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CARDIOVASCULAR DISEASE

Mediators of the effect of exercise-based cardiac rehabilitation on hospitalisation risk in people with coronary heart disease – the CaReMATCH individual participant data meta-analysis

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Abstract

Participation in exercise-based cardiac rehabilitation (ExCR) lowers hospitalisation risk in people with coronary heart disease. We investigated whether improvements in health-related quality of life (HRQoL), including physical and mental dimensions, mediated the effect of ExCR on hospitalisation risk in people with coronary heart disease. Individual participant data from five randomised controlled trials were pooled, which randomized participants to ExCR or usual care. All trials had to be published since 2010 to reflect contemporary medicine. A one-stage meta-analysis was performed to assess whether changes in HRQoL, including physical and mental dimensions, mediated the effect of ExCR on all-cause and cardiovascular disease (CVD)-related hospitalisation risk. HRQoL was assessed before and directly following the intervention period, and preceded hospitalisation assessments at 1- and 2-year follow-up. Compared to controls (n=1,986), ExCR (n=1,973) did not reduce 1-year, but significantly reduced 2-year all-cause (hazard ratio [HR] 0.72, 95% confidence interval [CI]: 0.45,1.14; HR 0.61, 95%CI: 0.43,0.87), respectively) and CVD-related hospitalisation risk (HR 0.58, 95%CI: 0.33,1.03; HR 0.56, 95%CI: 0.37,0.87), respectively). Improvements in HRQoL due to ExCR significantly mediated 2-year reductions in all-cause (mediation-effect − 0.0011, 95%CI: -0.0013,-0.0009, mediation 7.4%) and CVD-related hospitalisation risk (mediation-effect: -0.0008, 95%CI: -0.0010,-0.0007, mediation 6.2%). Mediation effects were more pronounced in those with a lower baseline HRQoL. Both physical (mediation: all-cause 5.8%; CVD-related 4.4%) and mental HRQoL-dimensions (mediation: all-cause 3.4%; CVD-related 2.6%) mediated the effect of ExCR. We found improvements in HRQoL, including physical and mental HRQoL-dimensions, to significantly mediate the lower risk for all-cause and CVD-related hospitalisations following participation in ExCR.

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide, accounting for approximately 9 million deaths per year [1, 2]. An important secondary prevention strategy includes participation in exercise-based cardiac rehabilitation (ExCR). Previous Cochrane reviews [3, 4] have shown that participation in ExCR reduces the risk of hospitalisation [3, 4]. However, the mechanisms underlying these clinical benefits are less frequently studied and remain largely unknown. Understanding these pathways may facilitate tailoring the design of future ExCR programmes to the needs of individual participants.

Rod S. Taylor, Dick H.J. Thijssen and Niels A. Stens have shared last co-authorship

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Studies demonstrated that ExCR results in improvements in health-related quality of life (HRQoL) [3, 4], including the physical and mental dimensions [5]. The physical dimension relates to improvements in physical fitness and/or functional capacity [6–8]. For example, participation in ExCR is associated with improvements in exercise capacity in people with CHD, [8, 9] whilst these improvements are related to a reduction in hospitalisation risk in observational cohorts [10]. Whereas, the mental dimension assesses discomfort, anxiety and depression. Previous work found that ExCR is associated with lower risks for depression, anxiety, and psychosocial stress [11, 12]. Currently, direct evidence from randomised controlled trials is lacking to determine whether improvements in HRQoL following ExCR mediate improvements in clinical outcomes.

In the Cardiac Rehabilitation Meta-Analysis of Trials in patients with Coronary Heart disease using individual participant data (IPD) (CaReMATCH) study [13], we aimed to determine whether ExCR-induced changes in HRQoL, including physical and mental dimensions, mediated the effect on all-cause and cardiovascular disease (CVD)-related hospitalisation in people with CHD.

Methods

The present mediation analyses were pre-specified in our CaReMATCH IPD meta-analysis protocol [14] and statistical analysis plan [15], and extend the primary CaReMATCH analyses [13]. Reporting followed the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) [16] and A Guideline for Reporting Mediation Analysis (AGReMA) (eTables 1–2) [17]. Ethical approval for the present study was waived by the Radboud university medical center ethics committee (2022–15847). Each included study had received approval by the relevant local ethics committees prior to the onset of their respective trial. Pseudo-anonymised IPD were shared from individuals that provided written informed consent.

