European Heart Journal (2023) **44**, 452–469
https://doi.org/10.1093/eurheartj/ehac747

META-ANALYSIS
Ischaemic heart disease

Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis

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Received 26 April 2022; revised 31 October 2022; accepted 30 November 2022

See the editorial comment for this article 'Evidence is indisputable that cardiac rehabilitation provides health benefits and event reduction: time for policy action', by S. L. Grace, https://doi.org/10.1093/eurheartj/ehac690.

Abstract

Aims Coronary heart disease is the most common reason for referral to exercise-based cardiac rehabilitation (CR) globally. However, the generalizability of previous meta-analyses of randomized controlled trials (RCTs) is questioned. Therefore, a contemporary updated meta-analysis was undertaken.

Methods and results Database and trial registry searches were conducted to September 2020, seeking RCTs of exercise-based interventions with ≥6-month follow-up, compared with no-exercise control for adults with myocardial infarction, angina pectoris, or following coronary artery bypass graft, or percutaneous coronary intervention. The outcomes of mortality, recurrent clinical events, and health-related quality of life (HRQoL) were pooled using random-effects meta-analysis, and cost-effectiveness data were narratively synthesized. Meta-regression was used to examine effect modification. Study quality was assessed using the Cochrane risk of bias tool. A total of 85 RCTs involving 23 430 participants with a median 12-month follow-up were included. Overall, exercise-based CR was associated with significant risk reductions in cardiovascular mortality [risk ratio (RR): 0.74, 95% confidence interval (CI): 0.64–0.86, number needed to treat (NNT): 37], hospitalizations (RR: 0.77, 95% CI: 0.67–0.89, NNT: 37), and myocardial infarction (RR: 0.82, 95% CI: 0.70–0.96, NNT: 100). There was some evidence of significantly improved HRQoL with CR participation, and CR is cost-effective. There was no significant impact on overall mortality (RR: 0.96, 95% CI: 0.89–1.04), coronary artery bypass graft (RR: 0.96, 95% CI: 0.80–1.15), or percutaneous coronary intervention (RR: 0.84, 95% CI: 0.69–1.02). No significant difference in effects was found across different patient groups, CR delivery models, doses, follow-up, or risk of bias.

Conclusion This review confirms that participation in exercise-based CR by patients with coronary heart disease receiving contemporary medical management reduces cardiovascular mortality, recurrent cardiac events, and hospitalizations and provides additional evidence supporting the improvement in HRQoL and the cost-effectiveness of CR.

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Structured Graphical Abstract

Key Question

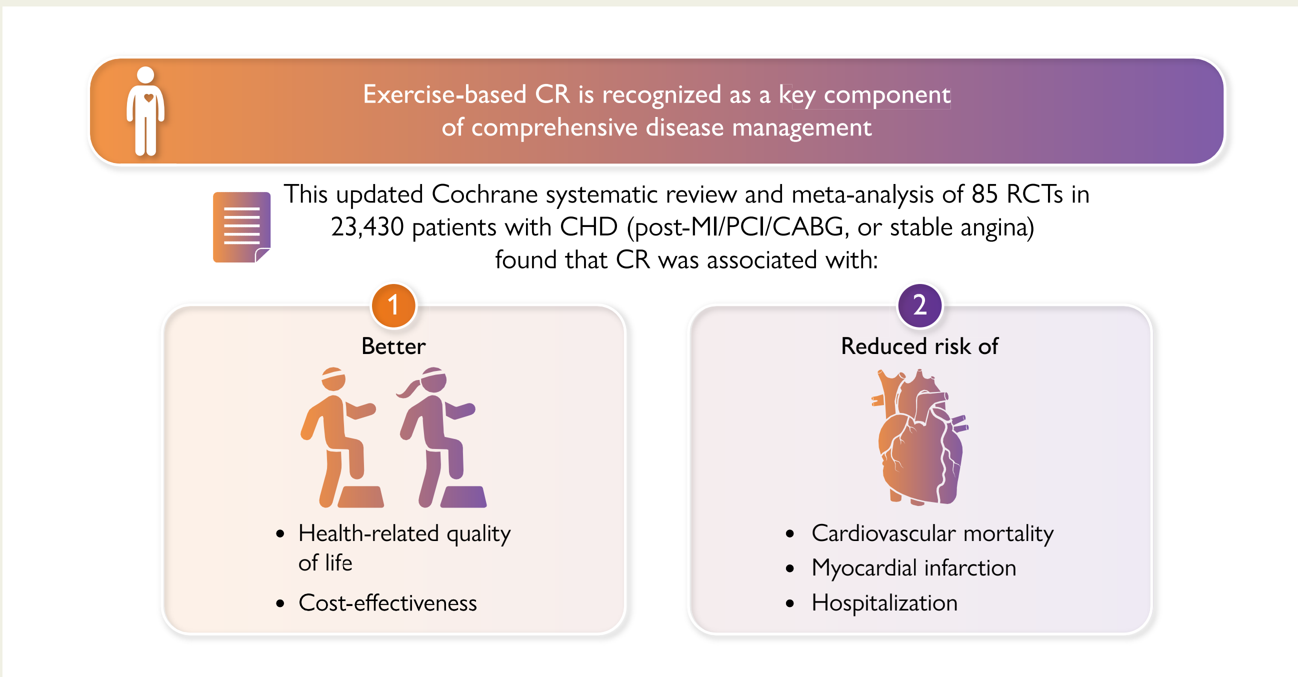
Compared to no exercise control, what are the clinical benefits of exercise-based cardiac rehabilitation (CR) for patients with coronary heart disease (CHD)?

Key Finding

In this meta-analysis of 85 randomized controlled trials of 23,430 CHD patients, exercise-based CR reduced the risk of cardiovascular mortality, recurrent cardiac events, and hospitalizations, improved health-related quality of life and was cost-effective.

Take Home Message

Exercise-based CR provides important benefits to CHD patients including improved quality of life, and better cardiovascular outcomes across different patient groups. In addition, it is cost-effective.



Exercise-based CR is recognized as a key component of comprehensive disease management. CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials.

Keywords Coronary heart disease • Cardiac rehabilitation • Exercise training • Physical activity • Prevention

Introduction

Coronary heart disease (CHD) is the most common cause of death globally.[1,2] With increasing numbers of people living longer with CHD, accessible and effective health services for the management of CHD are crucial. Exercise-based cardiac rehabilitation (CR) is recognized as a key component of comprehensive CHD management and is a Class I Grade A recommendation in international guidelines.[3,4]

Although meta-analyses of randomized controlled trials (RCTs) have shown the beneficial effect of CR in patients with CHD,[5–7] this evidence base has been questioned on the grounds of: (i) uncertainty in the impact on mortality; (ii) lack of data on health-related quality of life (HRQoL); (iii) inclusion of RCTs limited to low-risk patients and conducted in high-income country settings, and (iv) lack of trials conducted during the era of modern CHD therapy.[7–9]

To address these uncertainties, we undertook a contemporary update of the Cochrane systematic review and meta-analyses of RCTs to assess the effects of exercise-based CR in patients with CHD on mortality, clinical events, HRQoL, and cost-effectiveness. We also sought to explore whether intervention effects varied with patient case mix, study and intervention characteristics, and CR delivery settings.

