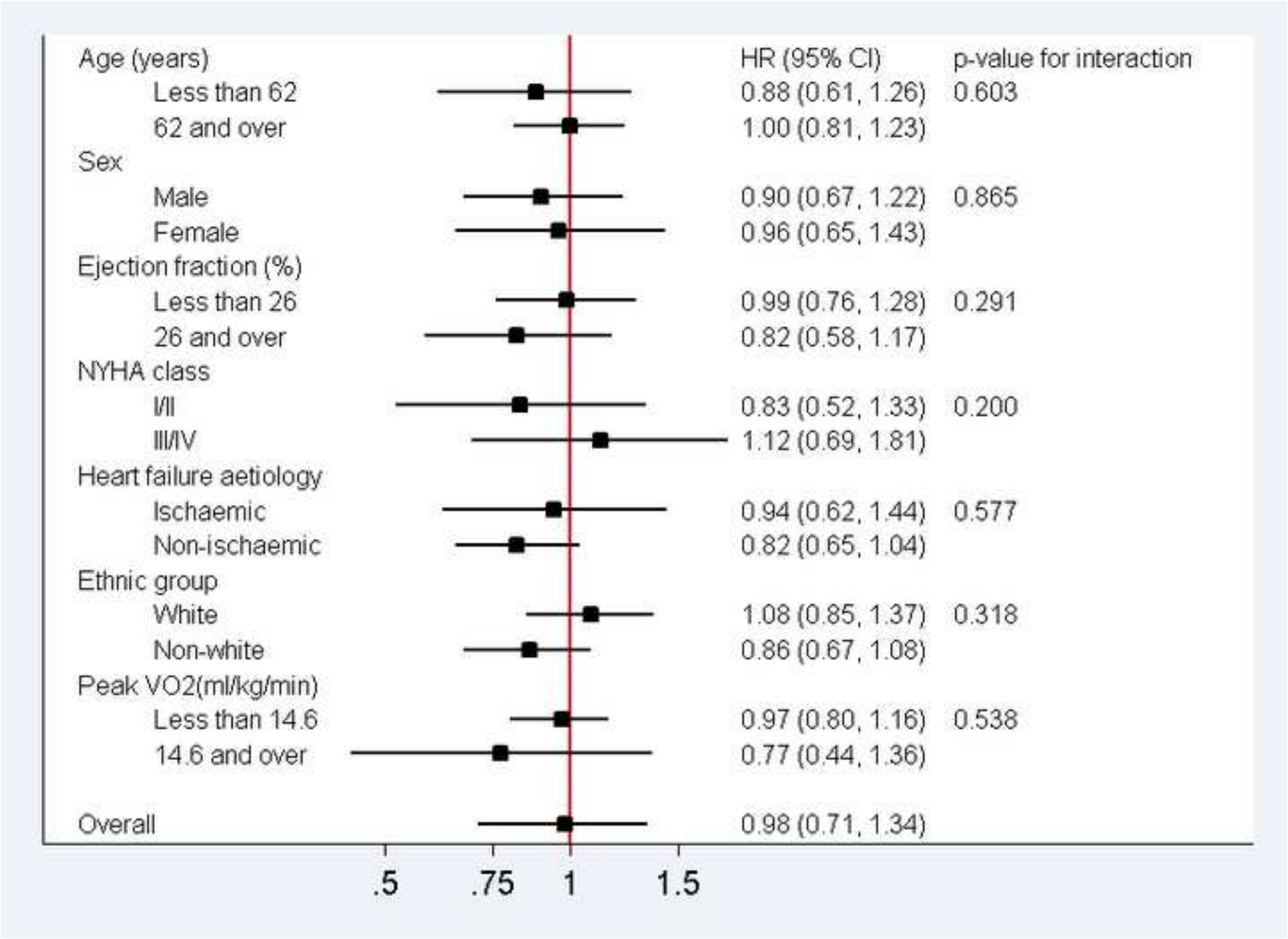

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Table

Table 1. Baseline characteristics of patients

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			
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			
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			
Ischaemic	1094 (57)	1080 (56)	2174 (57)
Non-ischemic	809 (43)	838 (44)	1647 (43)
Ethnicity			
White	1100 (70)	1140 (72)	2240 (71)
Non-white	472 (30)	445 (28)	917 (29)
VO_2 peak (ml/kg/min); mean (SD)	14.9 (4.4)	15.0 (4.6)	14.9 (4.5)

Data are n (%) unless otherwise indicated; percentages may not sum to 100 because of rounding;

NHYA: New York Heart Association; SD: standard deviation; VO_2 peak: peak oxygen uptake.

Table 2. Characteristics of included trials

Study characteristics	
Publication year	
1990 to 1999	2 (11)
2000 to 2009	12 (67)
2010 to 2012	3 (17)
Unpublished	1 (6)
Main study location	
Europe	14 (78)
North America*	4 (22)
Single study centre	
Single	12 (67)
Multiple	5 (28)
Not reported	1 (6)
Sample size	
0 to 99	10 (56)
100 to 999	7 (39)
1000 and over	1 (6)
Duration of follow-up in dataset (months), median (range)	

Mortality	18.6 (11.8 to 419)
Hospitalisation	11.2 (2.6 to 98)
Intervention characteristics	
Intervention type	
Exercise only programs	5 (28)
Comprehensive programs	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 to 90)
Frequency (sessions per week), median (range)	2.8 (2 to 7)
Length of exercise session (mins), median (range)	24 (15 to 120)
Exercise intensity, range	40-80% maximum heart rate 50-85% peak VO_2 12-18 Borg rating
Setting	

Centre-based only	6 (33)
Home-based only	3 (17)
Centre- and home-based	8 (44)
Not reported	1 (6)

Data are n (%) unless otherwise indicated; percentages may not sum to 100 because of rounding;

*****O'Connor study was categorised as North America but was also delivered to a small number of patients in France

Ref: Ms. No. EURJHF-18-404-RT. 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 European Journal of Heart Failure

We thank the reviewers and editor for their helpful comments. We provide a point-by-point response below plus a list of manuscript revisions. A tracked edited version of the manuscript has been attached.

Reviewer comment	**Author's response**	**Revised manuscript**
Abstract The first mention of IPD in abstract is not explained. The conclusion overstates the findings. The first line should be crystal clear such as: 'ExCR did not have a significant effect on mortality and hospitalisation in heart failure.' The second line could then explain the wide confidence interval and uncertainty. Introduction Well written with clear aims. Methods Typo: Should read 'full citations..' as opposed to 'fill'. Results In the effects of intervention on event outcomes: Please re-order the first sentence with the neutral result of this meta-analysis on mortality and then introduce the wide confidence interval and possible trend in favour of exercise. Discussion	Text corrected We agree with the reviewer's comment and made the change to the abstract as suggested. Thank you Text corrected. As above, we made the change to the results section as suggested.	"**Abstract** **Aims** To undertake an individual patient data (IPD) meta-analysis to assess the impact of…" **"Conclusion** ExCR did not have a statistically significant effect on the risk of mortality and hospitalisation in reduced ejection fraction HF. However, uncertainty around effect estimates precludes drawing definitive conclusions." "Full citations of included trials are included in eAppendix" "**Results** ***Effects of intervention on event outcomes*** Compared with control, ExCR did not have a statistically significant effect on mortality or hospitalisation. However, all time to event pooled treatment effects from random

Once again the results are overstated. The main findings of this study are neutral, the current wording implies some form of positivity. Please can all of these sentiments be changed in the manuscript.	As above, we made the change to the discussion and conclusions section as suggested, in order not to overstate the results	effects two-stage IPD meta-analysis were in favour of ExCR but with wide confidence intervals." "**Discussion** Compared with no exercise control, ExCR did not have a statistically significant effect on mortality or hospitalisation our overall summary estimates were in favour of ExCR for time to all-cause and HF-specific mortality, and time to first all-cause and HF-specific hospitalisation, in patients with reduced ejection fraction HF. Although we pooled IPD from 18 trials including 3912 patients, treatment effect estimates were imprecise."
In the present study, the authors assessed the impact of exercise-based cardiac rehabilitation in patients with heart failure. The authors analyzed mortality and hospitalizations in the total population as well as according to patients' characteristics, such as age, sex, race, functional class, etiology, ejection fraction, and exercise performance. The study is a very well conducted and extremely interesting meta-analysis. The authors conclude that cardiac rehabilitation appears to reduce the risk of mortality and hospitalization. This statement is statistically unproven, and the conclusions are not supported by data.	We agree with the reviewer's comment and, as above, revised the conclusions and other aspects of the manuscript accordingly.	

The authors should reevaluate their conclusions according to the real findings. I do realize that, regardless of the number of patients evaluated, it is likely a sample size problem. However, the conclusions are, at present, not supported by data. Comments to the editor: very important study, but conclusions are not supported by data. Please confirm my interpretation by a statistical review.	As above. Thank you.	
Editor's comments		
Figures can be attached as separate files, carefully labelled with symbols in a form consistent with text use. Unnecessary background patterns, lines and shading should be avoided. Captions should be listed on a separate sheet. The resolution of digital images must be at least 300 dpi. All figures must be mentioned in the text.	All figures submitted as jpeg or tiff files.	

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

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Keywords: cardiac rehabilitation, exercise training, meta-analysis, systematic review

Total word count: 3201

Abstract

Aims To undertake an individual patient data (IPD) meta-analysis ~~To~~ to assess the impact of exercise-based cardiac rehabilitation (ExCR) in patients with heart failure (HF) on mortality and hospitalisation ~~(all-cause and HF-specific)~~, and differential effects of ExCR according to patient characteristics: age, sex, ethnicity, New York Heart Association (NYHA) functional class, ischaemic aetiology, ejection fraction, and exercise capacity.

Methods Randomised trials of exercise training for at least 3 weeks compared with no exercise control with 6-months' follow up or longer, providing IPD time to event ~~IPD~~ on mortality or hospitalisation (all-cause or HF-specific). ~~Individual patient data (~~IPD~~)~~ were combined into a single dataset. We used Cox proportional hazards models to investigate the effect of ExCR and the interactions between ExCR and participant characteristics. We used both two-stage random effects, and 1-stage fixed effect, models.

Results IPD was obtained from 18 trials including 3912 patients with reduced ejection fraction HF. ~~P~~Compared to control, there was no statistically significant difference in ~~ooled~~ pooled time to event estimates ~~were~~ in favour of ExCR ~~but with wide~~ although confidence intervals were wide: all-cause mortality: hazard ratio (HR): 0.83 (95% confidence interval (CI): 0.67 to 1.04), HF-related mortality: HR 0.84 (95% CI: 0.49 to 1.46), all-cause hospitalisation: HR 0.90 (95% CI: 0.76 to 1.06), and HF-related hospitalisation: HR 0.98 (95% CI: 0.72 to 1.35) ~~compared with control~~. No strong evidence was found of differential intervention effects across patient characteristics.

Conclusion ExCR did not have a statistically significant effect on the ~~appears to reduce~~ risk of mortality and hospitalisation in reduced ejection fraction HF. However, ~~although~~ uncertainty around effect estimates precludes drawing definitive conclusions. ~~There was no strong evidence of a differential effect of ExCR across patients with different characteristics~~

Introduction

With increasing numbers of people living longer with symptomatic heart failure (HF), the effectiveness and accessibility of health services for HF patients have never been more important. Exercise-based cardiac rehabilitation (ExCR) is recognised as integral to the comprehensive care of HF patients.[1,2] Cardiac rehabilitation is a process by which patients, in partnership with health professionals, are encouraged and supported to achieve and maintain optimal physical health.[2] Exercise training is at the centre of rehabilitation provision for HF. In addition, it is now accepted that programmes should be comprehensive in nature and also include education and psychological care, as well as focus on health and life-style behaviour change and psychosocial wellbeing.[2,3]

Systematic reviews have shown ExCR offers important health benefits for HF patients.[4-7] The 2014 Cochrane review, based on aggregate trial data up to 12-months follow up, reported a reduction in the risk of overall hospitalisation (relative risk (RR) 0.75; 95% CI 0.62 to 0.92), HF-specific hospitalisation (RR 0.61; 95% CI 0.46 to 0.80) compared with no exercise control.[7] However, there is uncertainty as to whether there are differential effects of ExCR across HF patient subgroups. In 2004, the Exercise Training Meta-Analysis of Trials for Chronic Heart Failure (ExTraMATCH) Collaborative Group published an individual patient data (IPD) meta-analysis based on 9 randomised trials in 801 HF patients.[8] ExTraMATCH reported a reduction in all-cause mortality (hazard ratio (HR): 0.65, 95% CI 0.46 to 0.92) and in the composite of mortality and hospital admission (HR 0.72, 95% CI 0.56 to 0.93) with ExCR compared to no exercise control. There were no statistically significant treatment effects across subgroups. However, given the small number of trials, patients, and events, those subgroup analyses are likely to be underpowered. As the ExTraMATCH analysis did not take into account the cluster (or trial-level) nature of the data, it is likely to have underestimated the precision of the treatment effect. Since the ExTraMATCH analysis, there have been publications of trials of ExCR in HF, including HF-ACTION, a large US National Institute of Health funded trial with 2331 HF patients recruited from 82 centres.[9]

The ExTraMATCH II collaboration brings together the most comprehensive IPD meta-analysis of randomised trial data for ExCR in HF to date. Using contemporary IPD meta-analysis statistical methods, this study aimed to assess the impact of ExCR on the time to event outcomes (all-cause mortality, HF-specific mortality, all-cause hospital admission, and HF-specific hospital admission), and to identify subgroups of patients with HF that may respond differently to ExCR.