Study and participant selection

Relevant studies were identified from the 2016 and 2021 Cochrane systematic reviews of ExCR for CHD [3, 4]. To be eligible for inclusion, studies had to meet the following criteria: (1) studies had to be randomised controlled trials with at least six months follow-up; (2) participants had to be adults who had been diagnosed with CHD consisting of either myocardial infarction, angina pectoris or coronary artery disease defined by angiography, or those who had undergone revascularisation; (3) ExCR included some form of exercise training, either supervised or unsupervised, managed in an outpatient, community- or home-based setting, and may include psychosocial and/or educational interventions; (4) ExCR had to be compared against non-ExCR controls, comprising local standard medical care without any form of structured exercise training; (5) trials had to be published since 2010 to reflect contemporary ExCR practice [14, 15], and (6) each trial had to include a measure of HRQoL before and directly after the intervention period. Details on study and participant selection are described previously [3, 4, 14].

Data collection

Corresponding authors of eligible trials were contacted via email, and invited to participate and to share their pseudo-anonymized IPD. IPD from trials were stored in a secure and separate digital research environment (anDREa, Nijmegen, The Netherlands) and underwent a series of checks to ensure plausibility of values, completeness and consistency with the original trial publication. Any discrepancies between the data and the original publication were discussed with the authors of the original trial and, if necessary, corrected. Once the data had been validated and approved, all individual datasets were merged into a single dataset.

HRQoL (mediator). HRQoL was measured before randomization and directly following the intervention period. In case of multiple HRQoL measurements during follow-up, the timepoint directly following the end of the intervention period was used for the analysis. Included trials used one of three validated questionnaires to measure HRQoL, including the EuroQoL five dimensions (EQ-5D) questionnaire [18, 19], 16-item short form survey (SF-36) [20], or 15 dimension quality of life (15D) questionnaire [21]. To pool IPD from these questionnaires, raw data were mapped to utility index (UI) data [22–24].

Hospitalisation (outcome). Time-to-event data were defined as the interval between randomisation and hospitalisation or right-censoring. All-cause hospitalisation was defined as any unplanned hospitalisation. CVD-related hospitalisation was defined as any unplanned hospitalisation due to a myocardial infarction, sudden cardiac arrest, heart failure, stroke or any other evidenced cardiac, vascular or thrombo-embolic condition. To ensure temporal precedence of the mediator and outcome within mediation models, we excluded participants with a hospitalisation event before completing the intervention period.

Statistical analyses

A one-stage IPD meta-analysis was performed using mixed-effect linear and Cox regression models to evaluate the effect of ExCR on HRQoL, all-cause and CVD-related

hospitalisation in the total study cohort, respectively. To determine what extent improvements in HRQoL mediated the beneficial effects of ExCR on hospitalisation risk, we adopted traditional mediation analyses using the product-of-coefficients method [25]. This approach sequentially involved fitting three regression models (Fig. 1): (1) regressing hospitalisation on the treatment allocation (i.e. total effect, 'c-path'), (2) regressing the post-program HRQoL on treatment allocation, adjusting for the baseline HRQoL and covariables (i.e. age and sex) ('a-path'), and (3) regressing hospitalisation on the post-program HRQoL, adjusting for the baseline HRQoL, treatment allocation and covariables ('b-path'). Subsequently, the indirect effect (i.e., mediation effect = 'ab-path') was calculated by multiplying the 'a-path' and 'b-path'. Additionally, the indirect effect was expressed as a percentage of the total effect (hereafter 'proportion mediated'). The delta method was used to obtain 95% confidence intervals (CIs) around the indirect effect [26]. To evaluate whether the mediation effect depended