Methods

We conducted and reported this meta-analysis in accordance with the Cochrane Handbook for Interventional Reviews and the Preferred

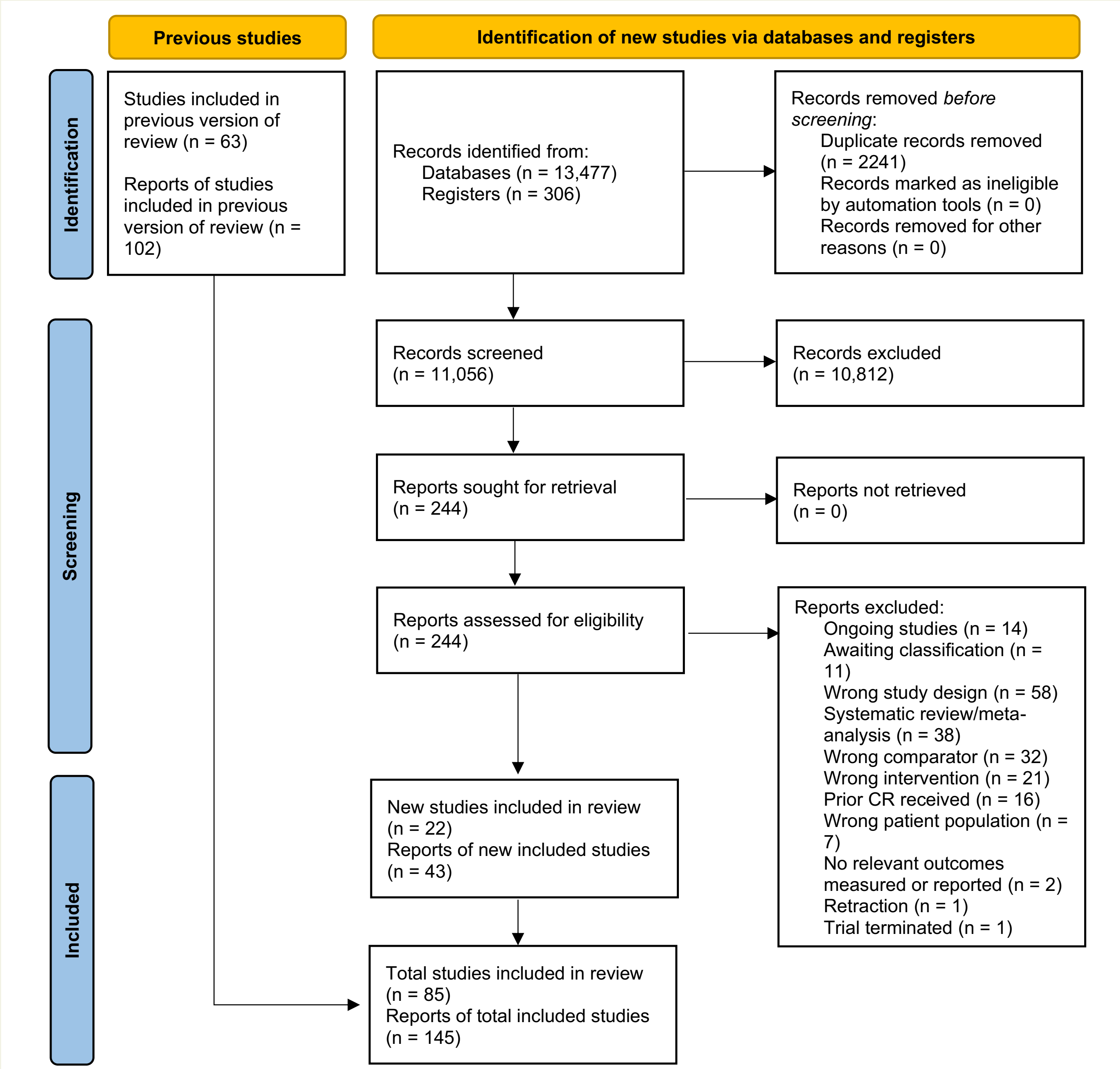


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection process.

Reporting Items for Systematic Reviews and Meta-Analyses and the synthesis without meta-analysis statements, respectively.[10–12]

Search strategy and study selection

We undertook update literature searches of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, and Science Citation Index Expanded from June 2014 (the search end date of the Cochrane 2016 review[5]) to September 2020 (strategy provided in Supplementary material online, *File S1*). We also searched two clinical trials registers (World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov), and hand-searched reference lists of retrieved articles and recent systematic reviews. Records collected from trial registry searches were used to identify trials not picked up in database searches, as well as ongoing studies. We sought RCTs of exercise-based CR (exercise training alone or in combination with psychosocial or educational interventions) compared with no-exercise or usual care control, with at least 6-month post-baseline follow-up outcome measures. All patients in both the intervention and control groups were generally reported to receive (local or national) guideline recommended medical treatment.

Two reviewers (G.O.D. and J.F.) independently confirmed trial eligibility. Disagreements were resolved by discussion or by a third reviewer (R.S.T.), if necessary.

Patient population

We included adults (≥18 years), in either hospital-or community-based settings, who had a myocardial infarction (MI), who had undergone revascularization [coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)], or who had angina pectoris or coronary artery disease defined by angiography.

Table 1 Summary of study, population, intervention, and comparator characteristics

Study characteristics	Number of studies (%) or median of study means (range)
Publication year	
1970–9	2 (2%)
1980–9	12 (14%)
1990–9	20 (24%)
2000–9	21 (25%)
2010–9	23 (27%)
2020 onwards	7 (8%)
Study continent	
Europe	48 (56%)
North America	13 (15%)
Asia	16 (19%)
Australia	5 (6%)
Other	3 (4%)
LMIC	21 (25%)
Single centre	61 (72%)
Sample size	137 (25–3959)
Duration of follow-up, months	12 (6–228)
Population Characteristics	
Sex	
Males only	21 (25%)
Females only	1 (1%)
Both males and females	61 (72%)
Not reported	2 (2%)
Age, years	56 (44–77)
Diagnosis	
Post-MI only	40 (47%)
Revascularization only	14 (16%)
Angina only	5 (6%)
Mixed CHD population	25 (29%)
Other[a]	1 (1%)
Intervention characteristics	
Intervention type	
Exercise only programme	38 (45%)
Comprehensive programme	47 (56%)
Dose of intervention	
Duration	6 months (0.75–42)
Frequency	1–7 sessions/week
Length	20 to 90 min/session
Intensity	• 50%–90% maximal/peak HR or HRR • 50%–95% VO_2 max • Borg RPE 11–16
Setting	
Centre-based only	40 (47%)
Combination of centre and home	21 (25%)
Home-based only	21 (25%)
Not reported	3 (3%)
Comparator	
Usual/standard care	50 (59%)
Usual care plus[b]	24 (28%)
'No exercise'	8 (9%)
Other	3 (4%)

Continued

Table 1 Continued

CHD, coronary heart disease; HR, heart rate; HRR, heart rate reserve; LMIC, low-middle-income country; RPE, ratings of perceived exertion; VO_2max, maximal oxygen uptake.
[a]He 2020 recruited patients with MI in the absence of obstructive coronary artery disease.
[b]Usual care plus education, guidance or advice about diet and exercise, but no formal exercise training.

Data abstraction and quality appraisal

Two reviewers (G.O.D. and J.F.) independently completed data extraction and assessed study quality using the Cochrane Risk of Bias (ROB) tool,[13] which was checked by a third reviewer (R.S.T.). Trials were assessed based on random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting. Information regarding study methods (country, design, follow-up, and setting), participant characteristics (numbers randomized, age, sex, diagnosis, and inclusion/exclusion criteria), intervention (exercise mode, duration, frequency, intensity), and control (description, i.e. usual care, no exercise), outcomes, funding sources, and notable author conflicts of interest were obtained.

