










# Exercise-based cardiac rehabilitation for coronary heart disease: the CaReMATCH individual participant data meta-analysis

Niels A. Stens <sup>1,2</sup>, Benjamin J.R. Buckley <sup>3,4</sup>, Grace O. Dibben<sup>5</sup>, Laurien M. Buffart <sup>1</sup>, Geert Kleinnibbelink <sup>1,2</sup>, Dorairaj Prabhakaran<sup>6,7</sup>, Ambalam M. Chandrasekaran<sup>6</sup>, Sanjay Kinra<sup>7</sup>, Ambuj Roy <sup>8</sup>, Gianluca Campo<sup>9</sup>, Arto J. Hautala<sup>10</sup>, Johan A. Snoek<sup>11,12</sup>, Ralph Maddison <sup>13</sup>, Núria Santaularia <sup>14,15,16</sup>, Scott A. Lear<sup>17</sup>, Julie Houle<sup>18</sup>, Gregory Y.H. Lip<sup>3,19</sup>, Niels van Royen <sup>2</sup>, Rod S. Taylor<sup>5,20†</sup>, and Dick H.J. Thijssen <sup>1,3,4\*†</sup>;  
CaReMATCH Collaborators

<sup>1</sup>Department of Medical BioSciences, Radboud University Medical Center, P.O. Box 9101, Nijmegen 6500 HB, The Netherlands; <sup>2</sup>Department of Cardiology, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>3</sup>Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, UK; <sup>4</sup>Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK; <sup>5</sup>MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK; <sup>6</sup>Centre for Chronic Disease Control, Public Health Foundation India, New Delhi, India; <sup>7</sup>Department of Non-communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK; <sup>8</sup>Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India; <sup>9</sup>Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy; <sup>10</sup>Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland; <sup>11</sup>Isala Heart Center, Isala, Zwolle, The Netherlands; <sup>12</sup>Sports Medicine Department, Isala, Zwolle, The Netherlands; <sup>13</sup>Institute for Physical Activity and Nutrition, Deakin University, Geelong, Australia; <sup>14</sup>Cardiac Rehabilitation Integrated Practice Unit, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain; <sup>15</sup>Faculty of Health Sciences at Manresa, Universitat de Vic—Universitat Central de Catalunya (UVic-UCC), Manresa, Spain; <sup>16</sup>Central Catalonia Chronicity Research Group (C3RG), Institut de Recerca i Innovació en Ciències de la Vida i de la Salut a la Catalunya Central (IRIS-CC), Vic, Spain; <sup>17</sup>Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada; <sup>18</sup>Nursing Department, Université du Québec à Trois-Rivières, Trois-Rivières City, Canada; <sup>19</sup>Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; and <sup>20</sup>Robertson Centre for Biostatistics, School of Health and Wellbeing, University of Glasgow, Glasgow, UK

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## Aims

The effectiveness of exercise-based cardiac rehabilitation (ExCR) for coronary heart disease (CHD) has been debated during the past decade. The objectives of the Cardiac Rehabilitation Meta-Analysis of Trials in people with CHD using individual participant data (IPD) (CaReMATCH) study were to (i) provide contemporary estimates on the effectiveness of ExCR for CHD and (ii) examine potential differential effects of ExCR across subgroups.

## Methods and results

Individual participant data from randomized controlled trials comparing ExCR with no ExCR controls were pooled. To reflect contemporary ExCR practice, trials had to be published since 2010. The outcomes of all-cause and cardiovascular disease (CVD)-related mortality and hospitalization and health-related quality of life (HRQoL) were analysed. From 30 eligible trials (10 677 participants), IPD were obtained from eight trials (4975 participants, 93.5% post-myocardial infarction). Compared with controls, participation in ExCR resulted in a lower risk for all-cause [hazard ratio (HR) 0.68, 95% confidence interval (CI): 0.53, 0.87] and CVD-related hospitalization (HR 0.62, 95% CI: 0.47, 0.83) and higher HRQoL up to 12 months of follow-up (mean difference in utility index: 0.032, 95% CI: 0.003, 0.061). No differences were found in all-cause and CVD

\* Corresponding author. Tel: +31 24 361 4273, Email: [Dick.Thijssen@radboudumc.nl](mailto:Dick.Thijssen@radboudumc.nl)

† The last two authors shared last co-authorship.

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mortality (HR 0.99, 95% CI: 0.74, 1.32; HR 0.80, 95% CI: 0.32, 2.04, respectively). Subgroup analyses showed stronger improvements of HRQoL with ExCR in people with lower HRQoL and lower education level and larger reductions in hospitalization risk in those with a lower left ventricular ejection fraction, lower baseline exercise capacity, beta-blockers use, and with a previous history of CVD. No other subgroup effects were observed.

**Conclusion**

Our IPD meta-analysis, reflecting trials published since 2010, highlighted that contemporary ExCR is effective in reducing risk of hospitalization and improving HRQoL in those with CHD. Importantly, we reveal treatment benefits to be robust and consistent across most participant subgroups. Together, these data support the class I recommendation of international clinical guidelines that ExCR should be offered to all people with CHD.

**Registration**

PROSPERO: CRD42020204988


**Lay summary**


Coronary heart disease is the most common cause of death globally. People with coronary heart disease are often referred to exercise-based cardiac rehabilitation (ExCR). These programmes include exercise training, sometimes combined with education or social support. Their aim is to improve health and quality of life.

The CaReMATCH project combined results from recent studies that randomly allocated people with coronary heart disease to either participate in ExCR or not. We investigated how well ExCR works and whether its effects differ between groups of people.


- People who took part in ExCR were less likely to be admitted to the hospital (for any reason, or for heart-related problems) and reported better quality of life. ExCR did not help people to live longer.
- The benefits for quality of life were greater who started the intervention with poorer quality of life or lower education levels. People with poorer heart function, lower fitness levels, or a history of heart disease also saw greater reductions in hospital admissions for heart-related problems compared with those who did not take part in ExCR.

**Graphical Abstract**

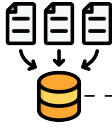
 This IPD meta-analysis (CaReMATCH), reflecting trials published since 2010, highlighted that contemporary ExCR is effective in reducing risk of hospitalization and improving HRQoL in those with CHD, with consistent treatment benefits across participant subgroups



RCT's published since 2010 to reflect contemporary practice



Contact coordinating investigator to share IPD






IPD shared of 8 trials (n = 4,975)

- ExCR frequently delivered in home setting (n=7)
- Median follow-up ~ 2 years
- Trials with a low risk of bias




**Effects of ExCR**

Compared to no-ExCR controls, participation in ExCR resulted in:




-  Reduced hospitalisation risk
-  Improved HRQoL
-  No observed effect on mortality risk

**Subgroup effects**

Equal positive effects between:

-  Young vs old
-  Men vs women
-  MI vs angina

Stronger positive effects in:

-  Lower LVEF
-  Lower fitness
-  History of CVD

**Keywords**

Coronary heart disease • Exercise-based cardiac rehabilitation • Meta-analysis • Individual participant data • Health outcomes • Randomized controlled trials

## Introduction

Coronary heart disease (CHD) is a leading cause of death worldwide.<sup>1</sup> Secondary prevention strategies through the application of exercise-based cardiac rehabilitation (ExCR) are recognized by international guidelines as an integral component of contemporary CHD management.<sup>2,3</sup> Although recent meta-analyses of trial-level data have documented the benefits of ExCR, its effectiveness based on trials conducted in the past decade has been questioned.<sup>4–6</sup> Potential reasons for the lower effectiveness of recent trials include (i) improved medical management of CHD<sup>7,8</sup> (which reduces the generalizability of older trials) and (ii) substantial heterogeneity in trial populations (which affect the overall effectiveness of ExCR). Attempts of randomized controlled trials (RCTs) to explore differential effects of ExCR across subgroups have been hampered by insufficient statistical power, but also through underrepresentation of particular subgroups (e.g. females, older, social and ethnic groups).<sup>4,9</sup> Furthermore, subgroup-level inferences from meta-analyses of aggregate data may not directly apply to individual participants so-called ‘ecological fallacy’.<sup>10</sup> In contrast, individual participant data (IPD) meta-analysis proves an appropriate approach to examine differences in treatment effectiveness across subgroups.