Methods

This study was conducted and reported in accordance with current IPD guidance and Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA IPD) statement.[10,11] The study was registered with the PROSPERO (CRD42014007170) and our full study protocol has been published elsewhere.[12,13]

Search strategy and selection criteria

Trials for inclusion were identified from the original ExTraMATCH IPD meta-analysis and the current Cochrane systematic review of ExCR for HF.[7,8] The Cochrane review searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, EMBASE, MEDLINE, CINAHL, PsycINFO, and the NHS Centre for Reviews and Dissemination. 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 searched. No language limitations were imposed. Details of the search strategy used are reported in the study protocol.[12]

Trials which met the following criteria were eligible for inclusion in this analysis: (i) randomised trials of adult patients (aged 18 years and older) with a diagnosis of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) based on objective assessment of left ventricular ejection fraction and on clinical findings; (ii) trial intervention (ExCR) that included an aerobic exercise training component performed by the lower limbs, lasting a minimum of 3 weeks,[7] either alone or as part of a comprehensive cardiac rehabilitation programme which may also include health education and/or a psychological intervention; (iii) a control arm which did not prescribe an exercise intervention; (iv) a minimum follow-up of 6 months; and (v) a sample size of at least 50 (to ensure that the logistical effort in obtaining, cleaning and organising the data was commensurate with the contribution of the dataset to the analysis).[14,15]

Data management

The principal investigators of included trials were invited by email to participate in this IPD meta-analysis and share their anonymised trial data. Included datasets had ethical approval and consent from their sponsors. The complete list of all requested variables and details regarding collaboration with principal investigators are reported in the study protocol.[12] Each dataset was saved in its original format and then converted and combined into one overall master dataset with standardised variables. All files are stored on a secure password protected computer server managed in accordance with the data management standard operating procedures of the nationally registered Exeter Clinical Trials Unit. Data from each trial were checked on range, extreme values, internal consistency, missing values, and consistency with published reports. Data discrepancies or missing information were discussed with trial investigators. Access to data at all stages of cleaning and analysis was restricted to core members of the research team (OC, RST, FCW, and SW).

Specification of outcomes, subgroups, and risk of bias assessment

We sought patient level time to event data from investigators for the following outcomes: time to all-cause and HF-specific mortality, and time to first all-cause and HF-specific hospitalisation. We also sought IPD on the following pre-defined patient characteristics: age, gender, ejection fraction, New York Heart Association (NYHA) functional class, HF aetiology (ischaemic or. non-ischaemic), ethnicity (white or other), and baseline (pre-randomisation) exercise capacity (e.g. peak oxygen uptake (VO_2)). Study quality/risk of bias was assessed using the TESTEX quality assessment tool.[16]

Statistical analysis

A detailed statistical analysis plan was prepared (available from authors). All analyses were carried out according to the principle of intention to treat (i.e. patients included according to their randomised trial arm) and included only patients with observed baseline data (where required) and outcome data at follow-up. Where missing data was 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. We checked for potential small study bias by assessing funnel plot asymmetry and using the Egger test.[22]

In the primary analysis, a two-stage approach was taken, with each trial first analysed using a Cox proportional hazards regression model and then trial-specific estimates of treatment effect (hazard ratio (HR)) or treatment–covariate interactions (HR of the interaction effect) were combined across trials using a random effects model. A random effects model was preferred due to the high degree of clinical heterogeneity across the individual trials, which included different patient populations, types of ExCR intervention, and comparators.[17] The 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% confidence interval (CI). Additionally, the I^2 and τ^2 statistics were reported alongside the associated p-value for the results of the main analyses.

Secondary analyses were based on a one-stage meta-analysis approach. Due to failure of convergence of one-stage random effects models, which was likely to be due to the low level of statistical heterogeneity between trials (indicated by the τ^2 statistic), a fixed effect approach was used: Cox regression models, stratified by trial. Stratification allowed the baseline hazard to vary between trials, rather than forcing the baseline hazards in individual trials to be proportionate to each other.[19] To investigate interactions between ExCR and patient characteristics, we used the approach recommended by Riley et al.[20] Continuous covariates were centred around the mean value within each trial; binary covariates were centred around the proportion within each trial.

To test the robustness of primary and secondary analyses, we undertook a number of pre-specified sensitivity analyses: (i) exclusion of the largest trial (HF-ACTION[9]); (ii) truncation of outcomes at 1-, 2- and 5-year follow-up. Small study effects were assessed for each outcome by funnel plot asymmetry and using the Egger test.[22] Results are reported as estimated HRs with 95% CIs. All analyses were undertaken using Stata 14.2 StataCorp LP, College Station, Texas, USA.

Results

Study selection

A total of 23 trials were deemed eligible for this IPD meta-analysis. Data from six trials have been analysed previously and were available from the ExTraMATCH database.[23-28] We were unable to include data from three trials (355 patients); for two trials data were no longer available [29,30] and the investigators of the other trial could not be contacted.[31] Of the remaining 17 trials, 14 investigators responded positively and shared their trial data. After obtaining IPD, one trial[32] was excluded as it was determined that it included patient data that overlapped with another trial.[33] A further trial was not included as insufficient data was provided to allow calculation of survival time or time to hospitalisation.[34] This resulted in the inclusion of 18 trials comprising 3912 patients (1948 ExCR, 1964 control) with a median follow-up of 19 months for mortality outcomes and 11 months for hospitalisation outcomes. Figure 1 summarises the study selection process. Full citations of included trials are included in eAppendix.[e1-e18]

Characteristics of included trials and participants

Patient baseline characteristics were well balanced between ExCR and control patients (see Table 1). The majority of patients were male (75%), with a mean age of 61 years (standard deviation (SD) 13). The mean baseline left-ventricular ejection fraction was 26.7% (SD 8.1%); no included trials recruited patients with preserved ejection fraction heart failure (ejection fraction >45%), and most patients were in NYHA functional class II (59%) or III (37%). Trials from Europe and North America were published between 1990 and 2012 (see Table 2). Sample size ranged from 50 to 2130 patients. All trials evaluated an aerobic exercise intervention; six also included resistance training.[e3,e4,e8,e9,e14,e15] 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. Three trials were conducted in an exclusively home-based setting.[e4,e9,e13] The dose of exercise training ranged widely across trials. ExCR was delivered over a period of 12 to 90 weeks, with between 2 and 7 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 to 85% peak VO_2.

Quality of included trials

The overall quality of included trials was judged to be moderate to good, with a median TESTEX score of 11 (range 9 to 14) out of a maximum score of 15 (eTable1). The criteria of allocation concealment and physical activity monitoring in the control groups were met in only three trials;[e4,e7,e17] the other TESTEX criteria were met in 50% or more of trials.

Effects of intervention on event outcomes

Compared with control, ExCR did not have a statistically significant effect on mortality or hospitalisation. However, all time to event pooled treatment effects from random effects two-stage IPD meta-analysis were in favour of ExCR but with wide confidence intervals ~~and not statistically significant~~; all-cause mortality: HR 0.83 (95% CI 0.67 to 1.04), p=0.107, 17 trials, 3782 patients, I^2 =26%, τ^2=0.04; HF-specific mortality: HR 0.84 (95% CI 0.49 to 1.46), p=0.527, 9 trials, 915 patients, I^2 =0%, τ^2=0.00; all-cause hospitalisation: HR 0.90 (95% CI 0.76 to 1.06), p=0.210, 11 trials, 3190 patients, I^2 =12.4%, τ^2=0.01; and HF-specific hospitalisation: HR 0.98 (95% CI 0.72 to 1.35), p=0.902, 13 trials, 3494 patients, I^2 =45%, τ^2=0.10 (Figure 2a-d). These primary analysis results were broadly consistent across secondary and sensitivity analyses (eTables 2, 3, 4, and 5). Inferences did not change following the addition of trial level data from trials that met our study inclusion criteria but were not able to contribute IPD (data not shown here, available from authors). There was no evidence of significant small study bias for the four outcomes (eFigure 1).

Differential effects across subgroups

Interaction analyses for the two-stage model revealed no consistent interactions between the effect of ExCR and any of the predefined subgroups (age, gender, ejection fraction, NYHA class, HF

aetiology, ethnicity and baseline peak VO_2) for all-cause mortality, HF-related mortality, all-cause hospitalisation, or HF-related hospitalisation (Figure 3a-d). Some evidence of an interaction effect between ExCR and a patient characteristic ($p<0.05$) was seen in four sensitivity analyses (eTables 2, 3, 4, and 5): (i) ExCR was associated with a larger reduction in all-cause mortality in older patients ($p=0.034$) in the two-stage model with 2-year truncation; (ii) ExCR was associated with a larger reduction in HF-mortality older patients ($p=0.017$) in the two-stage model with 2-year truncation; (iii) ExCR was associated with a larger reduction in HF-mortality in ischemic patients ($p=0.047$) in the one-stage model without truncation; and (iv) ExCR was associated with a larger reduction in all-cause hospitalisation inpatients with lower baseline peak VO_2 ($p=0.027$) in the two-stage model with 1-year truncation.

Discussion

Compared with no exercise control, ExCR did not have a statistically significant effect on mortality or hospitalisation ~~our overall summary estimates were in favour of ExCR for time to all-cause and HF-specific mortality, and time to first all-cause and HF-specific hospitalisation,~~ in patients with reduced ejection fraction HF. Although we pooled IPD from 18 trials including 3912 patients, treatment effect estimates were imprecise. We found no strong evidence for a differential effect of ExCR according to patient characteristics. .