Outcomes and certainty of evidence

Clinical event outcomes included overall and cardiovascular (CV) mortality, fatal and/or non-fatal MI (as reported by studies), CABG, PCI, overall hospitalization, and CV hospitalization. Other outcomes included HRQoL and CR costs, and cost-effectiveness per quality-adjusted life year (QALY). One reviewer (G.O.D.) assessed the certainty of the evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE),[14,15] and had it checked by a second reviewer (R.S.T.). GRADE assessment was applied to clinical event outcomes (overall and CV mortality, fatal and/or non-fatal MI, CABG, PCI, overall hospitalization, and CV hospitalization) at 6–12 months follow-up, the most frequently reported follow-up time point across trials. Evidence was downgraded from high certainty by one level based on the following domains: limitations in study design or execution (ROB), inconsistency of results, indirectness of evidence, imprecision, and publication bias.

Table 2 **Summary of meta-analysis effects of exercise-based cardiac rehabilitation on clinical event outcomes at longest follow-up, short-term follow-up (6–12 months), medium-term follow-up (13–36 months), and long-term follow-up (>36 months)**

Outcome follow-up time point	*n* participants	*n* studies	*n* events/participants Intervention	Comparator	RR (95% CI)	Statistical heterogeneity I^2 statistic χ^2test	GRADE assessment of certainty
Overall mortality							
Longest follow-up	16 829	47	919/8608	950/8221	0.96 (0.89–1.04)	0%	
6–12 months	8823	25	228/4590	242/4233	0.87 (0.73–1.04)	35%	⊕⊕⊕⊖ Moderate[a]
13–36 months	11 073	16	467/5611	498/5462	0.90 (0.80–1.02)	0%	
>36 months	3828	11	476/1902	493/1926	0.91 (0.75–1.10)	35%	
CV mortality							
Longest follow-up	7762	26	296/3997	382/3765	0.74 (0.64–0.86)***	0%	
6–12 months	5360	15	109/2799	114/2561	0.88 (0.68–1.14)	0%	⊕⊕⊕⊖ Moderate[a]
13–36 months	3614	5	199/1861	39/1753	0.77 (0.63 to 0.93)**	5%	
> 36 months	1392	8	56/690	100/702	0.58 (0.43–0.78)***	0%	
Fatal and/or non-fatal MI							
Longest follow-up	14 151	39	383/7181	437/6970	0.82 (0.70–0.96)*	9%	
6–12 months	7423	22	140/3820	174/3603	0.72 (0.55–0.93)*	7%	⊕⊕⊕⊖ Moderate[b]
13–36 months	9565	12	264/4830	237/4735	1.07 (0.91–1.27)	0%	
>36 months	1560	10	65/776	102/784	0.67 (0.50–0.90)**	0%	
CABG							
Longest follow-up	5872	29	211/3028	215/2844	0.96 (0.80–1.15)	0%	
6–12 months	4473	20	125/2324	232/2149	0.99 (0.78–1.27)	0%	⊕⊕⊕⊕ High
13–36 months	2826	9	123/1413	126/1413	0.97 (0.77–1.23)	0%	
>36 months	675	4	19/333	29/342	0.66 (0.34–1.27)	18%	
PCI							
Longest follow-up	3878	17	171/1960	201/1918	0.84 (0.69–1.02)	0%	
6–12 months	3465	13	91/1743	104/1722	0.86 (0.63–1.19)	7%	⊕⊕⊕⊖ Moderate[a]
13–36 months	1983	6	114/996	116/987	0.96 (0.69–1.35)	26%	
>36 months	567	3	28/281	37/286	0.76 (0.48–1.20)	0%	
All-cause hospitalization							
Longest follow-up	7802	21	504/3958	593/3844	0.77 (0.67–0.89)**	32%	
6–12 months	2030	14	130/1054	209/976	0.58 (0.43–0.77)***	42%*	⊕⊕⊕⊖ Moderate[b]
13–36 months	5995	9	392/3017	417/2978	0.92 (0.82–1.03)	0%	
CV hospitalization							
Longest follow-up	1730	8	152/871	174/859	0.85 (0.67–1.08)	12%	
6–12 months	1087	6	40/546	42/541	0.8 (0.41–1.59)	53%	⊕⊕⊖⊖ Low[a,c]
13–36 months	943	3	129/470	141/473	0.92 (0.76–1.12)	0%	

CABG, coronary artery bypass graft; CI, confidence interval; CR, cardiac rehabilitation; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, risk ratio.

[a]Downgraded by one level due to imprecision with a wide confidence interval.

[b]Downgraded by one level due to evidence of publication bias.

[c]Downgraded by one level due to substantial heterogeneity.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

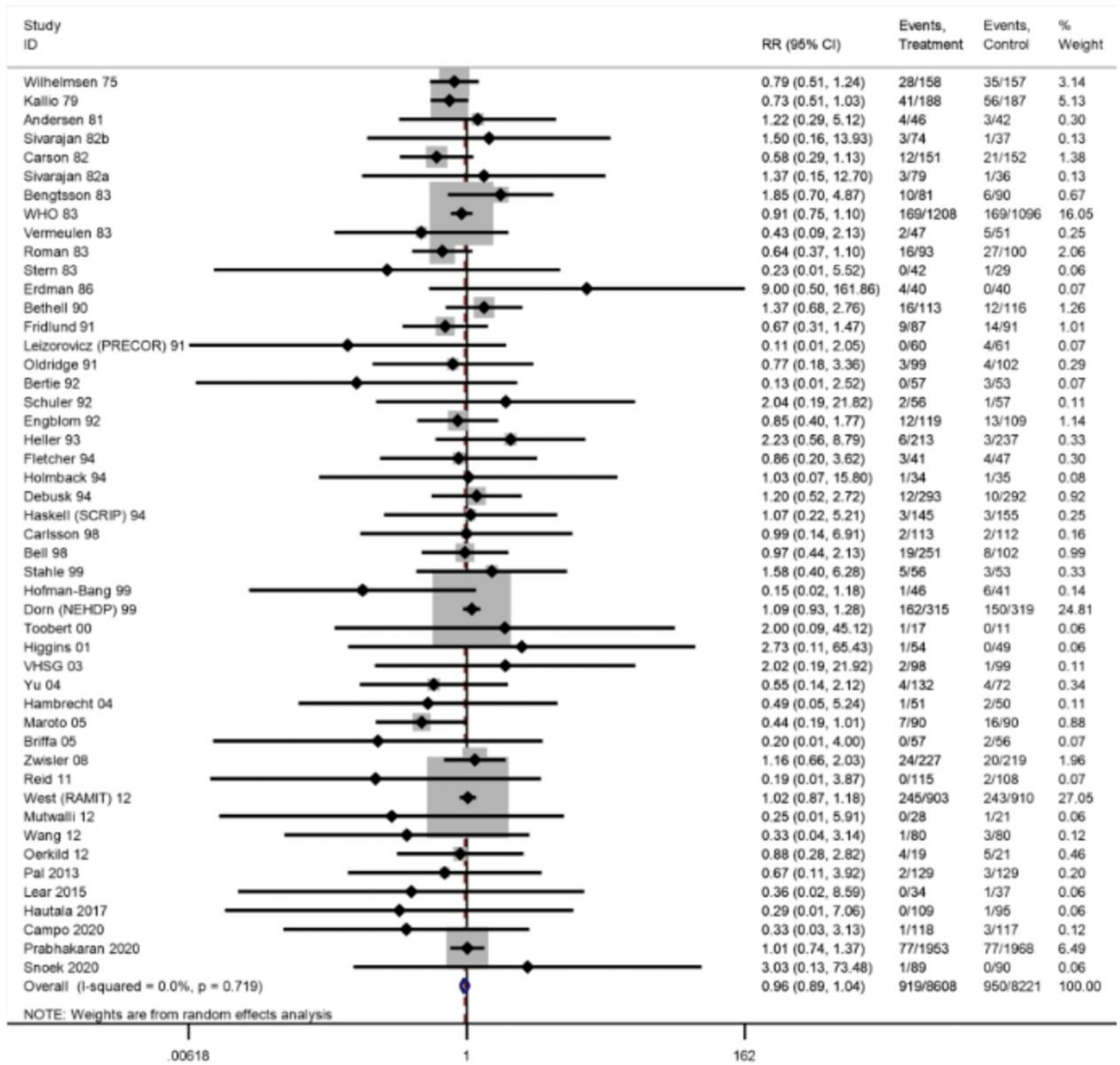


Figure 2 Forest plot: exercise-based cardiac rehabilitation vs. control for overall mortality.