Acknowledging the concerns around ExCR as an adjunct to contemporary medicine, the objectives of the Cardiac Rehabilitation Meta-Analysis of Trials in people with CHD using IPD (CaReMATCH) study were to (i) provide contemporary estimates on the effectiveness of ExCR for CHD and (ii) examine potential differential effects of ExCR across subgroups.

## Methods

This IPD meta-analysis was conducted in accordance to the published protocol<sup>11</sup> and its updated statistical analysis plan.<sup>12</sup> Reporting followed the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) (see [Supplementary material online, Table S1](#)).<sup>13</sup> The requirement of ethical approval for this project was waived by the ethics committee of the Radboud University Medical Center, Nijmegen, The Netherlands (2022-15847). Each included trial was approved by their local ethics committee.

### Search strategy and eligibility criteria

Trials were identified from the 2016<sup>14</sup> and 2021<sup>4,5</sup> Cochrane systematic reviews of ExCR for CHD. The Cochrane reviews searched Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE and Medline in Process (Ovid; [Supplementary material online, Table S2](#)); EMBASE (Ovid); CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus (EBSCO); Database of Abstracts of Reviews of Effects (DARE); Health Technology Assessment (HTA); Epub ahead of Print, In-Process & Other Non-Indexed Citations; and SCI-Expanded and CPCI-S on Web of Science, from inception to September 2020. In addition, conference proceedings, trial registers, reference lists of eligible trials, and identified systematic reviews were screened. Details of the search strategy and study selection have been presented in the [Supplementary material online, Methods](#) and elsewhere.<sup>4,14</sup>

Studies were eligible for inclusion if they (i) adopted an RCT design with a minimum follow-up of 6 months; (ii) included adults with diagnosed myocardial infarction (MI), who had undergone revascularization, and who had angina pectoris or CHD defined by angiography; (iii) included supervised or unsupervised ExCR that comprised some form of exercise training, either alone or in addition to psychosocial and/or educational interventions, and delivered in an outpatient, community- or home-based setting; and (iv) included usual care as the comparator, defined as local, optimized standard medical care without any form of structured exercise training. In addition,

to reflect contemporary practice, trials had to be published since 2010 ([Supplementary material online, Methods](#)).

### Data management and validation

We invited the corresponding authors of all investigative teams by email to participate and share pseudonymized IPD. Individual participant data were stored in a secure and separate research environment (anDREa, Nijmegen, The Netherlands), and access to data was restricted to executive members of the research team (N.S., B.B., G.D.). Study-level characteristics were extracted from the 2016<sup>14</sup> and 2021<sup>4</sup> Cochrane reviews. Individual participant data from each study were checked for plausibility of values, completeness, and consistency with the original publication (N.S., M.P.). Any discrepancies were discussed with the original trial investigator and corrected if appropriate. Once data validation was complete and satisfactory, individual study datasets were combined into a master dataset.

### Risk of bias

As part of the 2016<sup>14</sup> and 2021<sup>4,5</sup> Cochrane reviews, two researchers independently assessed the risk of bias in each included study using the Cochrane Collaboration’s risk of bias tool. A third researcher checked all bias assessments, and discrepancies were discussed until consensus was reached.

### Patient and public involvement

A patient and public involvement group from the Dutch Heart Council (Dutch: ‘Harteraad’) was consulted, which includes people with previous or ongoing cardiovascular disease (CVD). During two meetings, the patient and public involvement group was asked to contribute to the (i) study protocol, (ii) interpretation of results and implications for future research, and (iii) dissemination strategy among the general public.

### Outcomes and subgroups of interest

We sought participant-level time-to-event data on all-cause and CVD-related mortality and hospitalization, as well as raw data on health-related quality of life (HRQoL) at baseline and all post-randomization follow-up time points. In line with the original RCTs, cardiovascular mortality and hospitalization were defined as the incidence of death or unplanned hospitalization due to MI, sudden cardiac arrest, heart failure, stroke, or any other evidenced cardiac, vascular or thrombo-embolic condition, respectively. Follow-up for time-to-event outcomes was defined as the interval between randomization and event or censoring, whichever came first. Health-related quality of life was measured using one of four validated questionnaires, including the (i) Euro Quality of Life with 5 dimensions (EQ-5D) questionnaire,<sup>15,16</sup> (ii) Short Form 36-Item Health Survey (SF-36),<sup>17</sup> (iii) 15-dimensional quality of life questionnaire (15D),<sup>18</sup> or (iv) Quality of Life Index—cardiac version III.<sup>19</sup> SF-36 data were collapsed into a SF-6D preference-based score,<sup>20,21</sup> so we could pool with EQ-5D and 15D utility index data. The primary analyses on HRQoL included pooling of the EQ-5D, SF-6D, and 15D utility indices and secondary analyses based on (i) EQ-5D utility indices to contextualize improvements in light of minimal clinically important differences ([Supplementary material online, Methods](#)) and (ii) a standardized score calculated from all four questionnaires.

Baseline subgroup variables were *a priori* selected<sup>12</sup> and focused on demographics (i.e. age, education, employment, ethnicity, sex, living status, living area), CVD-related medication (i.e. beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antilipemic drugs, diuretics, antithrombotics, calcium channel antagonists, nitrates, and antiarrhythmic drugs), CVD risk factors (i.e. left ventricular ejection fraction (LVEF), obesity, exercise capacity (i.e. VO<sub>2</sub>peak), HRQoL, hypertension, dyslipidaemia, diabetes, smoking status, depression, heart failure, atrial fibrillation, previous and familial history of CVD), and CHD aetiology.