Unlike ~~In accord with the~~ the previous IPD meta-analysis, ExTraMATCH[8], our analyses did show~~ed~~ a definitive ~~the potential~~ benefit of ExCR in terms of either ~~both~~ time to all-cause mortality or ~~and~~ all-cause hospitalisation. ~~However, l~~in contrast to this previous analysis, our confidence intervals were wide and failed to reach statistical significance. The wide confidence intervals may be due to several factors, including: (i) variation in adherence to ExCR within trials; (ii) variation in treatment effect of ExCR among adherent patients; and (iii) variation in the composition/effectiveness of usual care within and across trials. A potential explanation for this reduction in strength of effect on clinical events is the inclusion of more recent trials in this updated IPD analysis that have utilised prognostic innovations in usual care treatments for HF, which include devices (resynchronisation and defibrillator therapy) and disease modifying drugs (beta-blockers, ACE inhibitors, angiotensin II receptor antagonists, and mineralocorticoid receptor antagonists). A similar reduction in mortality benefits of ExCR over time has been seen in trials where ExCR was provided to post-myocardial infarction and revascularisation patients.[35]

Our finding of a lack of consistent evidence for HF patient subgroup effects of ExCR agrees with both the previous ExTraMATCH and Cochrane 2014 analyses.[7,8] However, these two previous studies had major limitations that are likely to have limited their ability to detect subgroup effects. ExTraMATCH included data on only 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 found no association between trial level patient characteristics

(age, gender, ejection fraction) and ExCR. However, meta-regression analysis is highly prone to study level confounding (ecological fallacy) and should be interpreted with great caution.[36] Nevertheless, our findings are also consistent with the IPD subgroup analyses from the multicentre HF-ACTION trial. The HF-ACTION investigators reported no significant interaction effect of exercise training intervention on their composite primary outcome (all-cause mortality or hospitalisation) and the subgroups of age (≤70 vs. > 70 years), gender, race (white vs. non-white), HF aetiology (ischaemic vs. non ischaemic), ejection fraction (≤25% vs. >25%), or NHYA class (II vs. III/IV).[9,37]

Strengths and limitations

Our ExTraMATCH II study has a number of strengths. We believe this to be the first IPD meta-analysis including sufficiently large numbers of HF patients (3912) and events (701 all-cause deaths, 1642 first all-cause hospitalisations) to be able to identify differential effects of ExCR in patients with different characteristics. We were able to standardise the handling and analysis of time to event outcomes across trials. Our findings were broadly consistent across analytic approaches that included one-- and two-stage IPD meta-analysis models and a range of sensitivity analyses. Finally, we found no evidence of publication bias. Whilst systematic reviews and meta-analyses of IPD from randomised trials are recognised as the gold standard for assessing intervention effects,[39] our study has a number of limitations. First and foremost, there was a lack consistency in how included trials with IPD in our analyses defined and collected clinical event outcome data. As noted in recent commentaries on clinical events in HF trials, with the exception of all-cause mortality, the collection and reporting the other outcomes including cause-specific mortality and hospitalisation can be prone to confounding and bias.[39] We made considerable efforts to contact study authors in order to clarify issues around the definition of hospitalisations and HF-specific deaths. 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 our conclusions for these outcomes. Second, overall, IPD was available to ExTraMATCH II for 3912/4267 patients in 18/23 trials identified

as eligible, equating to an omission of only 8% of all participants across all eligible trials. However, not all included trials collected IPD for the time to event outcomes or patient characteristics assessed in this study. The large multicentre HF-ACTION trial did not collect HF-specific hospitalisation, thus reducing our statistical power for this outcome. Although, across the trials that provided outcome data, the proportion of patients with missing clinical event or baseline covariate data was low, this may have introduced bias in our results. Finally, we did not have patient level data on 'ExCR dose', i.e. adherence to duration, frequency and intensity of ExCR undertaken by an individual patient. Using IPD from HF-ACTION, Keteyian et al found exercise volume (defined as metabolic equivalent of task (MET)-hour per week) to be a predictor for the composite outcome of all-cause mortality or hospitalisation (p=0.03).[40] Whilst this analysis was indicates that patient level ExCR 'dose' is a key potential explanatory variable and one that was not available across the trials in our analyses.

Implications for practice and further research

In spite of the comprehensiveness of this IPD meta-analysis, 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 reduced ejection fraction HF; in particular, to increase the power to examine whether 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 triallists to more consistently collect, report, and share patient-level data in the future. Two central aspects of future data collection include a consensus on the definition, collection, and reporting of clinical event data, especially hospitalisation, plus the capture of data on patient level adherence to the amount of exercise training during the ExCR intervention period. Our forthcoming IPD meta-analysis will examine the impact of ExCR exercise capacity on health-related quality of life and explore how this treatment effect may vary across according to HF patient characteristics.[12,13]

Conclusion

~~Whilst~~ ExCR did not significantly ~~appeared to~~ reduce the risk of mortality and hospitalisation in patients with reduced ejection fraction HF. ~~,~~ Although we pooled the IPD from a number of randomised trials, treatment effect estimates remain imprecise. ~~lack of precision in the estimated HRs precluded making any definitive conclusions regarding the effect of ExCR~~. Further evidence is needed to definitively assess the effect of ExCR, and to investigate the potential for variation in treatment effects among HF patients with different characteristics.

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Acknowledgments: RST, NS, MP, FCW, OC designed the study and obtained the study funding. SW analysed the data. All authors contributed to writing and editing of the manuscript, with the lead taken by RST and SW. CO'C, KD, RH, KJ, RMc, JM, BBN, CP, MDW, GY ADZ contributed individual participant data for this study. All authors commented on the manuscript and agreed the final version.

We acknowledge the contribution of patient data from Dr Rainer Hambrecht, Dr Emanuella Zanelli, and the late Dr Romualdo Belardinelli and late Dr Pantaleo Giannuzzi. We thank Mr Tim Eames, Exeter Clinical Trials Unit, for his advice and support on data management for this study, and Professor Richard Riley, Professor of Biostatistics, Keele University, for his comments on a draft of this paper.

Conflict of Interest: RST and HMD are currently co-chief investigators and KJ a co-investigator on a National Institute for Health Research (NIHR) funded programme grant designing and evaluating the clinical and cost-effectiveness of a home-based cardiac rehabilitation intervention for heart failure patients (RP-PG-1210-12004). All other authors declare no conflicts.

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Figure legends

Figure 1. PRISMA flow diagram

Figure 2. Effect of ExCR on mortality and hospitalisation across patient subgroups

Figure 3. Effect of ExCR on mortality and hospitalisation across patient subgroups

Revised manuscript word count: 3211

Figure1

Click here to download Figure Flowchart - figure 1.jpg

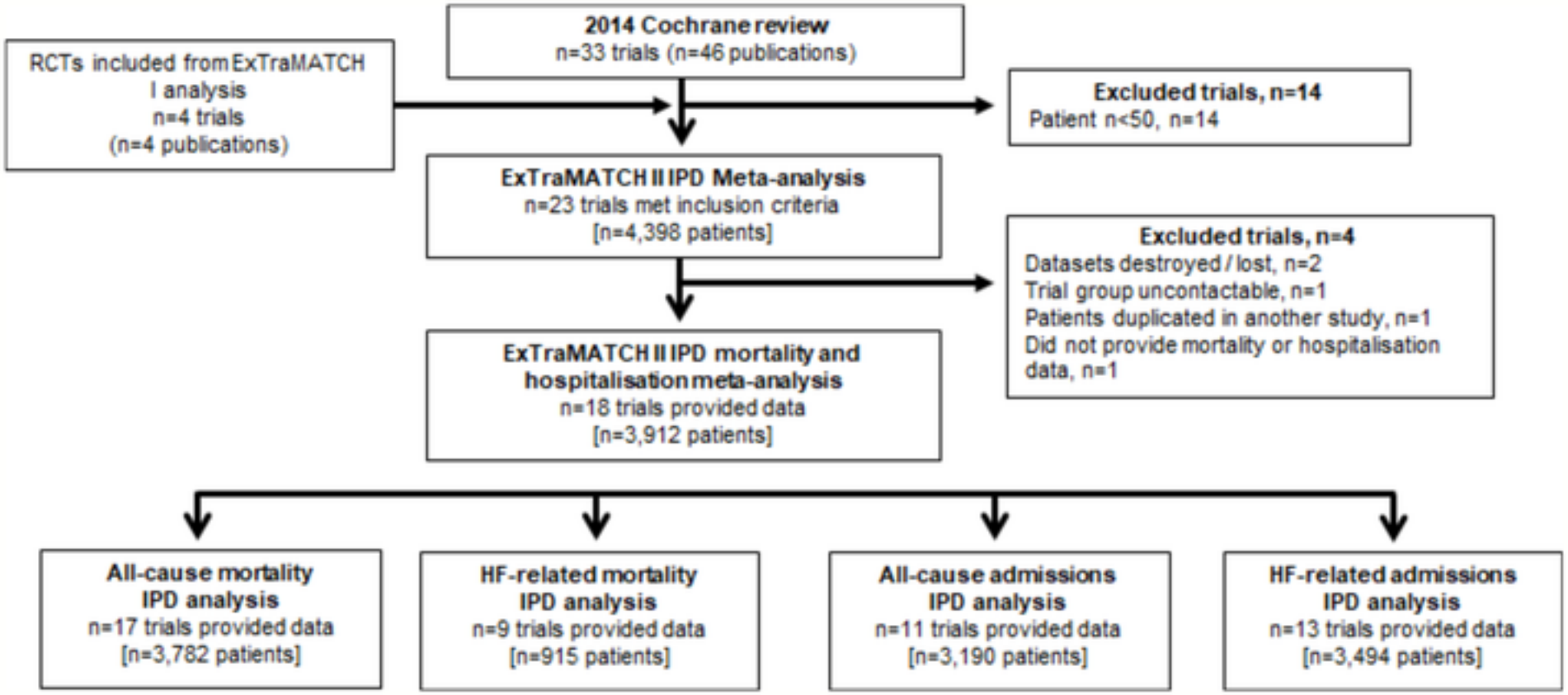

Figure3a

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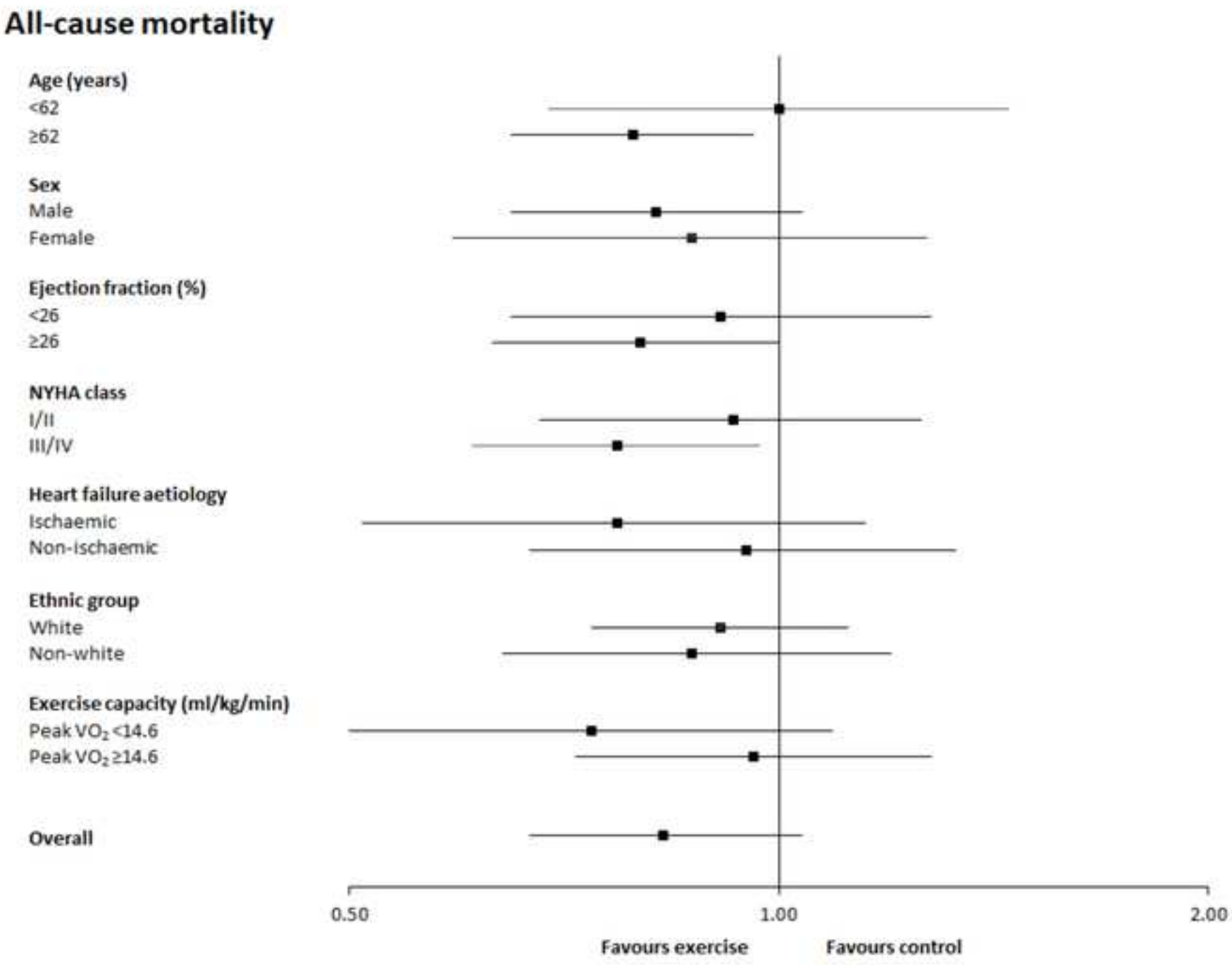