Statistical analysis

Outcome data were pooled at the longest reported follow-up and at three separate time periods: 'short-term' (6–12 months), 'medium-term' (13–36 months), and 'long-term' (>36 months) follow-up. Given the level of clinical heterogeneity (variation in CR interventions and populations), we purposively undertook random-effects meta-analyses, using the DerSimonian and Laird random-effects meta-analysis method, assuming that each study estimates a different underlying intervention effect. Dichotomous outcomes (overall and CV mortality, MI, CABG, PCI, and all-cause hospitalization, and CV hospitalization) are expressed as risk ratios (RRs) with 95% confidence intervals (CIs). For those clinical event outcomes with significant risk reductions, we calculated the number needed to treat for an additional beneficial outcome (NNT).[16] Where ≥2 trials reported the same validated HRQoL measures and domains [i.e. Short-Form-36 (SF-36), EuroQol-5D (EQ-5D)], continuous outcomes were pooled separately by each scale and reported as the mean difference (MD) and 95% CI. Given the heterogeneity in HRQoL outcome measures and reporting, for comprehensiveness, we used a vote-counting approach to synthesis in addition to meta-analyses, where the number of positive, negative, and non-significant results was summed. Cost-effectiveness data were synthesized narratively. Statistical heterogeneity was considered substantial where I^2 statistic >50%. For outcomes with ≥10 trials included in the meta-analysis, we used the funnel plot and Egger's test to examine small study bias.[17] The two-sided *P*-values <0.05 were considered statistically significant. A univariate random-effects meta-regression was used to explore heterogeneity and examine the following pre-defined treatment effect modifiers across clinical event outcomes only: (i) case mix (patients percentage presenting with MI), (ii) 'dose' of exercise [dose (units) = number of weeks of exercise training × average sessions per week × average duration of each session in min], (iii) type of CR (exercise only vs. comprehensive CR), (iv) length of follow-up (longest follow-up used where multiple time points are assessed), (v) publication year, (vi) sample size, (vii) CR setting (home or centre based), (viii) ROB (low in <3 of 5 domains), (ix) study continent (Europe, North America, Australia/Asia, or other), and (x) study country status [low-middle-income countries (LMICs) or high-income countries] according to the World Bank Group[18]. Given the number of statistical

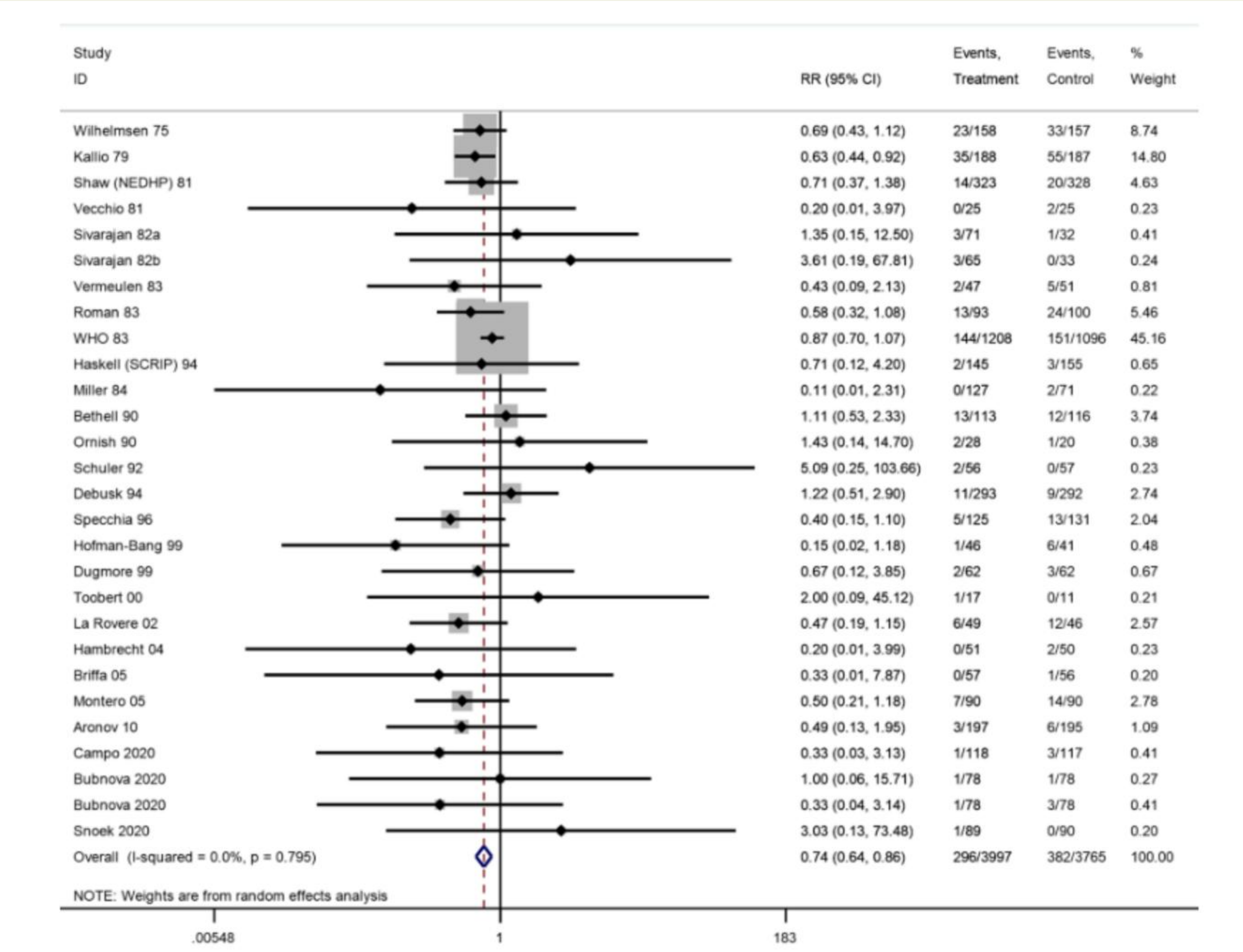


Figure 3 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular mortality.

comparisons performed in this review, the results interpretation was primarily based on 95% CIs rather than *P*-values. Statistical analyses were performed in RevMan Web version 3.12.1 and STATA version 16.1.

Results

Search and selection of studies

The search selection process is summarized in *Figure 1*. Updated database and trial registry searches resulted in a total of 13 783 hits, of which 11 056 unique records were identified, and 244 were selected for full-text review. The main reasons for exclusion were study design (e.g. non-RCT, <6-month follow-up), or use of exercise comparators. The 22 new RCTs (7795 participants; 43 publications),[19–40] identified in this update, provide a total evidence base of 85 RCTs (145 publications, 23 430 participants) comparing exercise-based CR with a no-exercise control group in patients with CHD.[19–103] The participants in the newly included trials represent about one-third of all participants included in this study (33%). A complete list of primary and associated supplementary references for included studies is provided in Supplementary material online, *File S2*.