## Statistical analyses

A statistical analysis plan was drafted prior to initiation of the statistical analyses (see [Supplementary material online, Methods](#)).<sup>12</sup> In summary, we adopted one-stage models as our primary analysis in the intention-to-treat population with complete follow-up data. Linear and Cox mixed effect regression models were used to quantify the overall effect of ExCR on HRQoL and time-to-event outcomes, respectively. Given the variation in trial follow-up timings, we pooled HRQoL data from the last follow-up timing with a maximum follow-up of 12 months, and models included the baseline HRQoL as a covariable. One-stage models were stratified for study and included a random intercept at study level and a random slope for treatment effect. In case model convergence was not attained, models were simplified following a hierarchical approach until model convergence was attained (see [Supplementary material online, Methods](#)). To evaluate the robustness of the one-stage approach, we performed (i) two-stage

meta-analyses using random effects<sup>22</sup> and (ii) one-stage meta-analyses for repeated measures of HRQoL across all available time points. We calculated the number needed to treat to prevent one event (NNT) for significant time-to-event outcomes by applying the pooled hazard ratio (HR) to the event rate of several real-world cohorts.<sup>23</sup>

To examine potential differential effects of ExCR across subgroups, the one-stage regression model was extended to include the main effects of a single subgroup variable and its interaction with the treatment variable. Each subgroup variable was centred around the mean (i.e. continuous variable) or proportion (i.e. categorical variable) within each trial to avoid ecological fallacy of participant-level interactions.<sup>10</sup> Presence of interaction effects was assessed by comparing the base model with the model including centred dummy variables for categorical variables with more than two strata through likelihood ratio tests, or by examining the subgroup\*treatment group interaction term within the one-stage model for all other subgroup

**Table 1** Baseline characteristics of participants randomized to ExCR or no ExCR controls

	ExCR	Control	Missing (%)
<i>n</i>	2481	2494	
Age, years	56.4 ± 0.2	56.4 ± 0.2	0.0
Sex, <i>n</i> women (%)	375 (15.1)	392 (15.7)	0.0
Ethnicity, <i>n</i> (%)			1.5
Caucasian	454 (18.6)	443 (18.1)	
Asian	1978 (80.9)	1998 (81.4)	
Other	12 (0.5)	13 (0.5)	
Education, <i>n</i> (%)			4.2
Degree	621 (26.2)	614 (25.6)	
Finished high school	743 (31.4)	815 (34.0)	
Did not finish high school	1004 (42.4)	967 (40.4)	
Employment, <i>n</i> (%)			0.5
Employed	1479 (59.9)	1487 (60.0)	
Unemployed	456 (18.5)	447 (18.0)	
Retired	535 (21.7)	545 (22.0)	
Living together with family or partner, <i>n</i> (%)	2220 (94.4)	2248 (94.6)	4.9
Medication, <i>n</i> (%)			
Beta-blockers	1607 (65.1)	1606 (64.9)	0.6
ACE inhibitors	1211 (49.1)	1165 (47.1)	0.6
ARB	234 (9.8)	227 (9.5)	4.2
Antilipemics	2296 (93.0)	2302 (93.0)	0.6
Diuretics	446 (18.1)	444 (17.9)	0.6
Antithrombotics	2430 (98.5)	2432 (98.3)	0.7
CHD aetiology, <i>n</i> (%)			0.6
Post-MI	2309 (93.5)	2314 (93.4)	
Angina	143 (5.8)	143 (5.8)	
Other	17 (0.7)	20 (0.8)	
Hypertension, <i>n</i> (%)	884 (36.5)	861 (35.4)	2.4
Dyslipidaemia, <i>n</i> (%)	343 (74.2)	309 (69.0)	81.7
Diabetes, <i>n</i> (%)	664 (26.9)	677 (27.2)	0.3
Current smoker, <i>n</i> (%)	657 (26.5)	648 (26.0)	0.2
Obese, <i>n</i> (%)	392 (15.9)	389 (15.7)	0.9
AF, <i>n</i> (%)	470 (21.9)	434 (20.1)	13.4
Family history of CVD, <i>n</i> (%)	296 (14.5)	290 (14.0)	17.4
VO <sub>2</sub> peak, mL kg <sup>-1</sup> min <sup>-1</sup>	24.3 ± 0.4	24.2 ± 0.4	86.3
HRQoL utility index	0.84 [0.68, 1.00]	0.84 [0.69, 1.00]	6.9

AF, atrial fibrillation; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CHD, coronary heart disease; ExCR, exercise-based cardiac rehabilitation; HRQoL, health-related quality of life; MI, myocardial infarction; VO<sub>2</sub>peak, peak oxygen uptake.

**Table 2** Trial-level characteristics of the eight trials of which individual participant data were pooled

First author (year) Acronym	Main study location	n	Primary exercise mode(s)	Resistance training	Reported components	ExCR			Control	
						Setting	Duration (weeks)	Frequency (sessions per week)	Intensity	Usual care definition
Campo (2020) HULK <sup>26</sup>	ITA	235	Walking and calisthenics	No	Exercise, health education	Hybrid	26	≥3–4	RPE 11–13	To underline the importance of aerobic physical activity, participants had a 15 min visit with a study doctor and received a detailed brochure on the benefits of physical activity.
Hautala (2017) EFEX-CARE <sup>27</sup>	FIN	204	Walking, running, cycling, or cross-country skiing	Circuit training for major muscle groups, 2–3 × 7 sets of ≥10 repetitions, 1–2 ×/week	Exercise, dietary counselling, check-up by physical therapist	Hybrid	Total: 52 Home: 52 Centre: 26	4–5	RPE 12–15 (aerobic), RPE 13 (resistance)	Participants randomized to usual care did not receive any individually tailored exercise prescriptions.
Houle (2012) <sup>28</sup>	CAN	65	Walking	No	Pedometer-based exercise, education, and socio-cognitive intervention	Home	52	7	30 min walking at moderate intensity (~100 steps/min) or RPE 11–14	Participants received recommendations regarding physical activity, diet, and medication and had no restrictions to participate in a structured ExCR programme or related healthcare professional. Participants received a blinded pedometer to assess exercise behaviour every 3 months.
Lear (2014) <sup>29</sup>	CAN	78	Participants were able to choose their preferred mode of exercise	No	Exercise, education on health, and diet	Home	16	3–5	50–80% of heart rate reserve	Participants received care from their primary care physician and were provided internet-based resources and simple guidelines on safe exercising and healthy diet.

Continued

Table 2 Continued

First author (year) Acronym	Main study location	n	Primary exercise mode(s)	ExCR			Control			
				Resistance training	Reported components	Setting	Duration (weeks)	Frequency (sessions per week)	Intensity	Usual care definition
Maddison (2015) HEART <sup>30</sup>	NZL	171	Walking <sup>a</sup>	No	Exercise, SMS texts, and pedometer to improve exercise adherence	Home	24	≥5	RPE 11–13 (early stages of programme), RPE 13–15 (later stages of programme)	All participants were free to participate in any other ExCR service or support that they wished to use, as well as encouragement to be physically active.
Prabhakaran (2020) Yoga-CaRe <sup>24</sup>	IND	3959	Yoga	No	Exercise and education	Hybrid	12	1.1 (total of 13 sessions)	Not reported	Participants received educational advice leaflets along with standard medical care as elsewhere in India, but does not include ExCR.
Santaulania (2017) <sup>31</sup>	ESP	85	Cycle ergometry	Upper and lower limb isotonic exercises, 3 sets of 10–15 repetitions, 3x/week for 10 weeks	Exercise only	Centre	10	3	75–90% of peak HR, RPE 11–15 (aerobic) RPE 11–14 (resistance)	Participants received information on CVD risk factors. Participants were provided guidance on how to return to physical activity and were provided instruction on breathing exercises and exercises to regain mobility and maintain muscle tone and peripheral circulation.
Snoek (2020) EU-CaRe <sup>32</sup>	NL	179	Walking <sup>a</sup>	No	Exercise only	Home	26	5	RPE 12–13	Participants in the control group did not receive any form of cardiac rehabilitation but received locally defined standard of care.