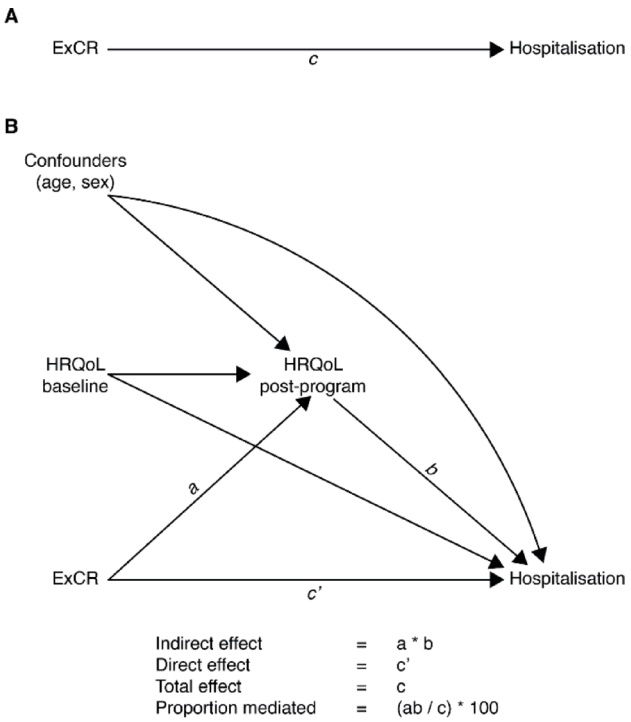


Fig. 1 Path diagram of a single mediator model. Mediation analyses were performed using the product-of-coefficients method, which sequentially involves fitting three regression models): (1) regressing hospitalisation on the treatment allocation (i.e. total effect, 'c-path', panel A), (2) regressing the post-program HRQoL on treatment allocation, adjusting for the baseline HRQoL and covariables (i.e. age and sex) ('a-path', panel B), and (3) regressing hospitalisation on the post-program HRQoL, adjusting for the baseline HRQoL, treatment allocation and covariables ('b-path', panel B). Subsequently, the indirect effect (i.e., mediation effect = 'ab-path') was calculated by multiplying the 'a-path' and 'b-path', and was additionally expressed as a percentage of the total effect ('proportion mediated'). ExCR exercise-based cardiac rehabilitation, HRQoL health-related quality of life

on the baseline HRQoL (i.e. moderated mediation), we repeated the mediation analyses described above, stratified by the median HRQoL at baseline. In addition to the overall HRQoL score, we explored the importance of improvements in the physical and mental dimensions of HRQoL by fitting parallel multi-mediator models [27] using the "mobility" and "anxiety/depression" dimension scores from the EQ-5D questionnaire as mediators. To assess the relative importance of HRQoL dimensions, we quantified the difference in indirect effects ('*ab-path'* mobility – '*ab-path'* anxiety/depression), and used percentile bootstrapping with 1,000 resamples to compute the corresponding 95% CI. All regression models were one-stage models and included a random intercept for each trial to control for the inherent clustering of participants within trials. Secondary analyses were performed, which included: (1) pooling results using two-stage models, and (2) dichotomizing HRQoL as clinically relevant improvements (i.e. improvement of HRQoL UI $\geq$ 0.05) [28], and (3) adopting a causal mediation framework [29].

In our protocol paper we proposed to also evaluate the mediating role of changes in exercise capacity on clinical outcomes [14, 15]. Due to paucity of data (eAppendix, eFigure 1), we were not able to perform a formal mediation analysis for exercise capacity. For transparency purposes we have analysed the association of changes in exercise capacity with hospitalisation risk independent from group allocation (eAppendix, eFigures 2–3, eTable 3). Analyses were performed in R version 4.1.1 (R foundation for Statistical Computing, Vienna, Austria) using the *meta* [30], *lme4* [31], and *coxme* [32]. Data were presented as means and standard errors (SE), medians [interquartile range (IRQ)] or frequencies (%) as appropriate. Two-tailed p-values $<$ 0.05 were considered statistically significant, but interpretation of results mainly focused on 95%CIs.

Results

Out of 30 eligible trials, we obtained IPD from 7 trials evaluating HRQoL (2,317 ExCR, 2,313 control); eFigure 4, eTable 4) [33–39]. We included IPD from 5 trials in our mediation analyses (1,973 ExCR, 1,986 control) [33, 35, 37–39] following exclusion of participants who experienced an event prior to completion of the intervention period to ensure temporal precedence of the mediator and outcome (eFigure 4, eTable 4). In these 5 trials ExCR was predominantly delivered in a home-based setting, either exclusively (n=2) [35, 39] or in combination with centre-based sessions (n=2) [33, 37]. All ExCR-interventions included aerobic exercise with exercise intensity frequently being guided by the Borg rating of perceived exertion (RPE

11–15; eTable 4). Participants had a mean age of 55.7 ± 0.2 years, were predominantly Asian (*n* = 3,457, 88.8%) and had a baseline HRQoL UI of 0.84 (0.65 to 1.00; Table 1). Participant characteristics were generally well-balanced between the ExCR and control group (Table 1). Individuals excluded to establish temporal precedence of the mediator and outcome were more frequently older, dyslipidemic, obese and treated with CVD medication (eTable 5).