A summary of the study, participant, intervention, and comparator characteristics of the 85 included studies is presented in *Table 1*. Seventy-nine (93%) of the 85 studies were two-arm parallel RCTs, with four studies comparing more than two arms, (two types of CR vs. control),[21,24,32,89] one study using quasi randomization methods,[38] and one cluster RCT.[62] Sixteen of the 22 new trials identified were undertaken in LMICs,[19–21,24–26,28,30–34,37–40] resulting in a total of 21 RCTs in LMICs. Three large multicentre trials contributed a total of 8956 participants (~40% overall).[34,98,99] The median age of participants across studies was 56 years, and over the last decade, the percentage of female patients included in trials increased from 11% to 17%. The median CR intervention duration and trial follow-up were 6 and 12 months, respectively. Thirty-eight of the 85 (45%) interventions were exercise only,[20–24,28,31–33,35,39–44,48,49,52,54,59,60,65,69,73,76,77,82–84,88–92,94,100] with 47 (55%) involving multiple components including education (20 trials),[25,26,29,34,37,38,51,53,55,57,61,62,70,78,85–87,97,101,102] psychosocial (seven trials),[36,46,58,72,74,80,95] or a combination of both (16 trials),[19,30,45,50,63,64,66–68,71,75,93,96,98,99,103] or other components (i.e. controlled diet, risk factor management, smoking cessation, relaxation; four trials).[27,47,79,81] Exercise was typically aerobic, with the inclusion of resistance training reported in 27% trials (23 out of 85).[22,27,28,30,35,39,41,43,44,46,47,50,54,65,69,77,83,86,89,90,100–102] The dose of exercise interventions varied widely, with frequency ranging between 1 and 7 sessions per week, length of sessions ranging between 20 and 90 min, and intensity ranging between 50% and 90% of maximal or peak heart

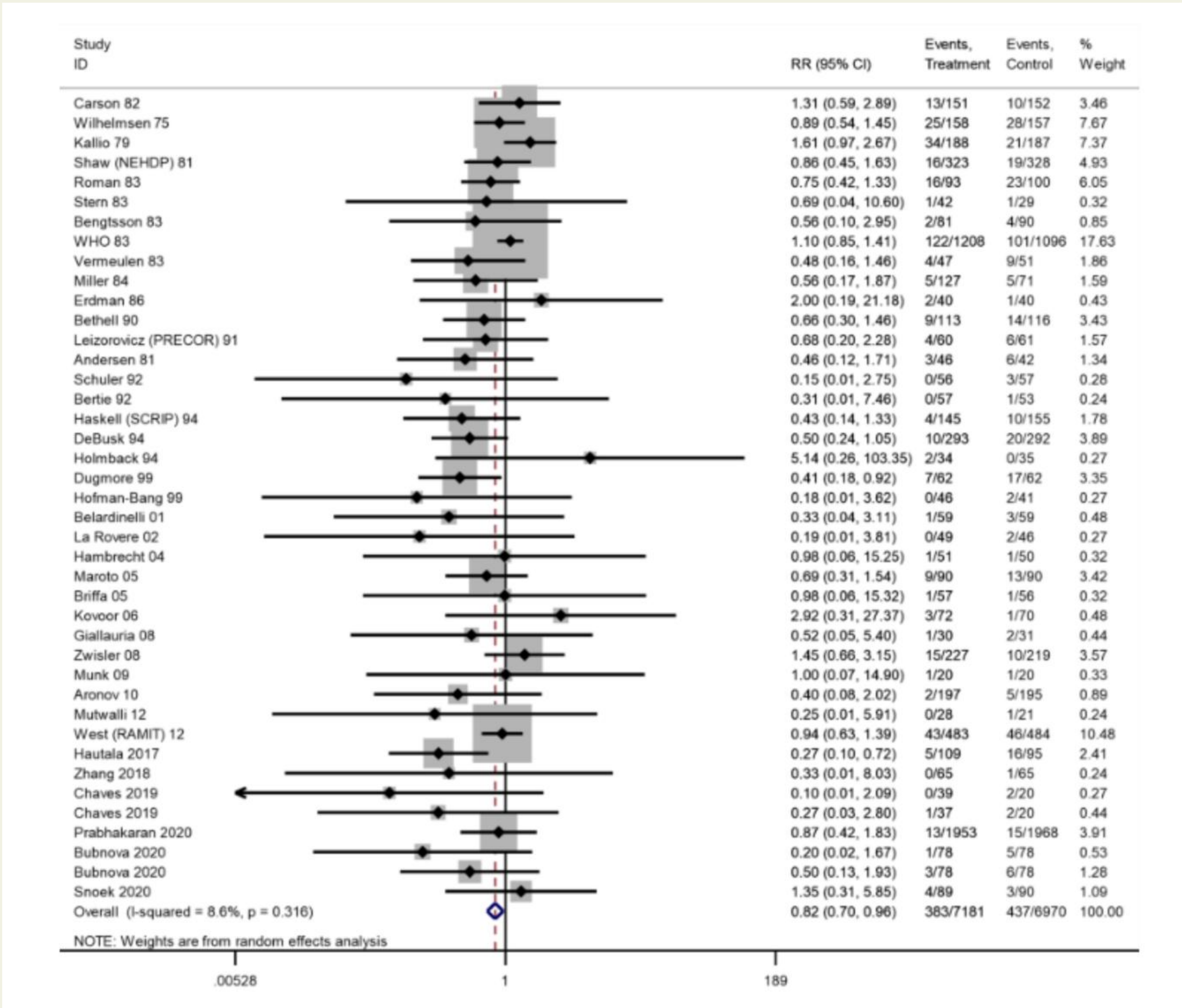


Figure 4 Forest plot: exercise-based cardiac rehabilitation vs. control for myocardial infarction.

rate, 50%–95% of aerobic capacity, or at a rating of perceived exertion between 11 and 16. Of the 21 home-based exercise programmes,[25,29,30,36,38,43–45,53,57,61–63,66,71,72,76,78,79,82,97] four were delivered electronically via mobile phones or the internet.[25,29,72,82]

Risk of bias and GRADE assessment

The overall ROB of included trials was judged to be low or unclear (see Supplementary material online, *Figure S1*), and the quality of reporting improved since 2010 (80% of studies had <3 low-ROB domains pre-2010 vs. 55% post-2010). The 30 (35%) trials reported sufficient and appropriate details of random sequence generation,[21–25,28–32,34–37,41,45,48,50,56,60,61,65,66,72,77,79,82,97,100,103] and 23 (27%) reported appropriate allocation concealment,[21–25,29–31,34,36,45,50,61,65,68,72,77,79,82,85,96,98,103] with 24 (28%) reporting sufficient details of outcome assessment blinding.[23–25,28,29,34–36,57,59,60,65,71–74,77,81,82,84,85,98,103] The 38 (44%) trials were assessed to have low-ROB for incomplete outcome data,[19,25,26,28,29,32–37,40,42,45,49,50,54,59,60,67,69,70,72,73,75,77,79,83,84,86,95,97,98,101,103] and 62 (73%) had low-ROB for selective reporting.[19,23–25,29,34–36,40–68,70–72,74–78,80,82–89,91,92,94–99,101–103] GRADE assessments for the clinical event outcomes at short-term follow-up ranged from low to high (*Table 2*), downgrading for imprecision (wide CIs), evidence of publication bias, or substantial statistical heterogeneity.

Outcomes

A summary of pooled clinical events across all four follow-up time points [longest reported follow-up, short-term (6–12 months), medium-term (13–36 months), and long-term (>36 months)] is presented in *Table 2*. GRADE assessments for certainty of evidence at short-term (6–12 months) follow-up across clinical event outcomes ranged from low-to-high certainty. We downgraded overall mortality, CV mortality, PCI, and CV hospitalization by one level for imprecision, due to wide CIs that overlapped the boundary with no effect. We downgraded MI and all-cause hospitalization by one level due to evidence of publication bias. We downgraded CV hospitalization by an additional level due to evidence of substantial heterogeneity.