<sup>a</sup>Walking was the primary exercise mode, but participants were allowed to deviate from walking and chose their preferred mode of exercise (eg. cycling, swimming). ExCR, exercise-based cardiac rehabilitation; HR, heart rate; RPE, rating of perceived exertion.

variables. When there was evidence of statistically significant subgroup effects, stratified analyses were performed to obtain the HR or mean difference (MD) within each stratum of the categorical subgroup variable, or for continuous variables, dichotomized by the median.

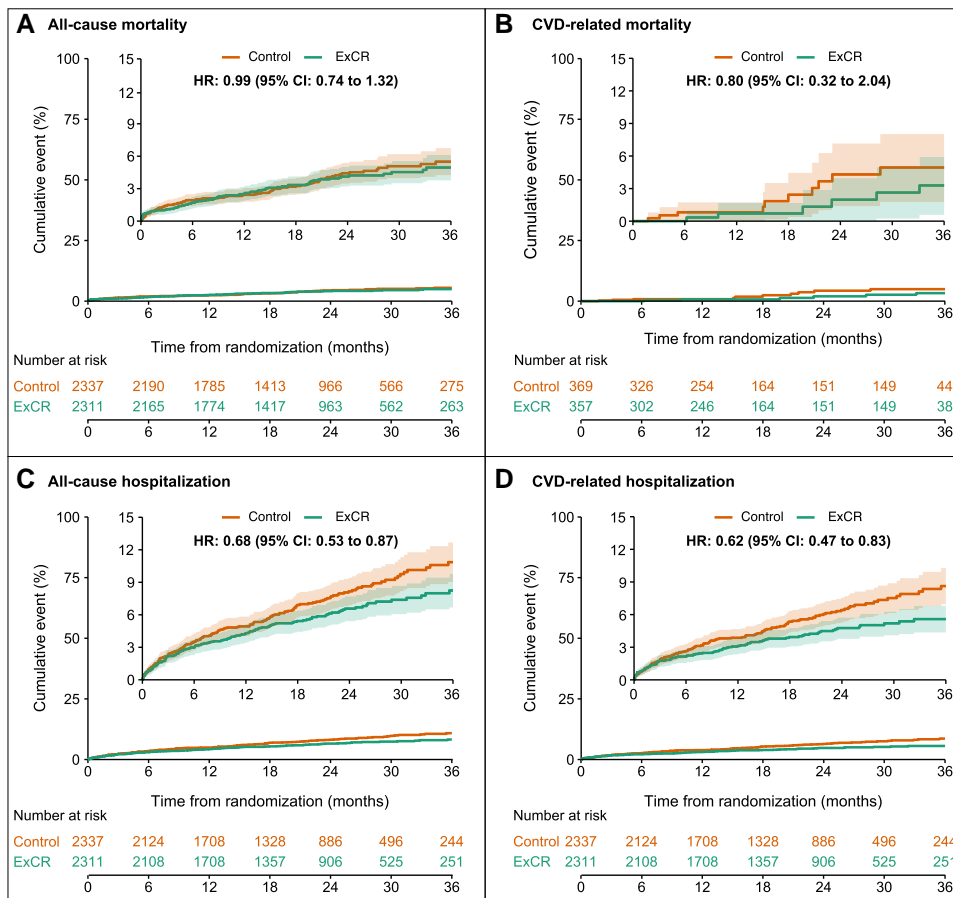
Sensitivity analyses were applied to evaluate the robustness of our primary research question, including (i) restricting follow-up for time-to-event outcomes to 1 and 2 years, (ii) omitting the largest trial from the analyses (i.e. Yoga CaRe trial),<sup>24</sup> (iii) including aggregate outcome data in two-stage models from trials that initially met the inclusion criteria but did not share IPD, and (iv) accounting for competing risks for time-to-event outcomes through subdistribution hazard functions.<sup>25</sup> Sensitivity analyses (i) and (ii) were repeated for the secondary research question. Analyses were performed in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) using the *meta*, *lme4*, *coxme*, and *ggeffects* packages. Data were presented as means and standard errors (SE), medians [interquartile range (IQR)], or frequencies (%) as appropriate. Two-tailed  $P < 0.05$  were considered statistically significant, although interpretation of results focused on 95% confidence intervals (CI).

## Results

From the 30 eligible trials ( $n = 10\,677$ ) identified from the 2016<sup>14</sup> and 2021<sup>4</sup> Cochrane reviews (see [Supplementary material online, Table S3](#)), nine provided IPD ( $n = 5118$ ).<sup>24,26–33</sup> One trial that provided IPD was excluded as we were unable to replicate the results presented in the trial publication.<sup>33</sup> In total, IPD from eight trials, including 4975 participants ( $n = 2481$  ExCR, 2494 control) were analysed (see [Supplementary material online, References, Figure S1](#), and [Tables S4](#) and [S5](#)).

### Participant and study characteristics

Participant characteristics were well-balanced between the ExCR and control group ([Table 1](#); [Supplementary material online, Table S6](#)). Participants were predominantly male ( $n = 4,208$ , 84.6%), Asian ( $n = 3,976$ , 81.2%), recently experienced a MI ( $n = 4,623$ , 93.5%) and



**Figure 1** Effect of exercise-based cardiac rehabilitation on time-to-event outcomes. Kaplan–Meier curves highlighting the effect of exercise-based cardiac rehabilitation on all-cause mortality (A), cardiovascular disease–related mortality (B), all-cause hospitalization (C), and cardiovascular disease–related hospitalization (D). Participation in exercise-based cardiac rehabilitation reduced the risk of all-cause and cardiovascular disease–related hospitalization [hazard ratio 0.68 (95% confidence interval: 0.53, 0.87); hazard ratio 0.62 (95% confidence interval: 0.47, 0.83), respectively], but did not yield improvements in all-cause and cardiovascular disease–related mortality compared with no exercise-based cardiac rehabilitation controls [hazard ratio 0.99 (95% confidence interval: 0.74, 1.32); hazard ratio 0.80 (0.32, 2.04), respectively]. Hazard ratios are derived from one-stage mixed effects Cox regression models. The insets show the same data on an expanded y axis, in which the shaded areas indicate the 95% confidence interval around the Kaplan–Meier estimates. Horizontal axes of Kaplan–Meier curves were truncated at 36 months of follow-up. CVD, cardiovascular disease; CI, confidence interval; ExCR, exercise-based cardiac rehabilitation; HR, hazard, ratio.

had a mean age of  $56.4 \pm 0.2$  years. Comorbidities were frequently reported [hypertension:  $n = 1745$  (35.9%), diabetes:  $n = 1341$  (27.0%), atrial fibrillation:  $n = 904$  (21.0%)]. Studies were published between 2012 and 2021, with the majority of participants being randomized between 2015 and 2019 ( $n = 3,931$ , 79%). Studies were mainly conducted in Europe ( $n = 4$ ) and high-income countries ( $n = 7$ ) (Table 2). Exercise-based cardiac rehabilitation was frequently delivered in a home-based setting, either exclusively ( $n = 4$ )<sup>28–30,32</sup> or in combination with centre-based exercise sessions ( $n = 3$ ).<sup>24,26,27</sup> All ExCR interventions included an aerobic exercise component (e.g. walking, cycling or yoga), with two studies additionally including resistance training.<sup>27,31</sup> The median duration of the ExCR programme was 25 (IQR: 15, 33) weeks and covered a median 4.3 (IQR: 3.4, 5.0) exercise sessions per week. Exercise intensity varied widely and was mainly guided by the Borg rating of perceived exertion (i.e. 11–15),<sup>26–28,30–32</sup> heart rate reserve (i.e. 50–75%),<sup>29</sup> or maximal heart rate (i.e. 75–90%).<sup>31</sup> The overall risk of bias of studies that provided IPD was graded as low, except for one study<sup>27</sup> for whom the risk of bias was deemed unclear due to a lack of detail reported across domains (see Supplementary material online, Figure S2).