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

n	ExCR	Control
	1,973	1,986
Age, years	55.8 (0.3)	55.7 (0.3)
Sex, *n* women (%)	271 (13.7)	278 (14.0)
Ethnicity, *n* (%)		
Caucasian	220 (11.3)	217 (11.1)
Asian	1,721 (88.6)	1,736 (88.9)
Other	1 (0.1)	0 (0.0)
Education, *n* (%)		
Degree	503 (25.5)	507 (25.5)
Finished high school	619 (31.4)	669 (33.7)
Did not finish high school	850 (43.1)	810 (40.8)
Employment, *n* (%)		
Employed	1,204 (61.2)	1,231 (62.2)
Unemployed	357 (18.1)	355 (17.9)
Retired	407 (20.7)	394 (19.9)
Living together with family or partner, *n* (%)	1860 (95.1)	1886 (95.6)
Medication, *n* (%)		
Betablockers	1,325 (67.2)	1,323 (66.6)
ACE inhibitors	984 (49.9)	957 (48.2)
ARB	122 (6.4)	131 (6.8)
Antilipemics	1,827 (92.6)	1,831 (92.2)
Diuretics	363 (18.4)	355 (17.9)
Antithrombotics	1,944 (98.5)	1,956 (98.5)
CHD etiology, *n* (%)		
Post-MI	1,881 (95.3)	1,888 (95.1)
Angina	89 (4.5)	88 (4.4)
Other	3 (0.2)	10 (0.5)
Hypertension, *n* (%)	652 (33.6)	622 (31.9)
Dyslipidemia, *n* (%)	147 (66.5)	130 (59.9)
Diabetes, *n* (%)	528 (26.8)	523 (26.3)
Current smoker, *n* (%)	553 (28.1)	557 (28.0)
Obese, *n* (%)	298 (15.1)	271 (13.7)
AF, *n* (%)	428 (23.9)	398 (22.0)
Family history of CVD, *n* (%)	272 (15.2)	275 (15.2)
VO_2peak, ml kg^{-1} min^{-1}	23.6 (0.7)	24.4 (0.7)
HRQoL utility index	0.84 [0.65, 1.00]	0.84 [0.66, 1.00]

AF atrial fibrillation, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blockers, *CHD* coronary heart disease, *CVD* cardiovascular disease, *ExCR* exercise-based cardiac rehabilitation, *HRQoL* health-related quality of life, *MI* myocardial infarction, *VO_2 peak* peak oxygen consumption

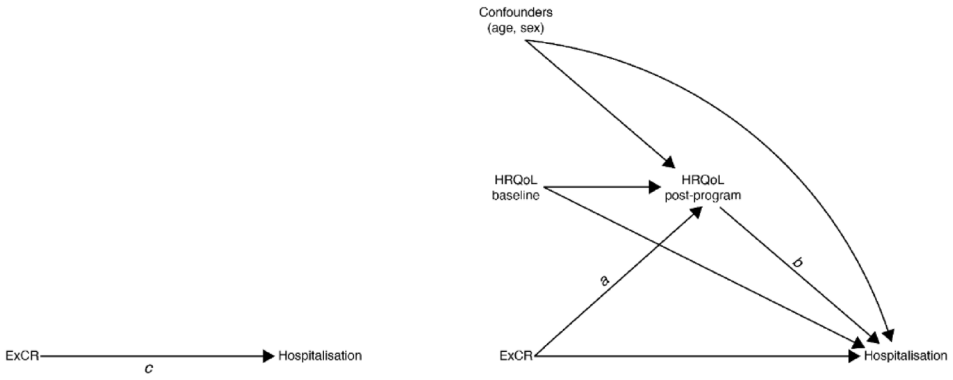
Effects of ExCR

Participation in ExCR significantly increased HRQoL compared to controls (mean difference (MD): 0.044, 95%CI: 0.005 to 0.082, '*a-path*' = 0.016, 95%CI: 0.008 to 0.025) (Fig. 2, eFigure 5), with the mean and the 95%CI including the possibility of a clinically meaningful improvement. Compared to controls, participation in ExCR did not significantly reduce 1-year all-cause hospitalisation (33 vs. 43 events, HR: 0.72, 95%CI: 0.45 to 1.14; '*c-path*'= −0.005, 95%CI: −0.014 to 0.003), or CVD-related hospitalisation risk (24 vs. 36 events, HR: 0.58, 95%CI: 0.33 to 1.03; '*c-path*'= −0.006, 95%CI: −0.014 to 0.001) (Fig. 2, eTable 6). At 2-year follow-up, these effects were statistically significant for all-cause hospitalisation (60 vs. 88 events, HR: 0.61, 95%CI: 0.43 to 0.87; '*c-path*'= −0.014, 95%CI: −0.026 to −0.003) and CVD-related hospitalisation (46 vs. 72 events; HR: 0.56, 95%CI: 0.37 to 0.87; '*c-path*'= −0.013, 95%CI −0.024 to −0.003) (Fig. 2, eTable 6).