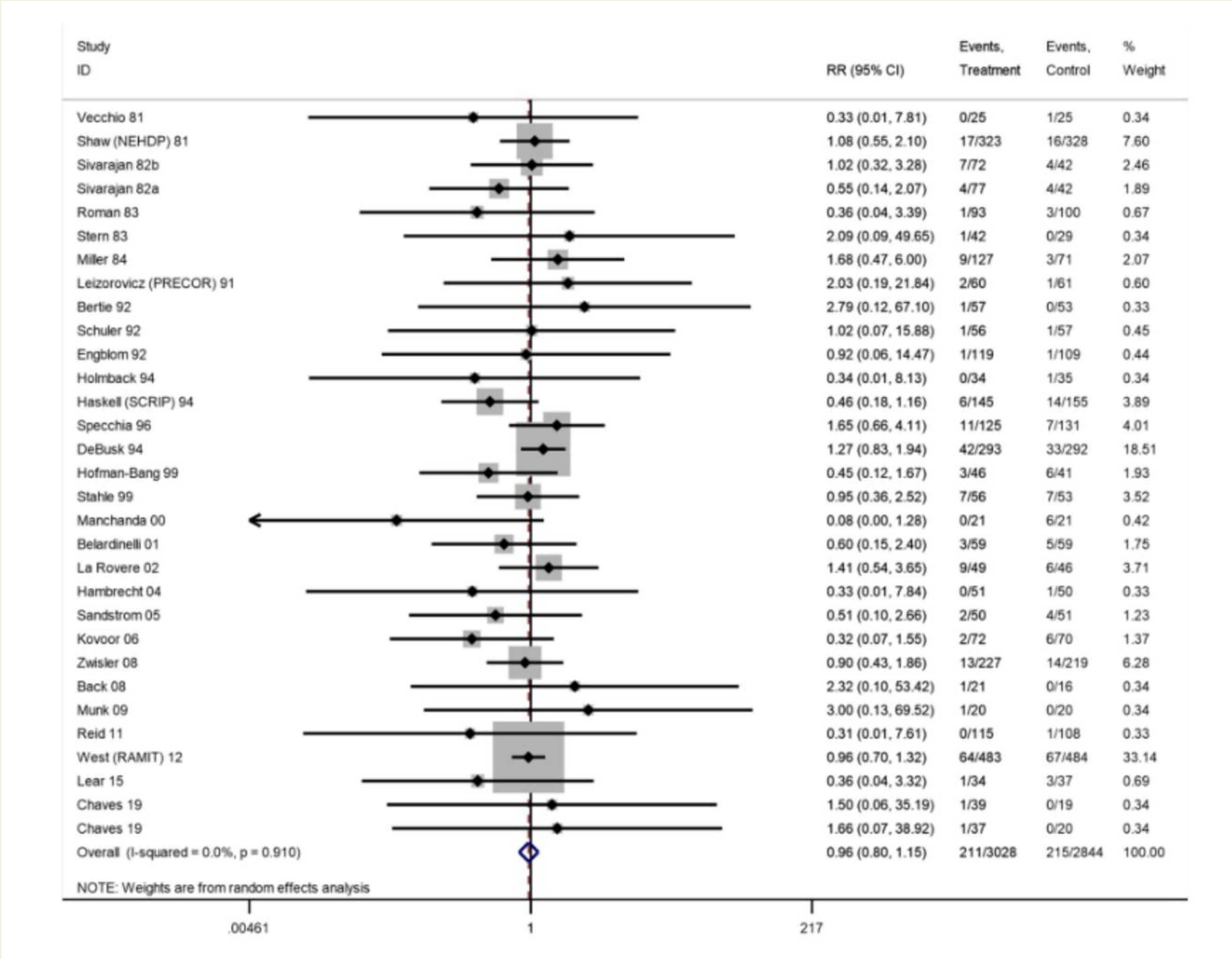


Figure 5 Forest plot: exercise-based cardiac rehabilitation vs. control for coronary artery bypass graft.

Mortality

Of the 60 trials (61 comparisons) that reported overall mortality, 13 trials reported zero events in both arms. There was no difference in risk of overall mortality at short-term follow-up (6–12 months; RR: 0.87, 95% CI: 0.73–1.04, $I^2 = 0\%$; moderate certainty evidence) or longest follow-up (47 trials, RR: 0.96, 95% CI: 0.89–1.04, $I^2 = 0\%$; *Figure 2*).

Across 33 trials (35 comparisons) reporting CV mortality, seven trials reported zero events in both arms. A 26% reduction in risk of CV mortality was seen at longest reported follow-up (26 trials, RR: 0.74, 95% CI: 0.64–0.86, $I^2 = 0\%$; *Figure 3*) with an NNT of 37. At short-term (6–12 months) follow-up, there was no significant difference in CV mortality (RR: 0.88, 95% CI: 0.68–1.14, $I^2 = 0\%$, moderate certainty).

Fatal and/or non-fatal MI

Across 42 trials (44 comparisons) reporting fatal and non-fatal MI, three trials reported zero events in both arms. An 18% reduction in risk was shown at longest follow-up (39 trials, RR: 0.82, 95% CI: 0.70–0.96, $I^2 = 9\%$; *Figure 4*) with an NNT of 100. The overall risk was driven by significant reductions in the short-term (6–12 months; RR: 0.72, 95% CI: 0.55–0.93, $I^2 = 7\%$, high certainty evidence) and long-term (>36 months; RR: 0.67, 95% CI: 0.50–0.90, $I^2 = 0\%$) with no difference in the medium-term follow-up (13–36 months; RR: 1.07, 95% CI: 0.91–1.27, $I^2 = 0\%$).

Revascularization events

Of 31 trials (33 comparisons) reporting CABG, two trials reported zero events in both arms. There was no difference in risk of CABG at longest follow-up (29 trials, RR: 0.96, 95% CI: 0.80–1.15, $I^2 = 0\%$; *Figure 5*). Of the 20 trials (21 comparisons) reporting PCI, three trials reported zero events in both arms. There was no significant difference in risk of PCI (17 trials, RR: 0.84, 95% CI: 0.69–1.02, $I^2 = 0\%$; *Figure 6*).

Hospitalization

Across 22 trials (24 comparisons) that reported overall hospitalization, one trial reported zero events in both arms. A 23% reduction in overall hospitalization risk with participation in exercise-based CR was shown at the longest follow-up (21 trials, RR: 0.77, 95% CI: 0.67–0.89, $I^2 = 32\%$; *Figure 7*) with an NNT of 37. Nine trials reported CV hospitalizations and one trial reported zero events in both arms. There was no significant difference in CV hospitalization at longest follow-up (eight trials, RR: 0.85, 95% CI: 0.67–1.08, $I^2 = 12\%$; *Figure 8*).