Figure3b

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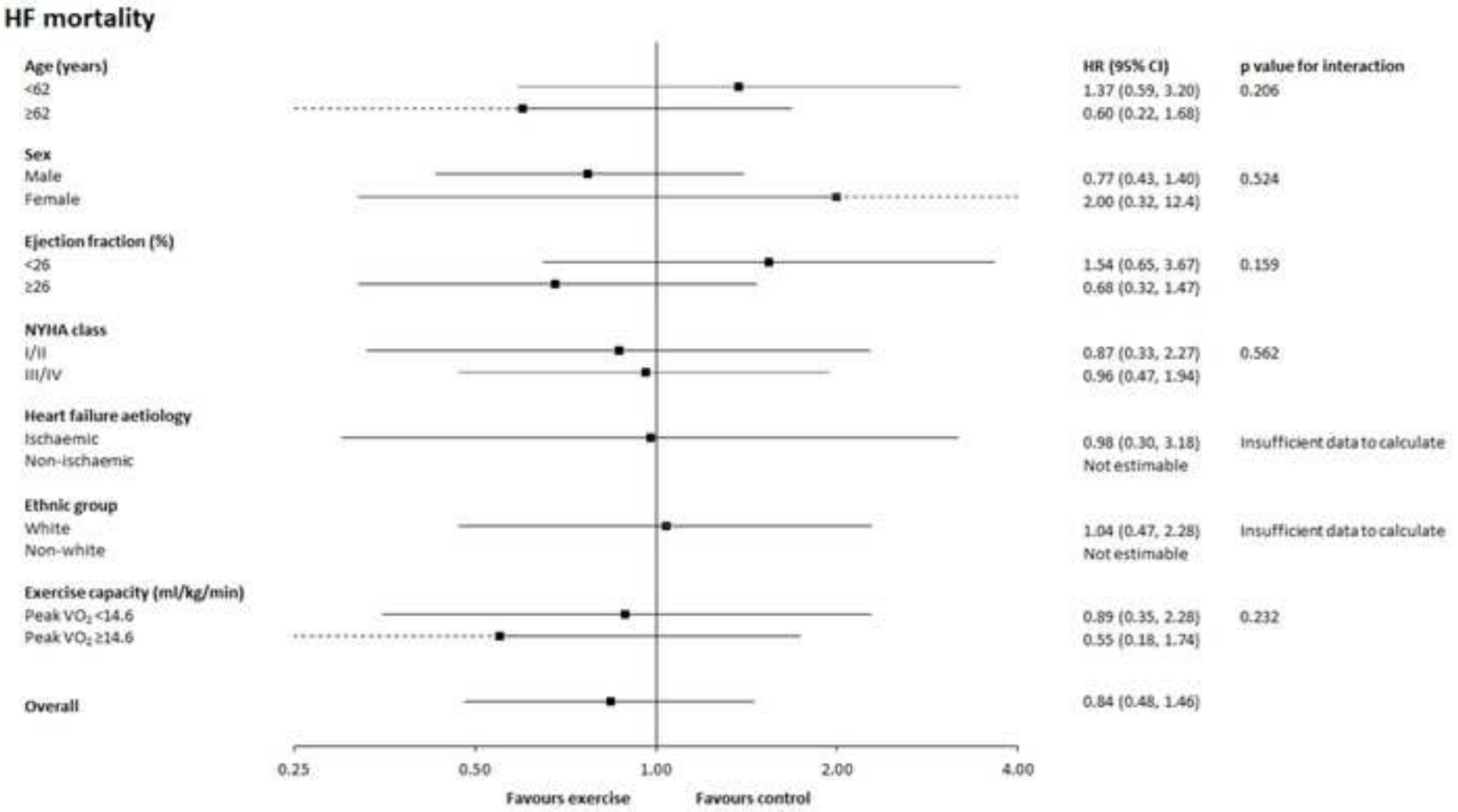

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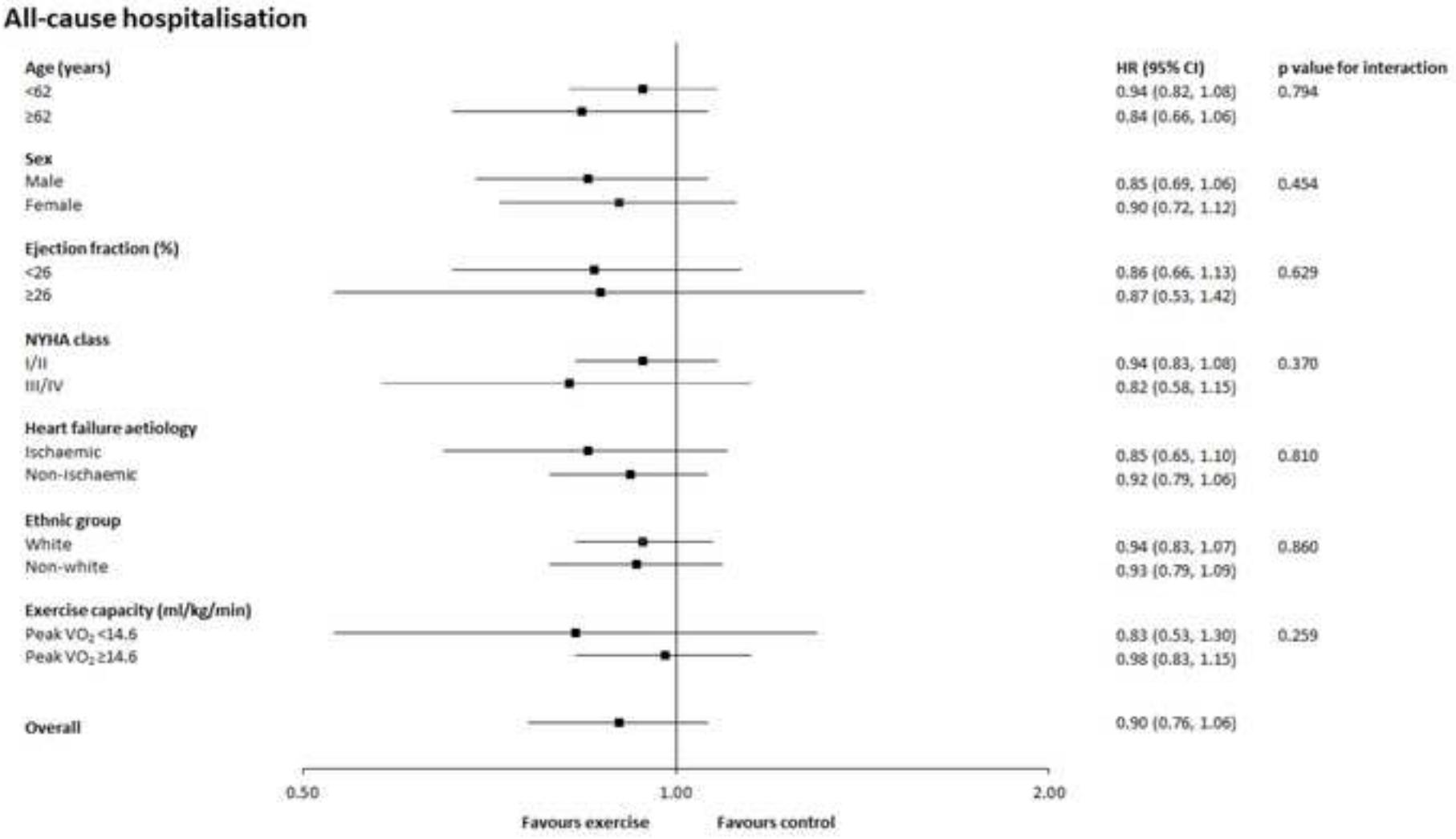

Figure3d

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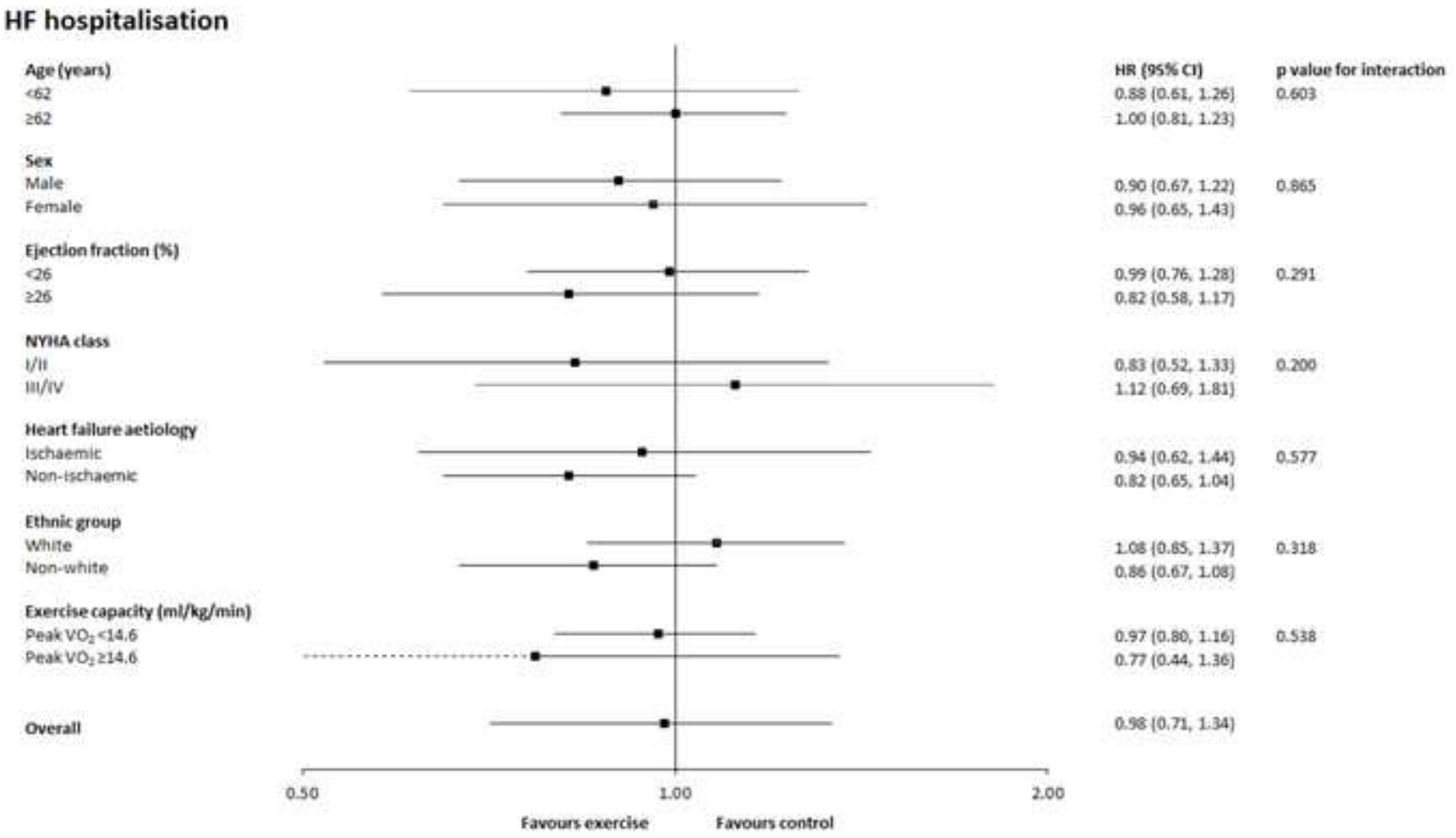