Mediation analyses

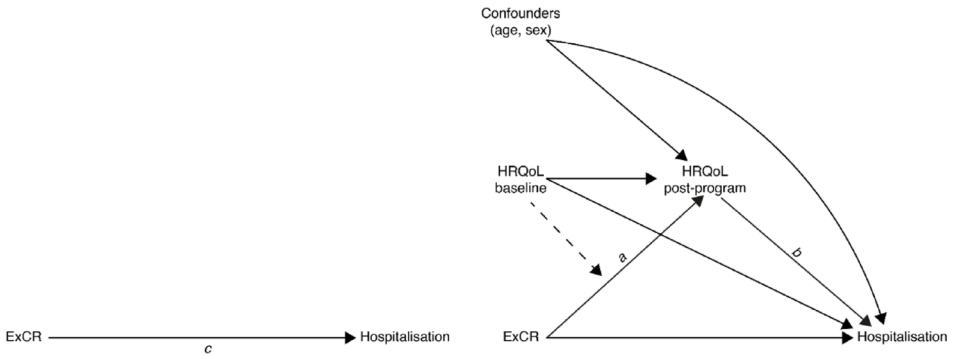
Overall, improvements in HRQoL were significantly related to a lower 1-year ('*b-path*'= −0.064, 95%CI: −0.096 to −0.032) and 2-year ('*b-path*'= −0.065, 95%CI: −0.109 to −0.022) risk of all-cause hospitalisation, and to a lower 1-year ('*b-path*'= −0.042, 95%CI: −0.070 to −0.014) and 2-year ('*b-path*'= −0.052, 95%CI: −0.091 to −0.014) risk of CVD-related hospitalisation (Fig. 2, eFigure 6). The effects of ExCR on 2-year follow-up of all-cause ('*ab-path*'= −0.0011, 95%CI: −0.0013 to −0.0009, proportion mediated: 7.4%) and CVD-related hospitalisation ('*ab-path*'= −0.0008, 95%CI: −0.0010 to −0.0007, proportion mediated: 6.2%) were significantly mediated by improvements in HRQoL (Fig. 2). Mediation effects were more pronounced in those with a lower baseline HRQoL for all-cause ('*ab-path*'= −0.00181, 95%CI: −0.00222 to −0.00142, proportion mediated: 10.6%) and CVD-related hospitalisation ('*ab-path*'= −0.00138, 95%CI: −0.00173 to −0.00104, proportion mediated: 9.3%) compared to those with a higher baseline HRQoL (all-cause hospitalisation: '*ab-path*'= −0.00015, 95% CI: −0.00049 to 0.00020, proportion mediated: 1.2%; CVD-related hospitalisation: '*ab-path*'= −0.00008, 95%CI: −0.00040 to −0.0002, proportion mediated: 0.7%) (Fig. 3, eFigure 7). When increases in HRQoL were categorized as clinically-important differences (n = 1,778, 44.9%), mediation effects remained directionally consistent, though 95%CI's were wider (eFigure 8). Inferences were consistent across other secondary analyses (eTables 7–8).

Improvements in both physical and mental HRQoL-dimensions significantly mediated the ExCR-induced lower



		Total effect		Indirect effect			
Outcome	Events (n ExCR)	c-path (MD, 95%CI)	HR of c-path (95%CI)	a-path (MD, 95%CI)	b-path (MD, 95%CI)	ab-path (MD, 95%CI)	Proportion mediated (%, 95%CI)
All-cause hospitalisation (n = 3,942)	148 (60)	-0.014 (-0.026, -0.003)	0.61 (0.43, 0.87)	0.016 (0.008, 0.025)	-0.065 (-0.109, -0.022)	-0.0011 (-0.0013, -0.0009)	7.4% (0.1%, 28.9%)
CVD-related hospitalisation (n = 3,959)	118 (46)	-0.013 (-0.024, -0.003)	0.56 (0.37, 0.87)	0.016 (0.008, 0.024)	-0.052 (-0.091, -0.014)	-0.0008 (-0.0010, -0.0007)	6.2% (0.5%, 28.8%)