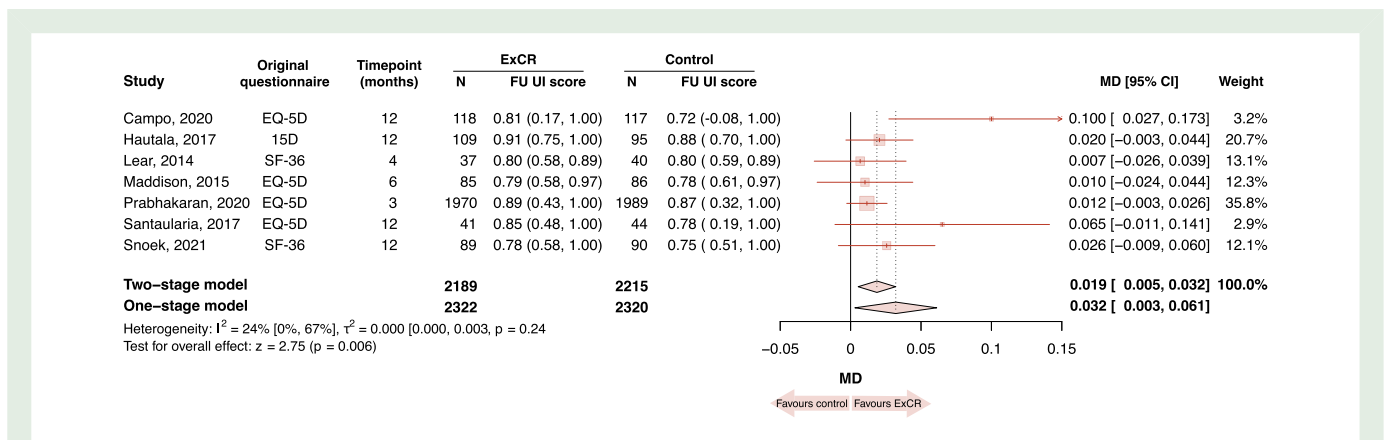
### Overall effect of exercise-based cardiac rehabilitation on outcomes

Compared with controls, participation in ExCR reduced the risk of all-cause (ExCR vs. control: 33.9 vs. 44.0 events per 1000 person years, HR 0.68, 95% CI: 0.53–0.87, range of NNT 4–7) and CVD-related hospitalization (23.7 vs. 33.5 events per 1000 person years, HR 0.62, 95% CI: 0.47–0.83, range of NNT 7–27) (Figure 1; Supplementary material online, Table S7) and improved HRQoL up to 12 months of follow-up (MD in utility index: 0.032, 95% CI: 0.003–0.061; Figure 2). In addition, the pooled mean and 95% CI for HRQoL includes the possibility of clinically meaningful improvements (see Supplementary material online, Figure S3). No differences were observed for all-cause and CVD-related mortality (20.5

vs. 20.5 events per 1000 person years, HR 0.99, 95% CI: 0.74–1.32; 8.8 vs. 10.0 events per 1000 person years, HR 0.80, 95% CI: 0.32–2.04, respectively; Figure 1). Inferences did not change upon including aggregate outcome data from trials that initially met the inclusion criteria but did not share IPD (see Supplementary material online, Figures S4–S8) or when excluding the Yoga CaRe trial (see Supplementary material online, Table S8). In addition, effects of ExCR were consistent across other secondary (Figure 2, Supplementary material online, Figures S9–S11) and sensitivity analyses (see Supplementary material online, Figures S12–S14). No evidence of small study bias was found (see Supplementary material online, Figure S15).

### Potential differential effects of exercise-based cardiac rehabilitation across subgroups

Evidence was found supporting the presence of differential effects of ExCR on outcomes across some CHD subgroups (Table 3). Larger improvements in HRQoL with ExCR were observed in participants with a lower baseline HRQoL (per 0.10 increment in baseline utility index: MD  $-0.007$ , 95% CI:  $-0.013$ ,  $-0.0006$ ) or those that did not finish high school (MD 0.037, 95% CI: 0.004, 0.070). A larger risk reduction for all-cause and CVD-related hospitalization in response to ExCR was observed in people with a previous history of CVD (HR 0.51, 95% CI: 0.29, 0.91, and HR 0.50, 95% CI: 0.25, 0.98, respectively) or those taking beta-blockers (HR 0.49, 95% CI: 0.30, 0.80, and HR 0.48, 95% CI: 0.27, 0.85, respectively; Supplementary material online, Table S9). In addition, larger reductions of CVD-related hospitalization risk due to ExCR were present in those with a lower LVEF (per % increment: HR 1.10, 95% CI: 1.02, 1.19) or lower  $VO_{2peak}$  (per mL  $kg^{-1} min^{-1}$  increment: HR 1.11, 95% CI: 1.01, 1.21). Secondary analyses indicated that current smokers experienced smaller reductions in all-cause hospitalization risk associated with ExCR (HR 1.88, 95% CI: 1.02, 3.45), whilst those on angiotensin receptor blockers exhibited greater improvements in



**Figure 2** Effect of exercise-based cardiac rehabilitation on health-related quality of life up to 12 months of follow-up. Forest plot highlighting that participation in exercise-based cardiac rehabilitation resulted in an increased health-related quality of life compared with controls [mean difference 0.032 (95% confidence interval: 0.003, 0.061)]. Given the variation in trial follow-up timings, we pooled health-related quality of life data from the last follow-up timing with a maximum follow-up of 12 months. All models were corrected for the baseline health-related quality of life. Some differences exist in sample sizes between one and two-stage models due to missing data. For each study, red horizontal lines represent the effect estimate and 95% confidence interval. Study weights were obtained via a random effects meta-analysis and are presented as shaded squares and percentages. The red diamond represents the pooled estimate and its 95% confidence interval. CI, confidence interval; EQ-5D Euro Quality of Life with 5 dimensions; ExCR, exercise-based cardiac rehabilitation; FU, follow-up; HRQoL, health-related quality of life; MD, mean difference; SF-36 Short Form 36-Item Health Survey; UI, utility index; 15D, 15-dimensional quality of life questionnaire.