12th June 2018

Dear Profs Metra & Volterrani

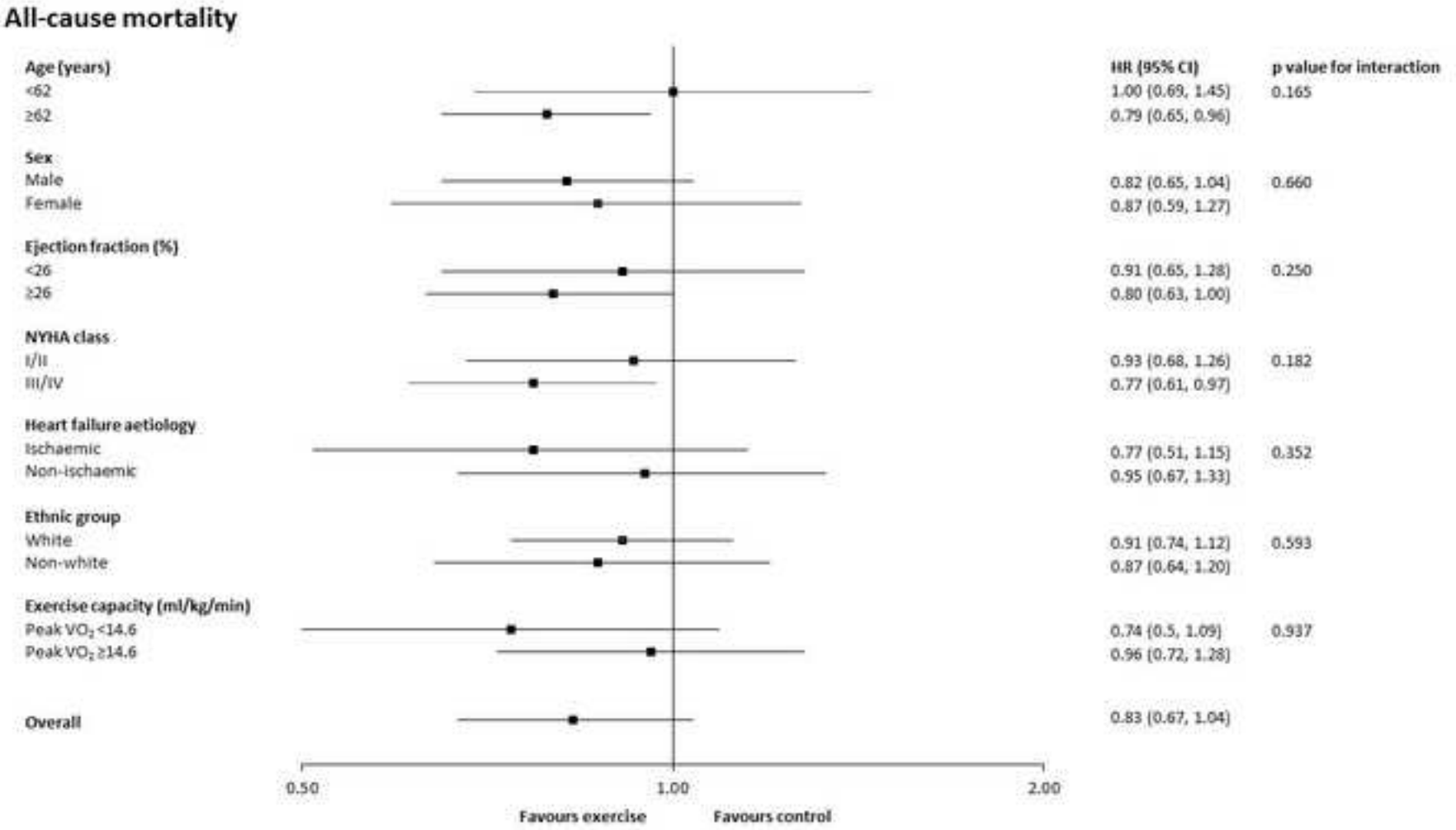
Ref.: Ms. No. EURJHF-18-404-RT Impact of exercise-based rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual-patient data meta-analysis of randomised trials European Journal of Heart Failure

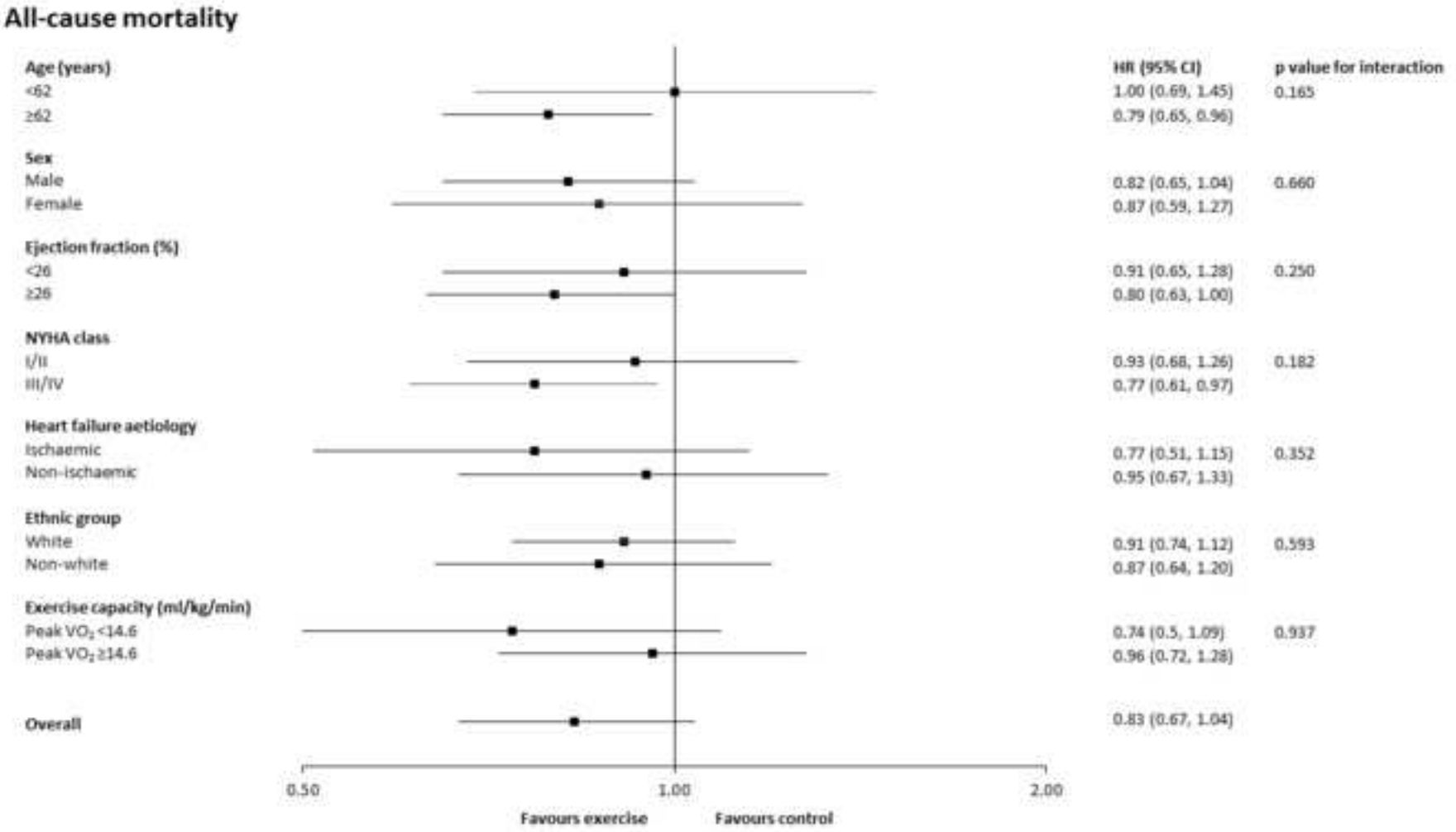
We thank you editors and reviewers for their helpful comments. We provide a point-by-point response below plus a list of manuscript revisions. A tracked edited version of the manuscript has been attached.