Health-related quality of life

Six trials reported SF-36 summary component scores with up to 12-month follow-up (*Figure 9*). There was evidence of increases in

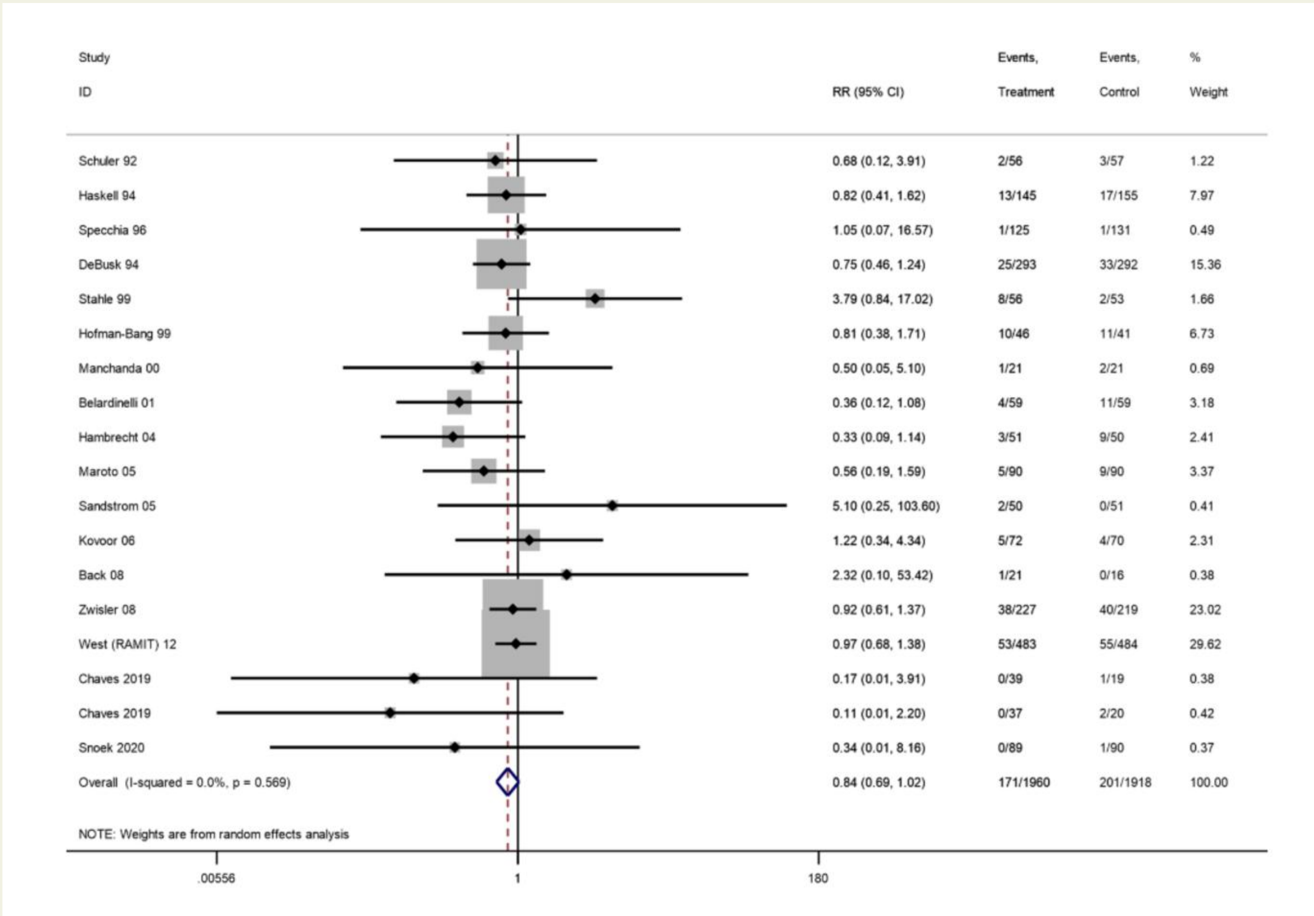


Figure 6 Forest plot: exercise-based cardiac rehabilitation vs. control for percutaneous coronary intervention.

both the mental component score (MD: 2.14, 95% CI: 1.07–3.22, $I^2 = 21\%$) and the physical component score (MD: 1.70, 95% CI: −0.08–3.47, $I^2 = 73\%$) with exercise-based CR. These findings were supported by improvements in selected SF-36 individual domain scores (*Figure 10*) that included physical functioning, physical performance, general health, vitality, social functioning, and mental health. There was no evidence of an improvement in pooled EQ-5D visual analogue scores (VASs; MD 0.05, 95% CI −0.01–0.10, $I^2 = 69\%$; *Figure 11*).

Vote-counting across the 32 trials that assessed HRQoL using a range of validated generic or disease-specific outcome measures confirmed the benefit of CR, with 20 (63%) trials reporting higher levels of HRQoL with exercise-based CR compared with control in one or more subscales and 12 (38%) trials reporting higher levels of HRQoL in >50% of the subscales (see Supplementary material online, *Table S1*).

Costs and cost-effectiveness

Only 8 of the 85 studies reported data on healthcare costs of CR with 5 studies reporting overall healthcare costs in both groups (*Table 3*). Total healthcare costs were lower with exercise-based CR than usual care in three studies (mean US$2378,[60] €1083,[27] and US$415[102] less per patient), higher healthcare costs were reported for exercise-based CR than usual care in three studies (mean US$395,[50] US$4,839,[72] and US $480[80] more per patient), and no difference was reported in one study. However, the difference was significant in only one (mean US$2378/patient; $P < 0.001$). Acceptable cost-effectiveness ratios per QALY in favour of exercise-based CR were reported in three trials (US $42,535,[50] €15,247,[72] and US$9,200[80]).

Small study bias

Egger's tests and visual inspection of funnel plots indicated there was no evidence of small study bias for overall mortality (Egger's test: $P = 0.05$; Supplementary material online, *Figure S2*), CV mortality (Egger's test: $P = 0.20$; Supplementary material online, *Figure S3*), CABG (Egger's test: $P = 0.12$; Supplementary material online, *Figure S4*), and PCI (Egger's test: $P = 0.39$; Supplementary material online, *Figure S5*). However, there was evidence of small study bias with funnel plot asymmetry and significant Egger's tests for MI (Egger's test: $P = 0.001$; Supplementary material online, *Figure S6*) and all-cause hospitalization (Egger's test: $P < 0.001$; Supplementary material online, *Figure S7*).

Meta-regression

There was no evidence of significant differences in treatment effects across patient, intervention, and study characteristics for all clinical event outcomes (see Supplementary material online, *Table S2*).

Discussion

This updated Cochrane review and meta-analysis of RCTs incorporated data from >23 000 CHD patients and confirmed the benefits of participation in exercise-based CR that include reductions in risk of CV