**Table 3 Effect of exercise-based cardiac rehabilitation on time-to-event outcomes and health-related quality of life across CHD subgroups**

	All-cause mortality HR (95% CI)	CVD-related mortality HR (95% CI)	All-cause hospitalization HR (95% CI)	CVD-related hospitalization HR (95% CI)	HRQoL MD (95% CI)
N (% event)	4648 (4.0%)	726 (2.5%)	4648 (6.8%)	4648 (5.1%)	4642
Subgroup variables					
Demographics					
Age, per 10-year increment	1.05 (0.78, 1.42)	1.27 (0.31, 5.17)	0.90 (0.71, 1.14)	1.02 (0.77, 1.34)	-0.007 (-0.019, 0.005)
Sex, male (ref) vs. female	0.80 (0.41, 1.58)	0.63 (0.08, 4.91)	0.73 (0.40, 1.34)	0.58 (0.27, 1.24)	0.006 (-0.029, 0.042)
Education					
Did not finish high school	Reference	Reference	Reference	Reference	Reference <sup>a</sup>
Finished high school	0.61 (0.30, 1.27)	0.01 (2.0*10 <sup>-06</sup> , 23.59)	0.80 (0.47, 1.36)	0.88 (0.47, 1.63)	0.002 (-0.028, 0.033) <sup>a</sup>
Degree	1.10 (0.49, 2.48)	0.51 (0.02, 13.03)	0.96 (0.53, 1.76)	0.83 (0.41, 1.68)	<b>-0.037 (-0.070, -0.004)<sup>a</sup></b>
Employment					
Employed	Reference	Reference	Reference	Reference	Reference
Unemployed	0.91 (0.43, 1.91)	Model did not converge	1.50 (0.74, 3.06)	1.16 (0.49, 2.72)	-0.001 (-0.035, 0.033)
Retired	1.38 (0.62, 3.04)	Model did not converge	0.82 (0.42, 1.58)	1.14 (0.52, 2.49)	0.012 (-0.026, 0.050)
Ethnicity					
Caucasian	Reference	Reference	Reference	Reference	Reference
Asian	Model did not converge	Model did not converge	Model did not converge	Model did not converge	0.087 (-0.141, 0.315)
Other	Model did not converge	Model did not converge	Model did not converge	Model did not converge	0.152 (-0.040, 0.343)
Living status, alone (ref) vs. together	0.66 (0.19, 2.24)	Model did not converge	1.27 (0.61, 2.67)	1.30 (0.53, 3.18)	-0.031 (-0.089, 0.028)
Living area, rural (ref) vs. urban	Model did not converge	Model did not converge	Model did not converge	Model did not converge	Model did not converge
CVD medication					
Beta-blockers	1.31 (0.70, 2.43)	0.53 (0.03, 9.98)	<b>0.49 (0.30, 0.80)</b>	<b>0.48 (0.27, 0.85)</b>	-0.021 (-0.048, 0.006)
Not taking beta-blockers	Not applicable	Not applicable	1.31 (0.88, 1.94)	1.22 (0.76, 1.95)	Not applicable
Taking beta-blockers	Not applicable	Not applicable	0.52 (0.38, 0.71)	0.45 (0.31, 0.67)	Not applicable
ACE inhibitors	1.03 (0.58, 1.86)	1.22 (0.18, 8.06)	0.81 (0.51, 1.28)	1.03 (0.60, 1.76)	0.001 (-0.024, 0.026)
Angiotensin receptor blockers	0.41 (0.14, 1.23)	0.92 (0.07, 12.94)	1.05 (0.52, 2.14)	0.95 (0.42, 2.11)	0.050 (-0.001, 0.100)
Antilipemic agents	2.26 (0.58, 8.84)	13.58 (0.059, 3127)	0.87 (0.37, 2.04)	0.78 (0.27, 2.24)	0.019 (-0.030, 0.067)
Diuretics	0.93 (0.50, 1.75)	3.14 (0.42, 23.67)	1.06 (0.64, 1.76)	1.35 (0.75, 2.44)	0.003 (-0.029, 0.036)
Antithrombotics	Model did not converge	Model did not converge	2.17 (0.23, 20.86)	1.23 (0.11, 13.78)	0.053 (-0.052, 0.159)
Calcium channel antagonists	Model did not converge	Model did not converge	0.92 (0.26, 3.22)	1.07 (0.21, 5.44)	0.001 (-0.044, 0.047)
Nitrates	2.05 (0.28, 14.86)	Model did not converge	0.64 (0.24, 1.71)	1.05 (0.31, 3.55)	0.010 (-0.056, 0.077)
Anti-arrhythmic agents (Class I and III)	Model did not converge	Model did not converge	Model did not converge	Model did not converge	0.007 (-0.191, 0.204)
CVD and risk factors					
LVEF, per % increment	1.03 (0.93, 1.14)	0.99 (0.85, 1.16)	1.03 (0.96, 1.10)	<b>1.10 (1.02, 1.19)</b>	-0.005 (-0.010, 0.001)
<53%	Not applicable	Not applicable	Not applicable	0.35 (0.17, 0.71)	Not applicable
≥53%	Not applicable	Not applicable	Not applicable	0.67 (0.28, 1.60)	Not applicable
Obese	1.32 (0.56, 3.12)	0.68 (0.05, 8.97)	0.62 (0.34, 1.12)	0.60 (0.30, 1.20)	0.010 (-0.025, 0.045)
VO <sub>2</sub> peak, per mL kg <sup>-1</sup> min <sup>-1</sup> increment	1.06 (0.93, 1.21)	1.12 (0.85, 1.47)	1.04 (0.97, 1.11)	<b>1.11 (1.01, 1.21)</b>	-0.003 (-0.005, 0.00004)