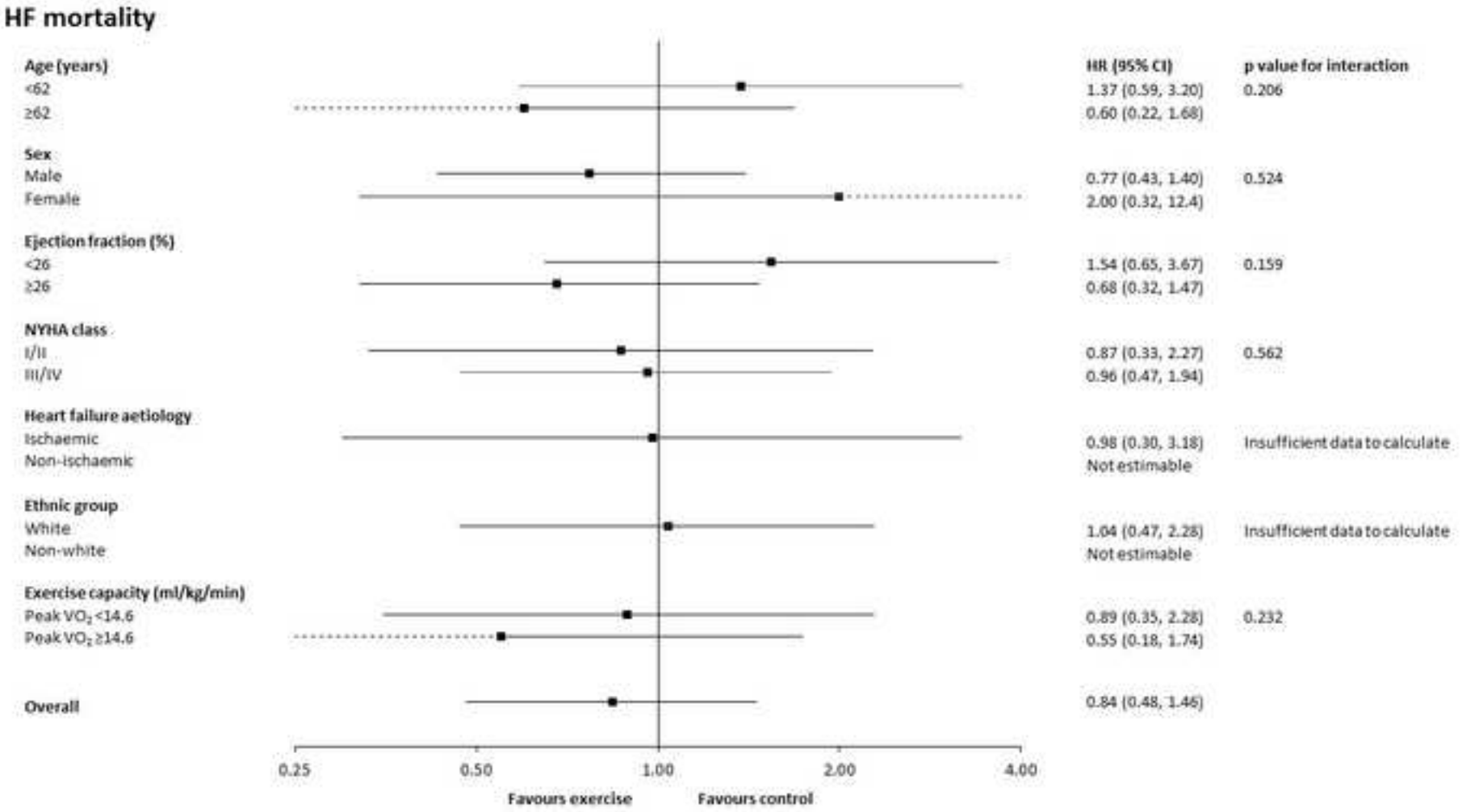
Many thanks for your consideration

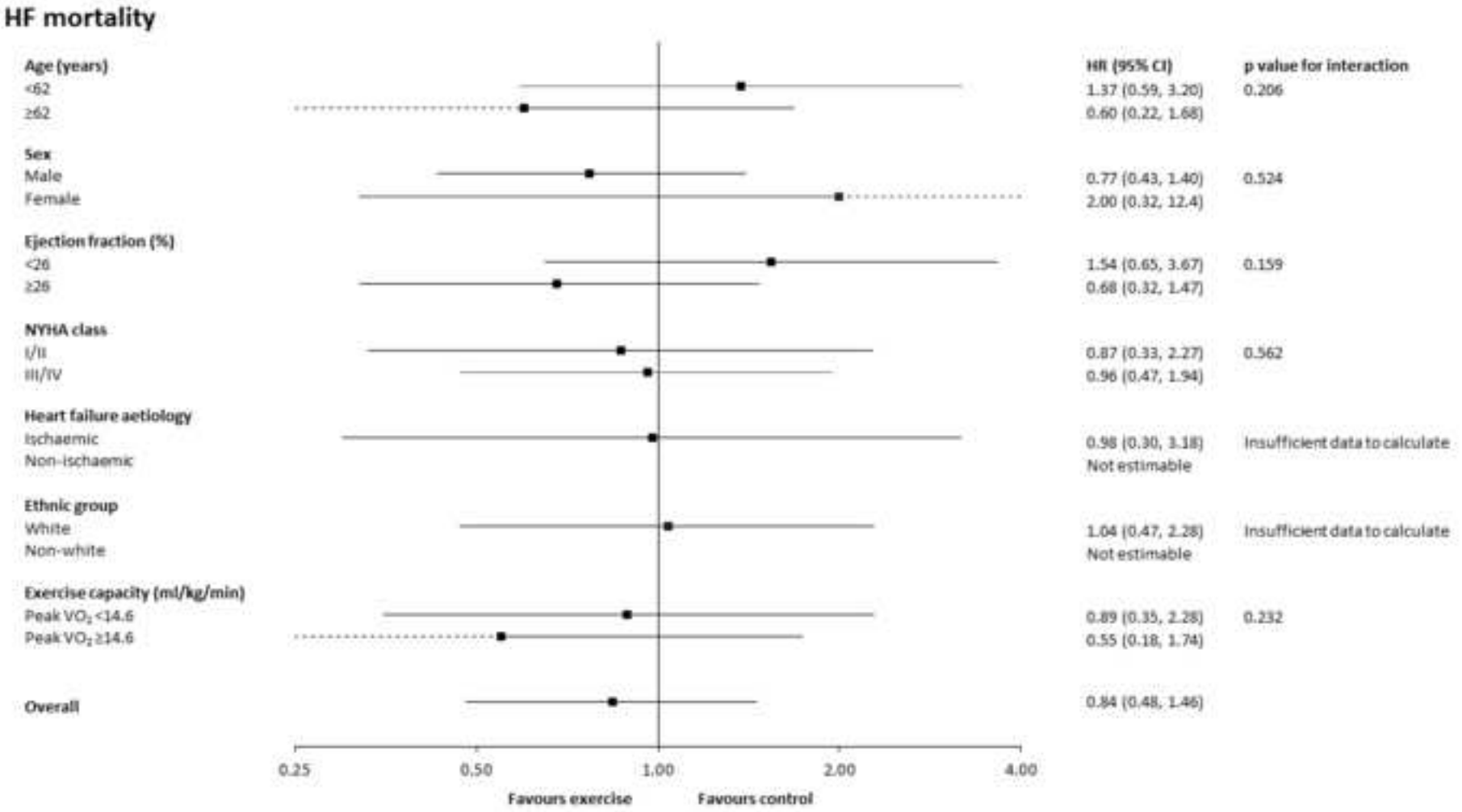
Prof Rod Taylor

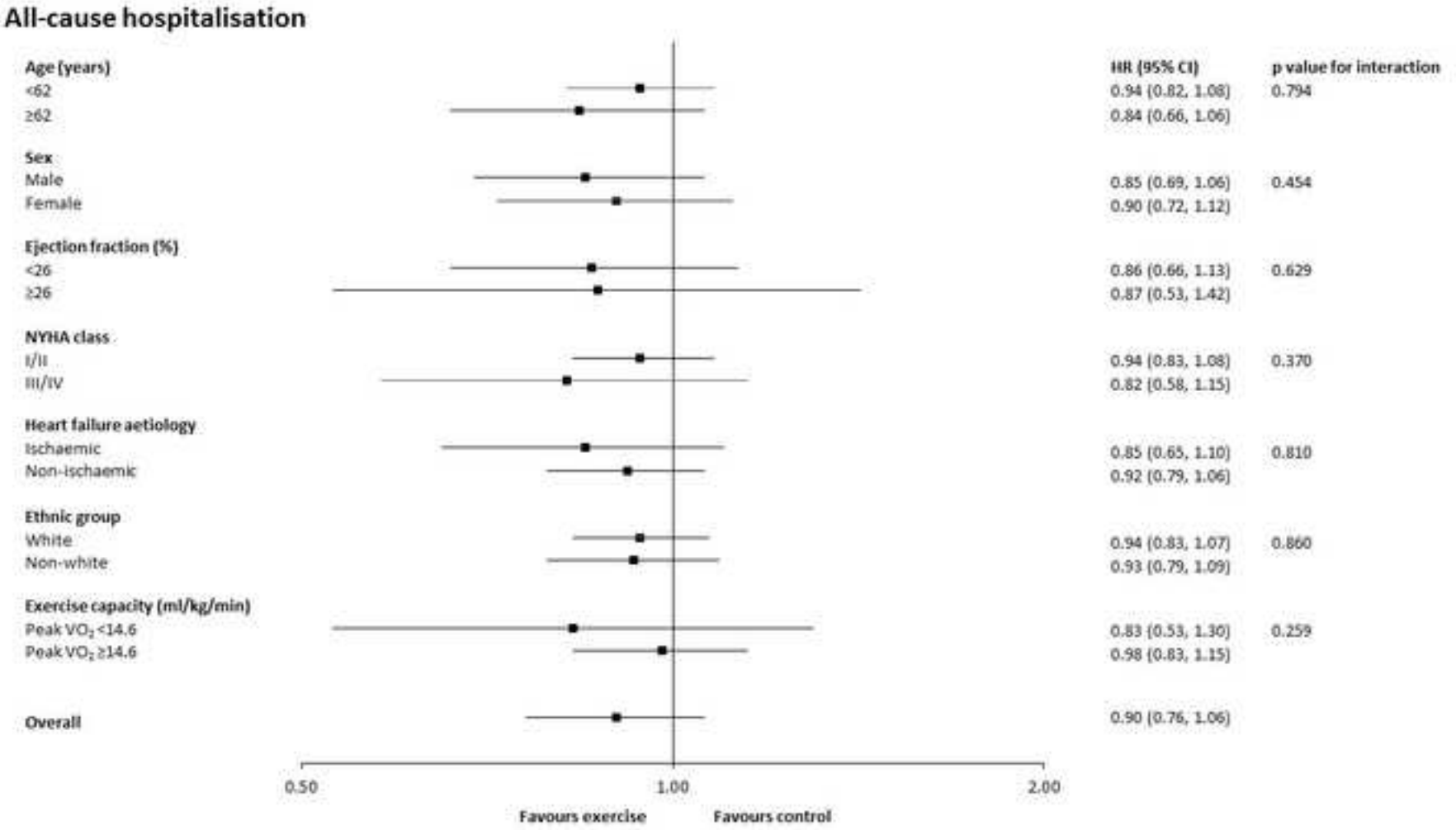
On behalf of the ExTraMATCH II collaboration and co-authors