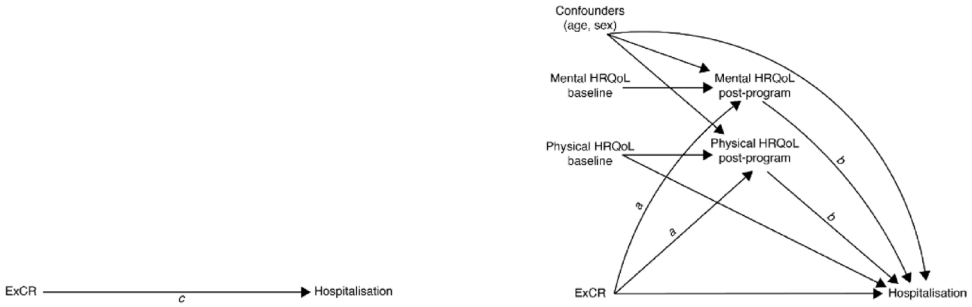
Fig. 2 Mediation analyses to evaluate whether improvements in HRQoL mediate the effect of ExCR on the two-year hospitalisation risk. Path diagrams for the total effect ('c-path', upper left panel) and the indirect effect through improvements in HRQoL ('ab-path', upper right panel) are presented, and mediation results have been tabulated. Mediation analyses highlighted that the effects of ExCR on two-year all-cause and CVD-related hospitalisation risk were significantly mediated through improvements in HRQoL. ExCR exercise-based cardiac rehabilitation, FU follow-up, HR Hazard ratio, HRQoL health-related quality of life, MD mean difference



			Total effect		Indirect effect			
Outcome	Baseline HRQoL	Events (n ExCR)	c-path (MD, 95%CI)	HR of c-path (95%CI)	a-path (MD, 95%CI)	b-path (MD, 95%CI)	ab-path (MD, 95%CI)	Proportion mediated (%, 95%CI)
All-cause hospitalisation (n = 3,942)	<0.84	78 (31)	-0.017 (-0.035, 0.0002)	0.51 (0.30, 0.88)	0.032 (0.017, 0.047)	-0.057 (-0.109, -0.005)	-0.0018 (-0.0022, -0.0014)	10.6% (-0.01%, 31.4%)
	≥0.84	70 (29)	-0.012 (-0.028, 0.003)	0.69 (0.43, 1.11)	0.002 (-0.006, 0.010)	-0.069 (-0.154, 0.015)	-0.0001 (-0.0005, 0.0002)	1.2% (0.63%, 32.67%)
CVD-related hospitalisation (n = 3,959)	<0.84	60 (23)	-0.015 (-0.030, 0.0003)	0.47 (0.23, 0.96)	0.031 (0.016, 0.046)	-0.044 (-0.090, 0.001)	-0.0014 (-0.0017, -0.0010)	9.3% (0.43%, 29.0%)
	≥0.84	58 (23)	-0.012 (-0.026, 0.002)	0.64 (0.38, 1.08)	0.001 (-0.007, 0.009)	-0.062 (-0.139, 0.015)	-0.0001 (-0.0004, 0.0002)	0.7% (0.59%, 27.4%)

Fig. 3 Mediation analyses to evaluate whether improvements in HRQoL mediate the effect of ExCR on the two-year hospitalisation risk, stratified by HRQoL at baseline. Path diagrams for the total effect ('c-path', upper left panel) and the indirect effect through improvements in HRQoL ('ab-path', upper right panel) are presented, and mediation results stratified by the baseline HRQoL utility index have been tabulated. Stratified mediation analyses highlighted that those with a lower baseline HRQoL gained stronger benefits of improvements in HRQoL due to ExCR on two-year all-cause and CVD-related hospitalisation risk compared to those with a higher HRQoL at baseline. CVD cardiovascular disease, ExCR exercise-based cardiac rehabilitation, HR Hazard ratio, HRQoL health-related quality of life, MD mean difference