Continued

Table 3 Continued

	All-cause mortality HR (95% CI)	CVD-related mortality HR (95% CI)	All-cause hospitalization HR (95% CI)	CVD-related hospitalization HR (95% CI)	HRQoL MD (95% CI)
<23.8 mL kg <sup>-1</sup> min <sup>-1</sup>	Not applicable	Not applicable	Not applicable	0.41 (0.10, 1.61)	Not applicable
≥23.8 mL kg <sup>-1</sup> min <sup>-1</sup>	Not applicable	Not applicable	Not applicable	0.60 (0.25, 1.43)	Not applicable
Baseline HRQoL (utility index), per 0.10 increment	0.77 (0.20, 2.97)	0.80 (0.04, 16.39)	0.79 (0.29, 2.16)	0.67 (0.22, 2.10)	<b>-0.007 (-0.013, -0.0006)</b>
<0.84	Not applicable	Not applicable	Not applicable	Not applicable	0.059 (-0.0004, 0.117)
≥0.84	Not applicable	Not applicable	Not applicable	Not applicable	0.078 (-0.007, 0.022)
Hypertension	1.75 (0.93, 3.31)	Model did not converge	1.62 (0.98, 2.66)	1.30 (0.72, 2.34)	0.001 (-0.028, 0.029)
Dyslipidaemia	1.36 (0.32, 5.79)	0.84 (0.12, 5.83)	1.02 (0.48, 2.18)	1.16 (0.46, 3.00)	-0.041 (-0.100, 0.018)
Diabetes	1.77 (0.97, 3.26)	2.46 (0.35, 17.14)	1.53 (0.96, 2.43)	1.32 (0.76, 2.31)	0.011 (-0.018, 0.040)
Current smoker	1.01 (0.47, 2.15)	Model did not converge	1.70 (0.95, 3.04)	1.70 (0.87, 3.33)	-0.017 (-0.046, 0.012)
Depression	0.01 (1.0*10 <sup>-6</sup> , 84.02)	Model did not converge	0.85 (0.20, 3.53)	0.77 (0.14, 4.18)	-0.019 (-0.132, 0.093)
Heart failure	Model did not converge	Model did not converge	Model did not converge	Model did not converge	Model did not converge
Atrial fibrillation	1.09 (0.44, 2.71)	Model did not converge	0.69 (0.35, 1.34)	0.89 (0.42, 1.90)	0.009 (-0.023, 0.041)
Previous history of CVD	0.73 (0.34, 1.54)	Model did not converge	<b>0.51 (0.29, 0.91)</b>	<b>0.50 (0.25, 0.98)</b>	0.011 (-0.021, 0.044)
No history of CVD	Not applicable	Not applicable	0.97 (0.69, 1.35)	0.77 (0.48, 1.23)	Not applicable
History of CVD	Not applicable	Not applicable	0.60 (0.38, 0.96)	0.50 (0.29, 0.86)	Not applicable
Family history of CVD	1.06 (0.45, 2.53)	Model did not converge	1.74 (0.94, 3.23)	1.45 (0.69, 3.02)	0.011 (-0.028, 0.050)
CHD aetiology					
Post-MI	Reference	Reference	Reference	Reference	Reference
Angina	0.75 (0.13, 4.22)	0.51 (0.06, 4.53)	1.04 (0.44, 2.45)	1.17 (0.43, 3.22)	-0.006 (-0.081, 0.069)
Other	Model did not converge	Model did not converge	1.45 (0.20, 10.36)	1.26 (0.09, 17.91)	-0.038 (-0.198, 0.121)

Presence of interaction effects was assessed by comparing the base one-stage model with the one-stage model including the centred dummy variables for categorical subgroup variables with more than two strata through likelihood ratio tests, or by examining the subgroup\*treatment group interaction term within the one-stage model for all other subgroup variables. When there was evidence of statistically significant moderation effects ( $P \leq 0.05$ , highlighted in bold), stratified analyses were performed to obtain the hazard ratios or beta coefficients within each stratum of the subgroup variable.

ACE, angiotensin-converting enzyme; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HRQoL, health-related quality of life; LVEF, left ventricular ejection fraction; MD, mean difference; MI, myocardial infarction; VO<sub>2</sub>peak, peak oxygen uptake.

<sup>a</sup>Associated MDs from stratified analyses are as follows: did not finish high school MD 0.044 (95% CI: 0.001, 0.086), finished high school MD 0.027 (95% CI: 0.006, 0.048), and degree MD -0.013 (95% CI: -0.034, 0.009).

HRQoL due to ExCR (MD 0.049, 95% CI: 0.012, 0.086; [Supplementary material online, Table S10](#)). Other subgroup effects were consistent across secondary (see [Supplementary material online, Table S10](#)) and sensitivity analyses (see [Supplementary material online, Tables S11–S13](#)).

## Discussion

The objectives of the CaReMATCH study were to (i) provide contemporary estimates on the effectiveness of ExCR for CHD and (ii) examine potential differential effects of ExCR across subgroups. Our findings highlight that participation in ExCR within the current era of medical management of optimal (non)pharmacological care resulted in a reduced risk of all-cause and CVD-related hospitalization and improved HRQoL. No notable differences were observed in all-cause and CVD-related mortality risk between treatment groups. In response to our secondary aim, we reveal that benefits of ExCR were consistently present across a wide spectrum of participant characteristics, with some factors associated with an even larger effect. Together, these findings support the benefits of ExCR as an adjunct to contemporary medicine, and also highlight the clinical benefits of prescribing ExCR across CHD subgroups ([Graphical Abstract](#)).

### Main effects of exercise-based cardiac rehabilitation

It is important to note that the previous 2016<sup>14</sup> and 2021<sup>4,5</sup> Cochrane reviews include RCTs that were conducted between 1975 and 2020, which has raised questions regarding the generalizability of this evidence to more contemporary management of CHD, that has changed substantially since these earlier trials were conducted. Indeed, meta-regression analyses indicate that the effects of ExCR on all-cause mortality have diminished over time.<sup>4,6</sup> In addition, these older trials are subject to a higher or unclear risk of bias (see [Supplementary material online, Figure S2](#)), which makes them prone to overestimating ExCR effects. Our pooling of IPD from recently conducted RCTs with a low risk of bias (see [Supplementary material online, Figure S2](#)) provides more reflective evidence on the effectiveness of ExCR. Whilst our study showed no observable effect of ExCR on all-cause mortality, we found ExCR to reduce the risk of hospitalization and improve HRQoL outcomes. These observations were reinforced when we included aggregate outcome data from trials that initially met our inclusion criteria but did not share IPD, but also when excluding the Yoga CaRe trial, highlighting the robustness of our findings.

### Differential effects of exercise-based cardiac rehabilitation

A major benefit of IPD meta-analyses is the superior statistical power to explore effect modification of treatment effects across participant-level characteristics compared with conventional meta-analysis of aggregate data<sup>34</sup> and individual RCTs.<sup>35</sup> Our analysis of subgroups showed the benefits of ExCR to be largely consistent across a wide spectrum of participant characteristics, including demographics, CVD-related risk factors and medication, and CHD aetiology. Interestingly, some subgroups showed larger benefits of ExCR than others. A potentially relevant observation is that greater benefits of ExCR may be expected in those with a higher disease burden, as stronger effects of ExCR were found in those taking beta-blockers (see [Supplementary material online, Table S9](#)) or angiotensin II receptor blockers, those with a lower LVEF, lower VO<sub>2</sub>peak, or previous history

of CVD. In line with our observations, the secondary analysis of the HF-ACTION trial revealed stronger effects of ExCR on hospitalization risk in individuals with multi-morbidity compared with those with less or no comorbidities.<sup>36</sup> These observations that ExCR is at least equally effective in those with a higher disease burden are highly relevant, since these individuals are less frequently referred to ExCR.<sup>37,38</sup>

### Practical implications

Despite ExCR being a class IA recommendation for people with CHD,<sup>2,3</sup> participation and referral rates remain low,<sup>39,40</sup> particularly among women,<sup>39,40</sup> ethnic groups,<sup>39</sup> and frail or older individuals.<sup>37,38</sup> Barriers to participation in ExCR are multifactorial<sup>6</sup> and include questioning the effectiveness of ExCR in contemporary medicine and/or assuming inferior effects of ExCR in subgroups. This ultimately contributes to low referral rates. The results of our IPD meta-analysis underline the robust benefits from participating in ExCR programmes across different subgroups of people with CHD. This highlights that studies should focus on initiatives to improve availability, uptake, and delivery of ExCR, for example, through improved clinician training, adopting automated referral, and meeting people's needs through home-based and digitally supported ExCR programmes.<sup>6</sup>

### Strengths and limitations

Strengths of this study include the pooling of IPD from 4975 randomized individuals following the latest methodological guidance on the conductance of IPD meta-analyses and using standardized definitions of outcomes measures and subgroup variables. In addition, IPD originated from recent RCTs with primarily a low risk of bias. Our study has some limitations. First, due to trial eligibility criteria (see [Supplementary material online, Table S4](#)), participants in RCTs may not necessarily reflect those participating in ExCR into routine clinical practice (e.g. due to differences in ethnicity, socio-economic status, and comorbidities). Whilst our findings were robust within the studied sample, caution should be applied in generalizing the results to CHD patients widely, including older adults and different ethnic groups. Second, cause-specific mortality data were not frequently collected in the trials sharing IPD, and we were therefore likely underpowered to examine a potential effect of ExCR on CVD-related mortality. Finally, a large number of subgroup variables were investigated, warranting some caution when interpreting results due to multiplicity (i.e. increased risk of type I error). However, our interpretation focused on 95% CI intervals rather than *P*-values alone.