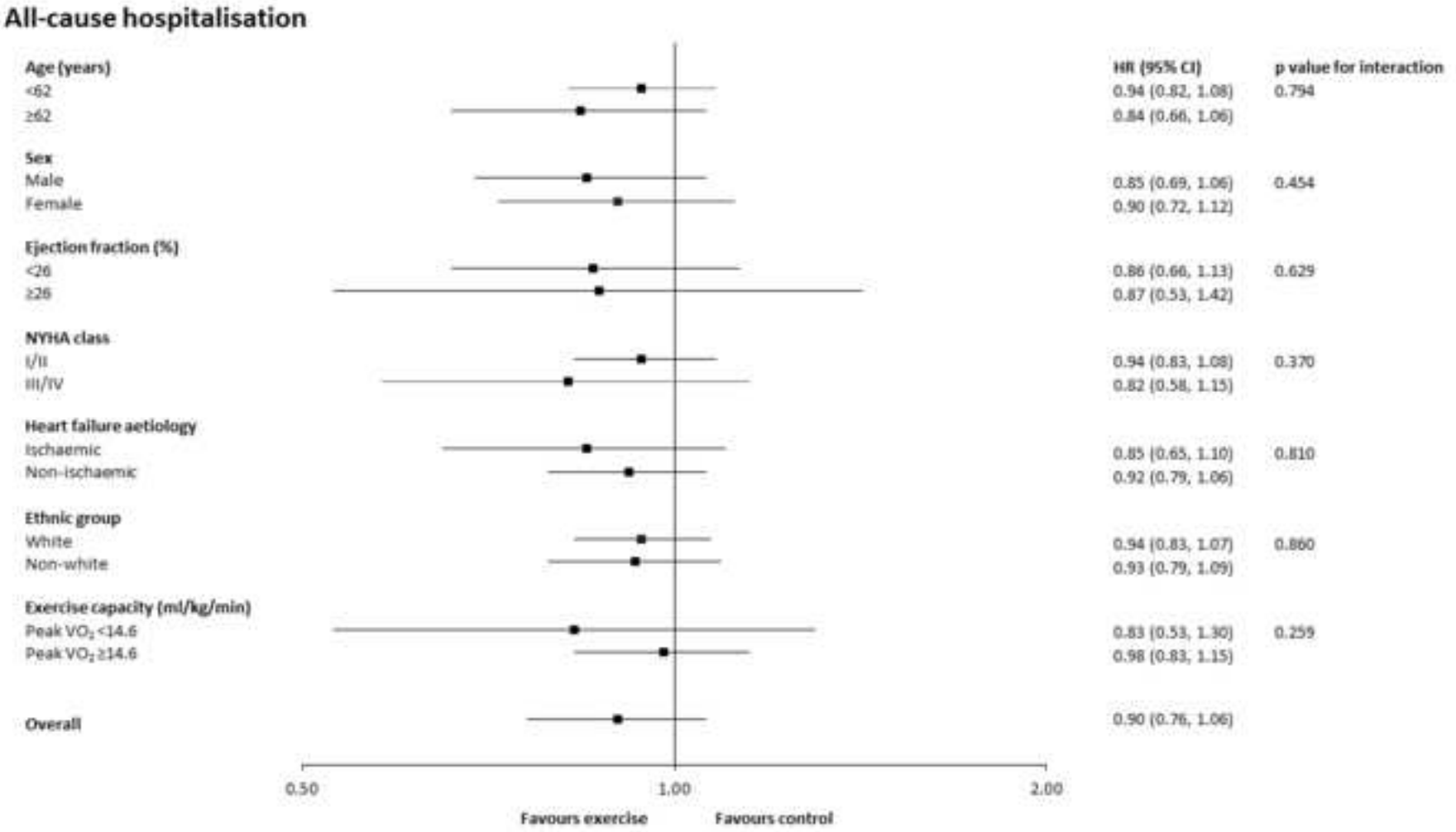


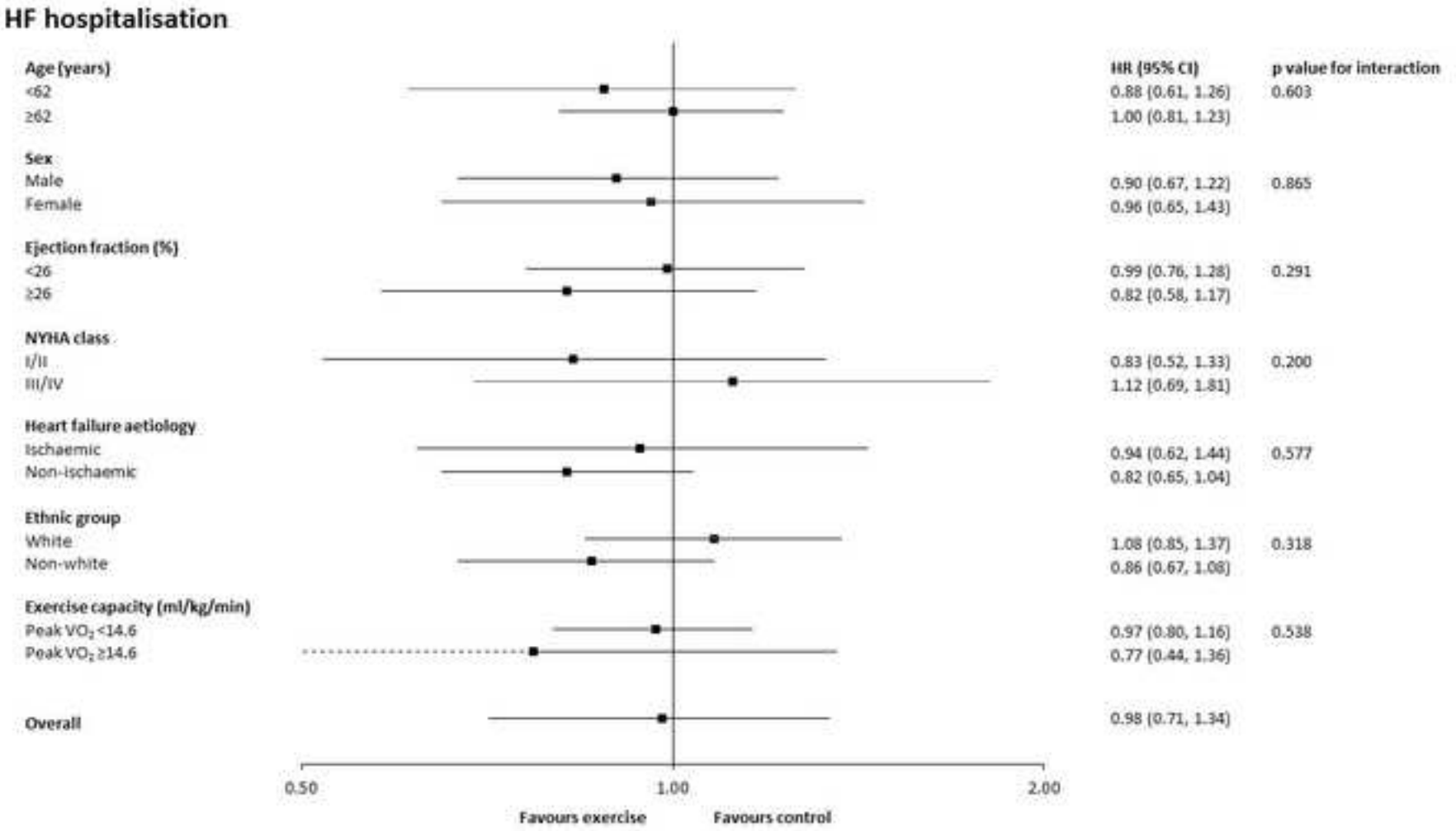


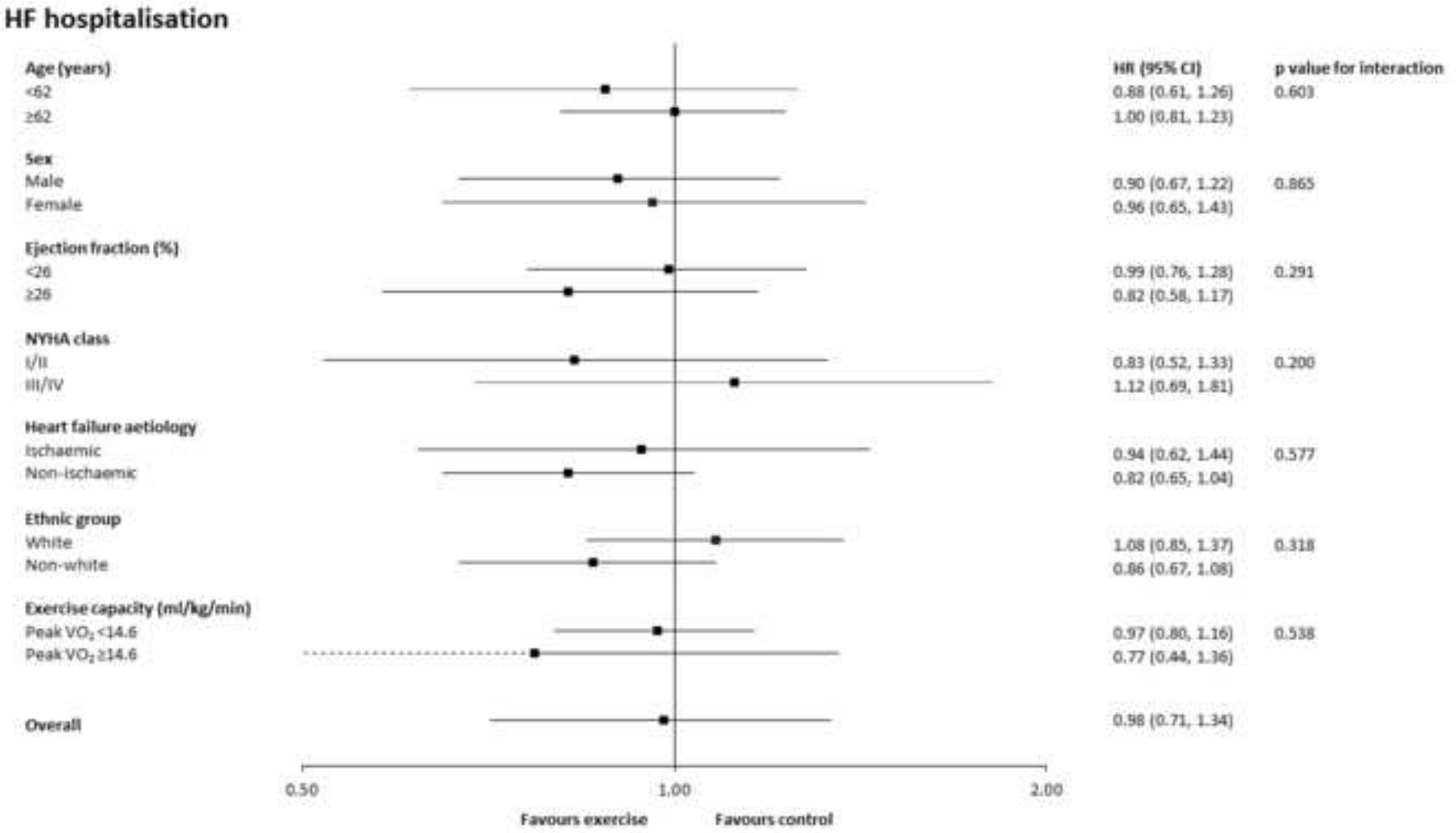




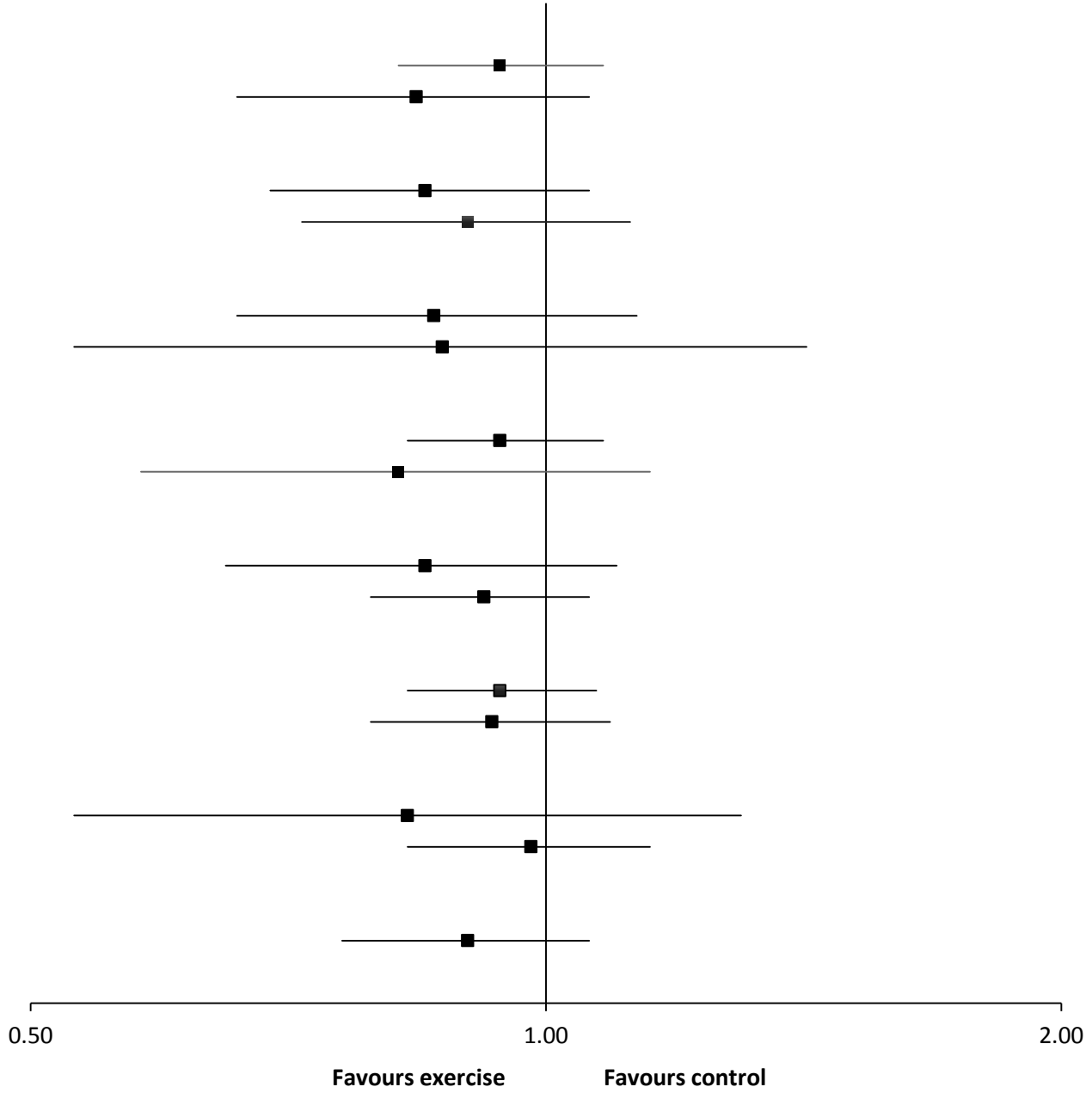






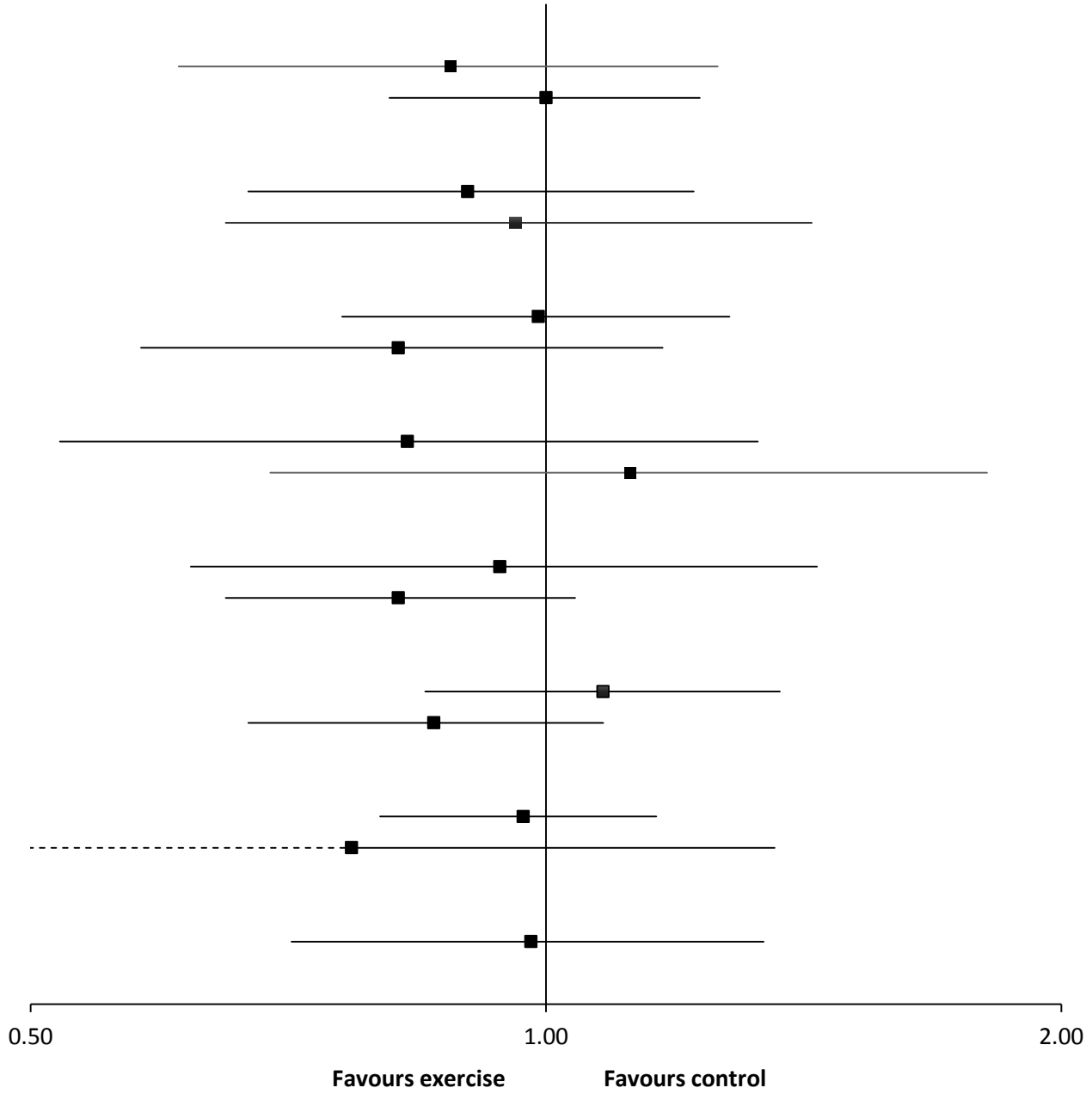


All-cause hospitalisation



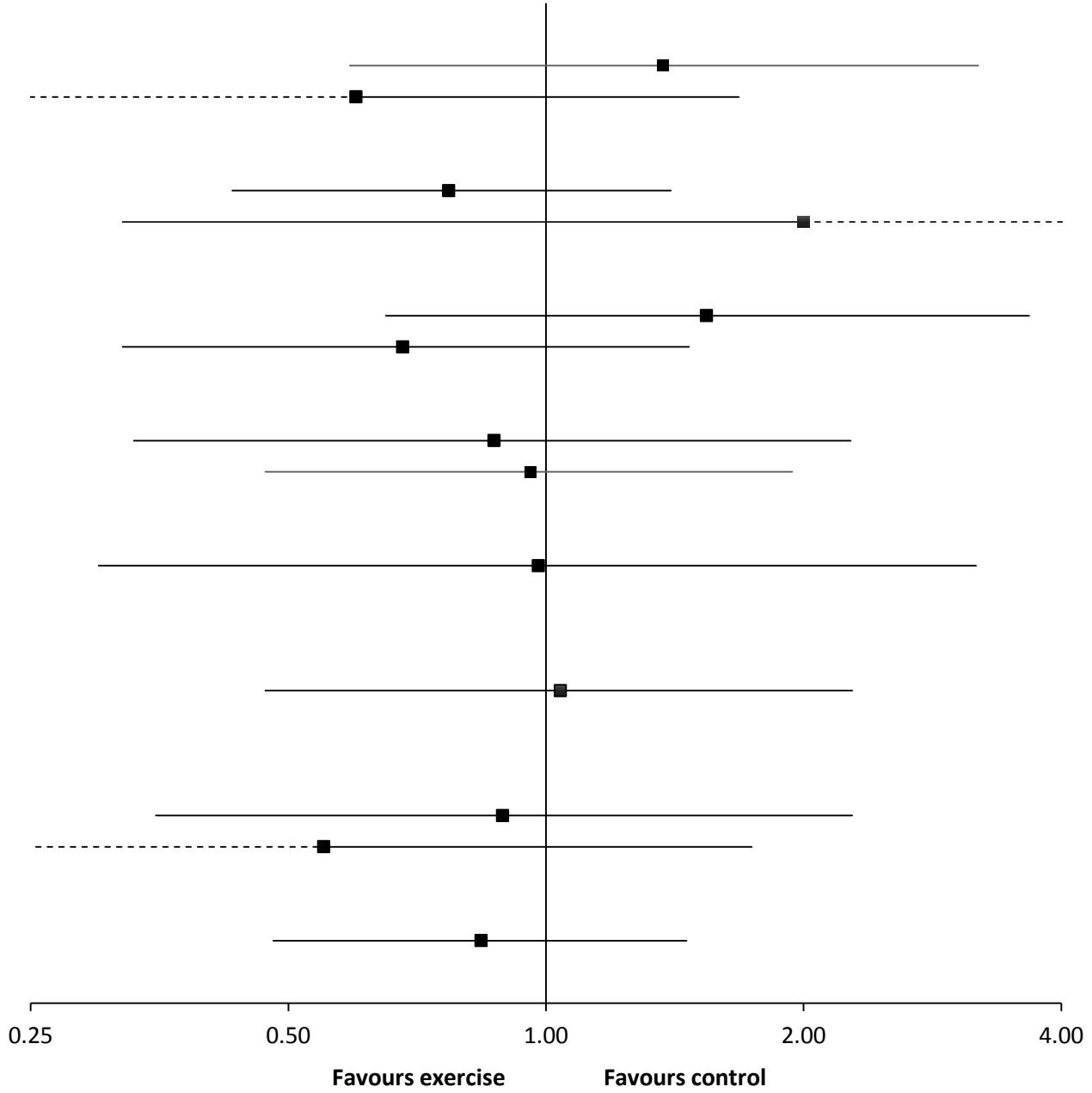
	HR (95% CI)	p value for interaction
Age (years)		
<62	0.94 (0.82, 1.08)	0.794
≥62	0.84 (0.66, 1.06)	
Sex		
Male	0.85 (0.69, 1.06)	0.454
Female	0.90 (0.72, 1.12)	
Ejection fraction (%)		
<26	0.86 (0.66, 1.13)	0.629
≥26	0.87 (0.53, 1.42)	
NYHA class		
I/II	0.94 (0.83, 1.08)	0.370
III/IV	0.82 (0.58, 1.15)	
Heart failure aetiology		
Ischaemic	0.85 (0.65, 1.10)	0.810
Non-ischaemic	0.92 (0.79, 1.06)	
Ethnic group		
White	0.94 (0.83, 1.07)	0.860
Non-white	0.93 (0.79, 1.09)	
Exercise capacity (ml/kg/min)		
Peak VO_2 <14.6	0.83 (0.53, 1.30)	0.259
Peak VO_2 ≥14.6	0.98 (0.83, 1.15)	
Overall	0.90 (0.76, 1.06)	

HF hospitalisation



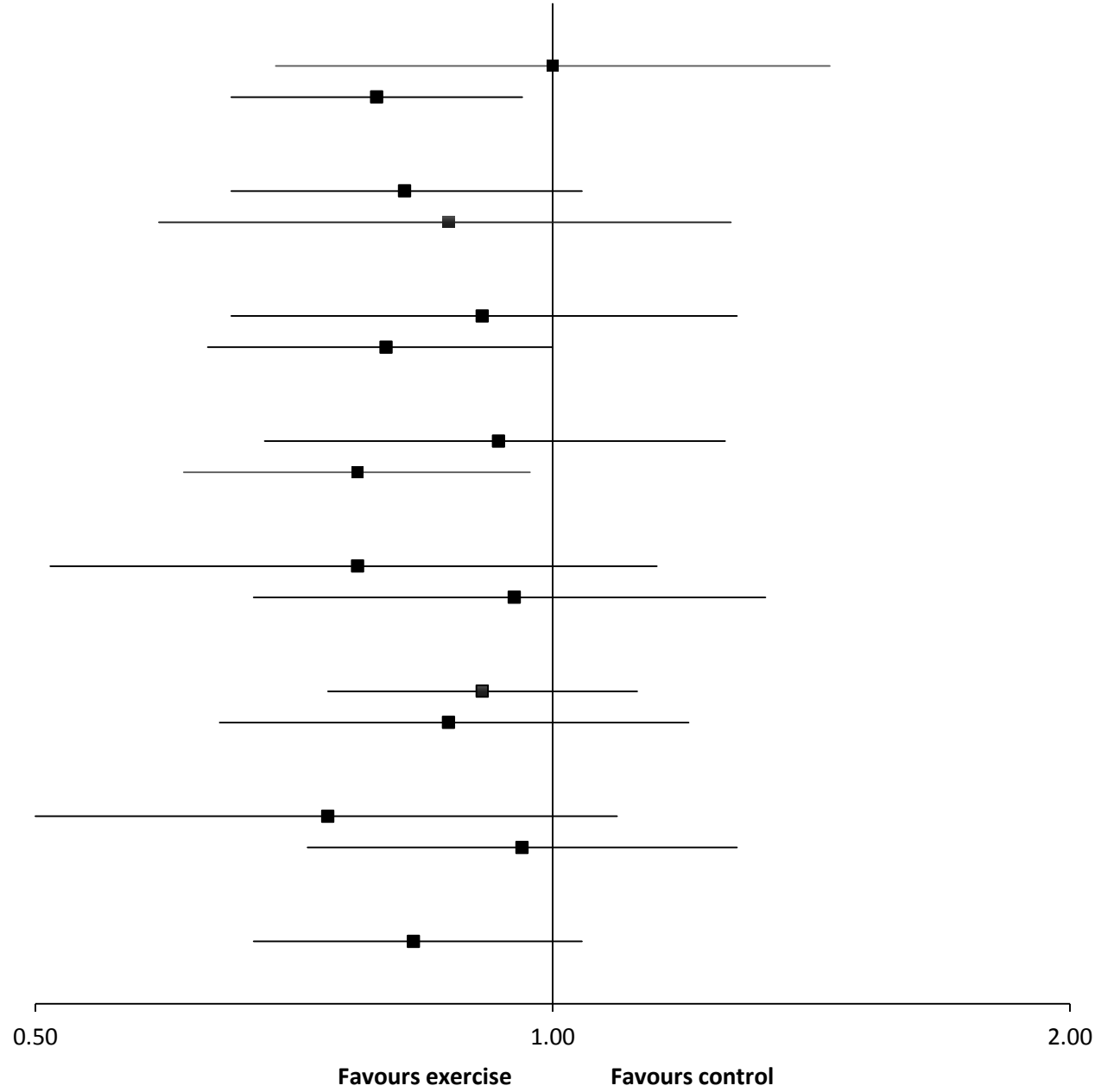
	HR (95% CI)	p value for interaction
Age (years)		
<62	0.88 (0.61, 1.26)	0.603
≥62	1.00 (0.81, 1.23)	
Sex		
Male	0.90 (0.67, 1.22)	0.865
Female	0.96 (0.65, 1.43)	
Ejection fraction (%)		
<26	0.99 (0.76, 1.28)	0.291
≥26	0.82 (0.58, 1.17)	
NYHA class		
I/II	0.83 (0.52, 1.33)	0.200
III/IV	1.12 (0.69, 1.81)	
Heart failure aetiology		
Ischaemic	0.94 (0.62, 1.44)	0.577
Non-ischaemic	0.82 (0.65, 1.04)	
Ethnic group		
White	1.08 (0.85, 1.37)	0.318
Non-white	0.86 (0.67, 1.08)	