risk for 2-year all-cause ('*ab-path'* physical= −0.0009, 95%CI: −0.0011 to −0.0006, proportion mediated: 5.8%; '*ab-path'* mental= −0.0005, 95%CI: −0.0007 to −0.0003, proportion mediated: 3.4%) and CVD-related hospitalisation risk ('*ab-path'* physical=0.0006, 95%CI: −0.0008 to −0.0004, proportion mediated: 4.4%; '*ab-path'* mental= −0.0004, 95%CI: −0.0005 to −0.0002, proportion mediated: 2.6%) (Fig. 4, eFigure 9). Direct comparison between the physical and mental HRQoL-dimensions revealed no notable differences in effect sizes in mediation effects for all-cause (*ab* physical – *ab* mental= −0.0004, 95%CI: −0.0020 to 0.0010) and CVD-related hospitalisation (*ab* physical – *ab* mental= −0.0002, 95%CI: −0.0016 to 0.0009) (Fig. 4, eFigure 9).



		Total effect		Indirect effect					
Outcome	Events (n ExCR)	c-path (MD, 95%CI)	HR of c-path (95%CI)	HRQoL dimension	a-path (MD, 95%CI)	b-path (MD, 95%CI)	ab-path (MD, 95%CI)	Proportion mediated (%, 95%CI)	ab physical - ab mental (MD, 95%CI)
All-cause hospitalisation (n = 3,740)	139 (56)	-0.015 [-0.027, -0.003]	0.60 [0.41, 0.88]	Physical	-0.025 [-0.045, -0.004]	0.035 [0.015, 0.054]	-0.0009 [-0.0011, -0.0006]	5.8% (0.1%, 25.5%)	-0.0003 [-0.0020, 0.0010]
				Mental	-0.038 [-0.062, -0.013]	0.013 [-0.003, 0.030]	-0.0005 [-0.0007, -0.0003]	3.4% (-2.3%, 17.3%)	
CVD-related hospitalisation (n = 3,754)	113 (44)	-0.014 [-0.024, -0.003]	0.54 [0.33, 0.87]	Physical	-0.025 [-0.045, -0.004]	0.024 [0.007, 0.042]	-0.0006 [-0.0008, -0.0004]	4.4% (-0.4%, 22.6%)	-0.0002 [-0.0016, 0.0009]
				Mental	-0.037 [-0.062, -0.012	0.010 [-0.005, 0.025]	-0.0004 [-0.0005, -0.0002]	2.6% (-3.2%, 13.6%)	

Fig. 4 Parallel multiple mediation models to evaluate whether improvements in physical- and mental-dimensions of HRQoL mediate the effect of ExCR on the two-year hospitalisation risk. Path diagrams for the total effect ('c-path', upper left panel) and the indirect effect through improvements in physical and mental dimensions of HRQoL ('ab-path', upper right panel) are presented, and mediation results have been tabulated. In essence, a parallel multiple mediation model of k mediators requires k + 1 regression models to quantify all individual indirect effects, including (1) regressing each individual mediator on treatment allocation (i.e., a distinct 'a-path' model for each mediator), and (2) regressing the outcome on all mediators of interest (a common 'b-path' model). This approach effectively allows to test each individual mechanism while accounting for the shared association between them. To assess the relative importance of improvements in physical and mental HRQoL dimensions, we quantified the difference in indirect effects ('ab-path physical' – 'ab-path mental'), and used percentile bootstrapping with 1,000 resamples to compute the corresponding 95% CI. Parallel multiple mediation analyses highlighted that improvements in both physical and mental HRQoL dimensions mediated the effect of ExCR on two-year hospitalisation risk, with no notable differences in effect size between these dimensions. ExCR exercise-based cardiac rehabilitation, HR Hazard ratio, HRQoL health-related quality of life, MD mean difference

Discussion

This study examined whether ExCR-induced improvements in HRQoL mediated clinical improvements (i.e., all-cause and CVD-related hospitalisation) in people with CHD. First, ExCR significantly improved HRQoL and reduced the risk of all-cause and CVD-related hospitalisation compared to usual care following two years of follow-up. Second, HRQoL partly mediated the reduced all-cause and CVD-related hospitalisation risk following ExCR. Mediation effects were more pronounced in those with a lower baseline HRQoL. Third, improvements in both the physical and mental HRQoL-dimension significantly mediated the lower risk for hospitalisation. Collectively, improvements in HRQoL, including both physical and mental dimensions, mediate the clinical benefits of ExCR in people with CHD.