## Conclusions

Participation in ExCR reduced the risk of all-cause and CVD-related hospitalization and improved HRQoL compared with usual care, with no observed differences in all-cause and CVD-related mortality. The benefits of ExCR were largely consistent across a wide spectrum of participant characteristics, supporting that ExCR should be widely prescribed to people with CHD. Our findings reinforce the importance of ExCR in contemporary clinical practice, highlighting the need for initiatives to improve global access and referral to ExCR for people with CHD.

## Supplementary material

Supplementary material is available at [European Journal of Preventive Cardiology](#).

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## Author contribution

N.A.S., B.J.R.B., G.O.D., L.M.B., G.K., G.Y.H.L., N.v.R., R.S.T., and D.H.J.T. conceptualized and designed the study. N.A.S., B.J.R.B., and G.K. wrote the protocols, with feedback from G.O.D., L.M.B., G.Y.H.L., N.v.R., R.S.T., and D.H.J.T. D.P., A.M.C., S.K., A.R., G.C., A.J.H., J.A.S., R.M., N.S., S.A.L., and J.H. acquired and contributed individual participant data from their respective trial. Formal analyses, programming of code, data curation, and visualization of results were performed by N.A.S. Validation of data was performed by M.P. and N.A.S. Interpretation of results was performed by N.A.S., B.J.R.B., G.O.D., L.M.B., R.S.T., and D.H.J.T. The first version of the manuscript was drafted by N.A.S., and feedback was provided by all other authors (B.J.R.B., G.O.D., L.M.B., G.K., D.P., A.M.C., S.K., A.R., G.C., A.J.H., J.A.S., R.M., N.S., S.A.L., J.H., G.Y.H.L., N.v.R., R.S.T., D.H.J.T.). All authors have approved the final manuscript. Those involved in the CaReMATCH collaborators were involved in the design and conduct of the respective trial included in CaReMATCH.

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**Conflict of interest:** none declared.

## Information about previous presentations

The findings of CaReMATCH were presented at the ESC Preventive Cardiology 2024 congress.

## Data availability

The individual participant data underlying this article were provided by the investigators of the respective trials and remain property of these original investigators. Consequently, any future requests for data sharing should be directed to the coordinating investigators of the included trials in CaReMATCH.

## Appendix

CaReMATCH: Alun D. Hughes (MRC Unit for Lifelong Health and Ageing at University College London, London, United Kingdom),

Ajay S. Vamadevan (Centre for Chronic Disease Control and India Public Health Foundation of India, New Delhi, India), Andrea Raisi (Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy), Anil R Jain (SAL Hospital and Medical Institute, Ahmedabad, India), Arnoud W.J. van't Hof (Department of Cardiology, Maastricht University Medical Center and Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands), Bhaskara Rao (CARE Hospital Heart institute, Vishakapatnam, India), Bishav Mohan (Dayanand Medical College, Ludhiana, India), Davinder S Chadha (Command Hospital, Bengaluru, India), Dimple Kondal (Centre for Chronic Disease Control, New Delhi, India), Divya Soni (Centre for Chronic Disease Control, New Delhi, India), Ed P. de Kluiver (none), Elisabetta Tonet (Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy), Gianni Mazzoni (Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy), Giovanni Grazi (Center for Exercise Science and Sport, University of Ferrara, Ferrara, Italy), Ian Roberts (London School of Hygiene and Tropical Medicine, London, United Kingdom), Jabir Abdullakutty (Lisie Hospital, Kochi, India), Kalpana Singh (Centre for Chronic Disease Control, New Delhi, India), Kaushik Chattopadhyay (London School of Hygiene and Tropical Medicine, London, United Kingdom; University of Nottingham, Nottingham, United Kingdom), Kavita Singh (Centre for Chronic Disease Control, New Delhi, India), Kolli S Reddy (Public Health Foundation of India, New Delhi, India), Kushal Madan (Sir Ganga Ram Hospital, New Delhi, India), Manjunath C Nanjappa (Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India), Nagamalesh U Madappa (M S Ramaiah Medical College and Hospital, Bengaluru, India), Nagraj Desai (JSS Medical College, Mysuru, India), Narsimhan Calambur (CARE Hospital, Hyderabad, India), Subramaniam Natarajan (G.Kuppuswamy Naidu Memorial Hospital, Coimbatore, India), Natrajan KU (Amrita Institute of Medical Sciences, Kochi, India), Nikhil Tandon (All India Institute of Medical Sciences, New Delhi, India), Nishi Chaturvedi (MRC Unit for Lifelong Health and Ageing at University College London, London, United Kingdom; Imperial College London, London, United Kingdom), Paul Poirier (Faculty of Pharmacy, Université Laval, Québec, Canada; Institut universitaire de cardiologie et de pneumologie de Québec, Québec, Canada), Poppy Malinson (London School of Hygiene and Tropical Medicine, London, United Kingdom), Prabhavathi Bhat (Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India), Pradeep A Praveen (Centre for Chronic Disease Control, New Delhi, India; All India Institute of Medical Sciences, New Delhi, India), Prakash C Negi (Indira Gandhi Medical College, Shimla, India), Prasad MR (KLE Academy of Higher Education & Research/College/university, Belgaum, India), Raghava Sarma (Lalitha Super Specialities Hospital, Kothapeta, India), Raji Devarajan (Centre for Chronic Disease Control, New Delhi, India), Ravindra K Tongia (Escorts Fortis Hospital, Jaipur, India), Rita Pavasini (Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy), Sadananda S Kanchanahalli (Sri Jayadeva Institute of Cardiovascular Sciences and Research, Mysuru, India), Satish Patil (SRI BM.Patil medical college, Vijayapura, India), Shah Ebrahim (London School of Hygiene and Tropical Medicine, London, United Kingdom), Shankar Patil (SRI BM.Patil medical college, Vijayapura, India), Sharad Chandra (King George's Medical University, Lucknow, India), Srikumar Swaminathan (Frontier Lifeline Hospital, Chennai, India), Srinivas Mallya (SAL Hospital and Medical Institute, Ahmedabad, India), Stefano Volpato (Department of Medical Science, University of Ferrara, Ferrara, Italy), Stuart Pocock (London School of Hygiene and Tropical Medicine, London, United Kingdom), Subhash C Manchanda (Sir Ganga Ram Hospital, New Delhi, India), Sudhir R Naik (Apollo Hospital, Jubilee Hills, Hyderabad, India), and Sunil Kumar (JSS Hospital, Mysuru, India).

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