Exercise capacity (ml/kg/min)		
Peak VO_2 <14.6	0.97 (0.80, 1.16)	0.538
Peak VO_2 ≥14.6	0.77 (0.44, 1.36)	
Overall	0.98 (0.71, 1.34)	

HF mortality



	HR (95% CI)	p value for interaction
Age (years)		
<62	1.37 (0.59, 3.20)	0.206
≥62	0.60 (0.22, 1.68)	
Sex		
Male	0.77 (0.43, 1.40)	0.524
Female	2.00 (0.32, 12.4)	
Ejection fraction (%)		
<26	1.54 (0.65, 3.67)	0.159
≥26	0.68 (0.32, 1.47)	
NYHA class		
I/II	0.87 (0.33, 2.27)	0.562
III/IV	0.96 (0.47, 1.94)	
Heart failure aetiology		
Ischaemic	0.98 (0.30, 3.18)	Insufficient data to calculate
Non-ischaemic	Not estimable	
Ethnic group		
White	1.04 (0.47, 2.28)	Insufficient data to calculate
Non-white	Not estimable	
Exercise capacity (ml/kg/min)		
Peak VO_2 <14.6	0.89 (0.35, 2.28)	0.232
Peak VO_2 ≥14.6	0.55 (0.18, 1.74)	
Overall	0.84 (0.48, 1.46)	

All-cause mortality



	HR (95% CI)	p value for interaction
Age (years)		
<62	1.00 (0.69, 1.45)	0.165
≥62	0.79 (0.65, 0.96)	
Sex		
Male	0.82 (0.65, 1.04)	0.660
Female	0.87 (0.59, 1.27)	
Ejection fraction (%)		
<26	0.91 (0.65, 1.28)	0.250
≥26	0.80 (0.63, 1.00)	
NYHA class		
I/II	0.93 (0.68, 1.26)	0.182
III/IV	0.77 (0.61, 0.97)	
Heart failure aetiology		
Ischaemic	0.77 (0.51, 1.15)	0.352
Non-ischaemic	0.95 (0.67, 1.33)	
Ethnic group		
White	0.91 (0.74, 1.12)	0.593
Non-white	0.87 (0.64, 1.20)	
Exercise capacity (ml/kg/min)		
Peak VO_2 <14.6	0.74 (0.5, 1.09)	0.937
Peak VO_2 ≥14.6	0.96 (0.72, 1.28)	
Overall	0.83 (0.67, 1.04)