To our knowledge, this is the first mediation analysis using data of randomised controlled trials aiming to understand the underlying pathways that mediate the clinical benefits of ExCR in people with CHD. A strength of this study is the pooling of 3,959 individualised participant data from 5 trials across a 2-year follow-up. The findings of the mediation analyses reinforce previous studies [3, 40]. The stronger mediation effect in those with the lower baseline HRQoL is in line with the secondary analysis of the HF-ACTION trial, which suggested that frail individuals with heart failure gained the largest clinical benefit from participation in ExCR compared to less or non-frail participants [41]. The clinical benefits of increases in quality of life appear biologically plausible, supported by a recent randomized controlled trial in which lower-income individuals receiving unconditional monthly cash benefits showed a reduced hospitalisation risk compared to those who did not [42]. Together, this highlights the need to specifically focus and understand the clinical benefits of ExCR in people who are less frequently referred to ExCR (e.g., frailty, older age, low HRQoL).

The clinical benefits of participation in ExCR have traditionally been attributed, at least in part, to improvements in cardiorespiratory health. For example, previous studies have consistently demonstrated that participation in ExCR is related to improvements in peak exercise capacity [8, 9], and that such improvements are associated with a reduced

hospitalisation risk in observational cohorts [10]. Although we were unable to formally evaluate peak exercise capacity as a mediator due to a small sample size, our findings indicate that improvements in self-reported physical functioning mediate improvements in clinical outcomes. The physical HRQoL domain may be broader than peak exercise capacity alone, and likely captures multi-dimensional improvements in attributes required for activities of daily living. Supporting this concept, previous studies found peripheral muscle strength, frailty and submaximal exercise capacity to be dose-dependently associated with CVD and all-cause mortality in both healthy individuals and those with CVD [43–47]. Nonetheless, effects are not solely targeted at the physical HRQoL-dimension, as the mental dimension also mediated the clinical benefits of ExCR. In essence, the mental dimension assesses an individual's vitality, social functioning, and general mental health, and previous work found that participation in ExCR is associated with a lower risk for depression, anxiety, and psychosocial stress [48, 49]. Interestingly, the extent to which the mental dimension mediates the clinical benefits of ExCR was similar to that of the physical component. Our data highlight that improvements in both physical and mental HRQoL following participation in ExCR may directly improve clinical outcomes, and further underline the essential role of a multidisciplinary approach of contemporary ExCR.

Clinical relevance

The insights of our mediation analyses may allow tailoring the design of future programmes. For example, our data support specific attention to improve HRQoL for directly reducing hospitalisation risk, especially among those with a lower HRQoL at baseline. In addition, effects of ExCR are multiple and complex. For example, an important clinical observation from our analysis is that HRQoL explained only 6.2–7.4% of the clinical benefits of ExCR. A previous study found that ExCR is associated with improvements in measures of maximal and submaximal exercise capacity, traditional CVD risk factors, and/or vascular/cardiac function [50]. Whether and the extent to what improvements in these variables mediate the clinical benefits of ExCR should be explored in future studies.

Limitations

Some limitations should be acknowledged. First, to ensure temporal precedence of the mediator and outcome, we excluded participants who dropped out or experienced a hospitalisation event before the end of the intervention period. Nonetheless, the characteristics and total effect of participation in ExCR on hospitalisation risk were comparable regardless of whether these individuals were included (eTables 5–6). We therefore assume mediation effects of improvements in HRQoL due to ExCR to be comparable as well. Second, external validity may be affected due to strict trial eligibility criteria and heterogeneity across trials (e.g., ethnicity, socio-economic status, comorbidities). Whilst the effects of ExCR have been documented to be consistent across patient subgroups [13], caution should be applied in generalizing mediation effects to CHD patients widely, including older adults and different ethnic groups. Third, whilst randomization eliminates potential treatment-mediator and treatment-outcome confounding, it does not rule out residual mediator-outcome confounding. Fourth, due to paucity of data, the study was underpowered to perform a mediation analysis for exercise capacity as per protocol (eAppendix, eFigures 2–3, eTable 3) [14, 15].

Conclusion

In conclusion, we demonstrated that improvements in HRQoL, including the physical and mental dimensions, mediated the reduced risk on all-cause and CVD-related hospitalisation with ExCR. This suggests that improvements in the physical and mental dimensions of HRQoL are both relevant components for the clinical effects as well as the evaluation of ExCR programmes. Nonetheless, our mediation analysis only partly explained the clinical benefits, highlighting the complexity and holistic impact of ExCR and the role of other mediators.

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