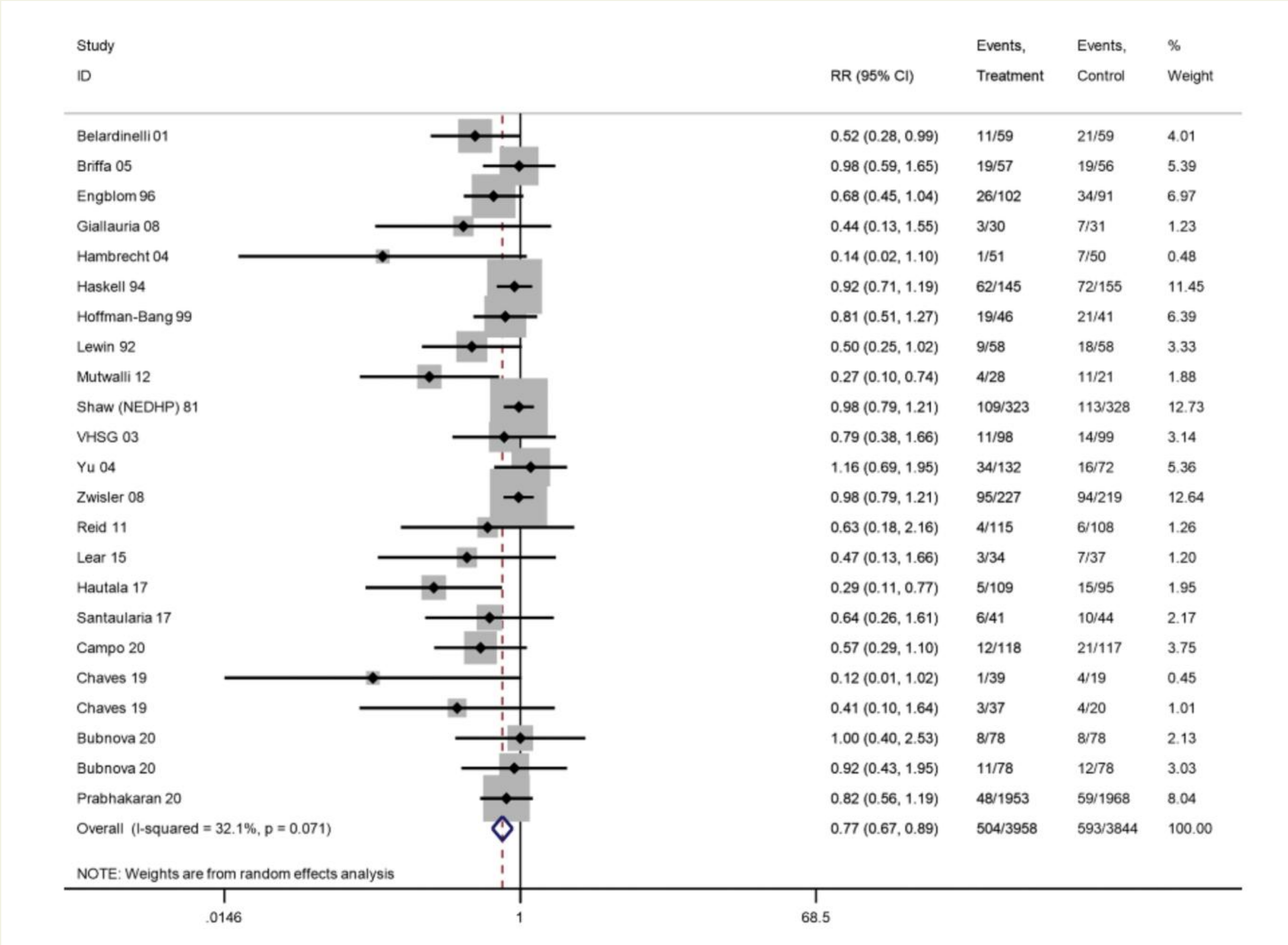


Figure 7 Forest plot: exercise-based cardiac rehabilitation vs. control for overall hospitalization.

mortality, MI, and all-cause hospitalization at a median follow-up of 12 months (Structured graphical abstract). No significant differences in effect were found across patient case mix, the type or set of CR programme, the dose of exercise prescribed, study sample size, location, length of follow-up, year of publication, and ROB. Reduced hospitalizations are likely to have benefits for both healthcare services as well as for patients in terms of health resource usage and associated costs, and early return home to families and community support networks. Importantly, this updated review demonstrates that the benefits of CR extend across recent trials that are more representative of the modern therapeutic approach in CHD, the expanded CHD population, and low- and middle-income settings (21 trials undertaken in LMICs with 7851 participants), where the prevalence of CHD continues to rise.[104]

Additionally, we found gains in HRQoL with increased scores across six of the eight SF-36 domains, mental component scores, EQ-5D VAS, and synthesis without meta-analysis across 32 trials reporting HRQoL data. Based on the minimally important clinical differences, the increases in the individual domain scores were not clinically important,[105] but increases in EQ-5D VAS scores could be clinically meaningful.[106] Minimally important clinical differences for the summary component scores are yet to be published for CHD patients. Although HRQoL is important to patients and improvements have been demonstrated in generic measures, this finding might have been more convincing if a generic measure had been accompanied by the additional use of a CHD disease-specific HRQoL measure. To provide more persuasive evidence, we recommend that future trials consider routinely incorporating both types of HRQoL outcome measures for at least 12 months to delineate which, if any, aspects of HRQoL may yield an improvement. Trial-based economic evaluations showed that CR is a cost-effective use of healthcare resources compared with usual care.

Coronary heart disease is clinically changing from a life-threatening disease to a chronic disease trajectory, as reflected in the terminology of current clinical guidelines on chronic coronary syndromes.[4] This crucial shift strongly calls for interventions that contribute to improvements in the rehospitalization rate and the well-being and HRQoL of people living with chronic diseases. Thus, this latest Cochrane review of RCTs still reinforces the importance of exercise-based CR as part of integrated CHD care alongside modern invasive and pharmacological therapy.

Limitations

Our review has a number of potential limitations. First, although we found that the methodological quality and reporting of studies have improved over the last decade and that poor reporting did not appear to alter the review findings, several ROB assessments across trials were judged to be unclear, with many studies inadequately reporting

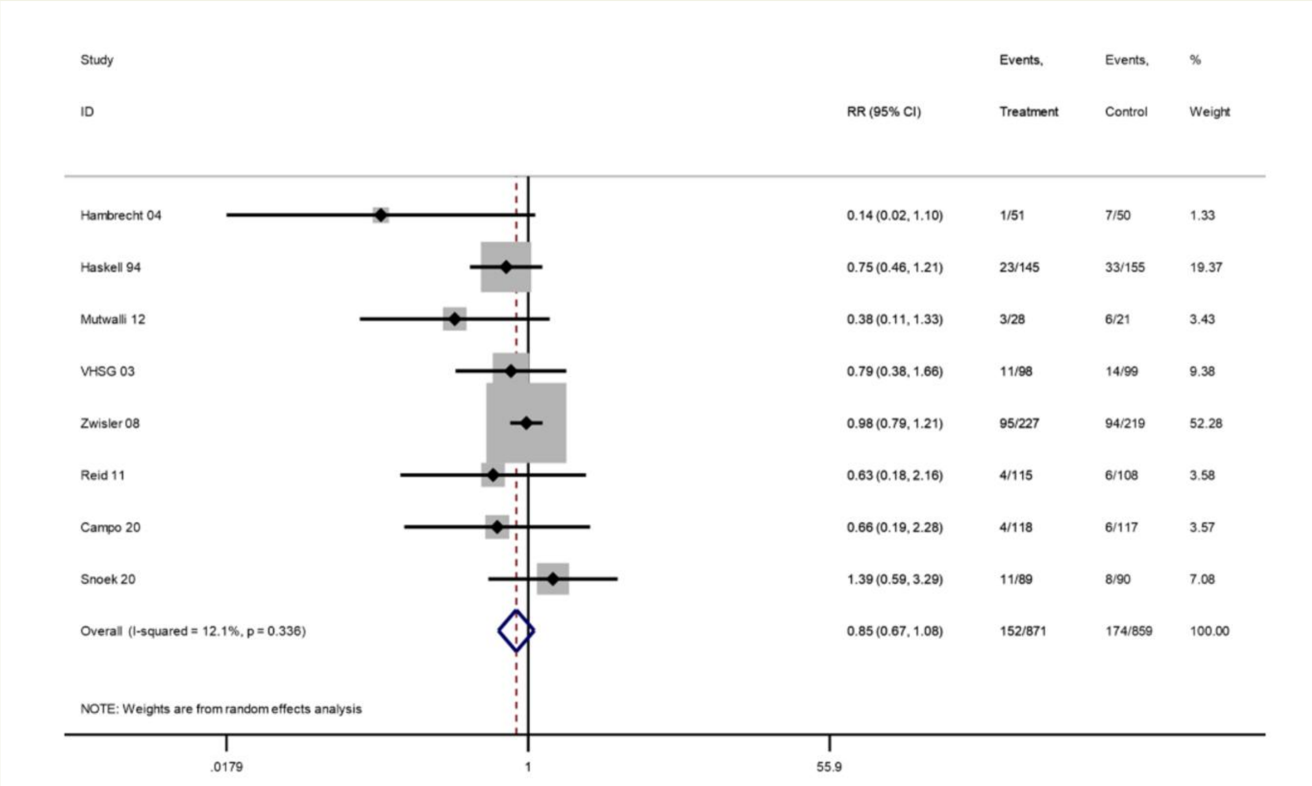


Figure 8 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular hospitalization.

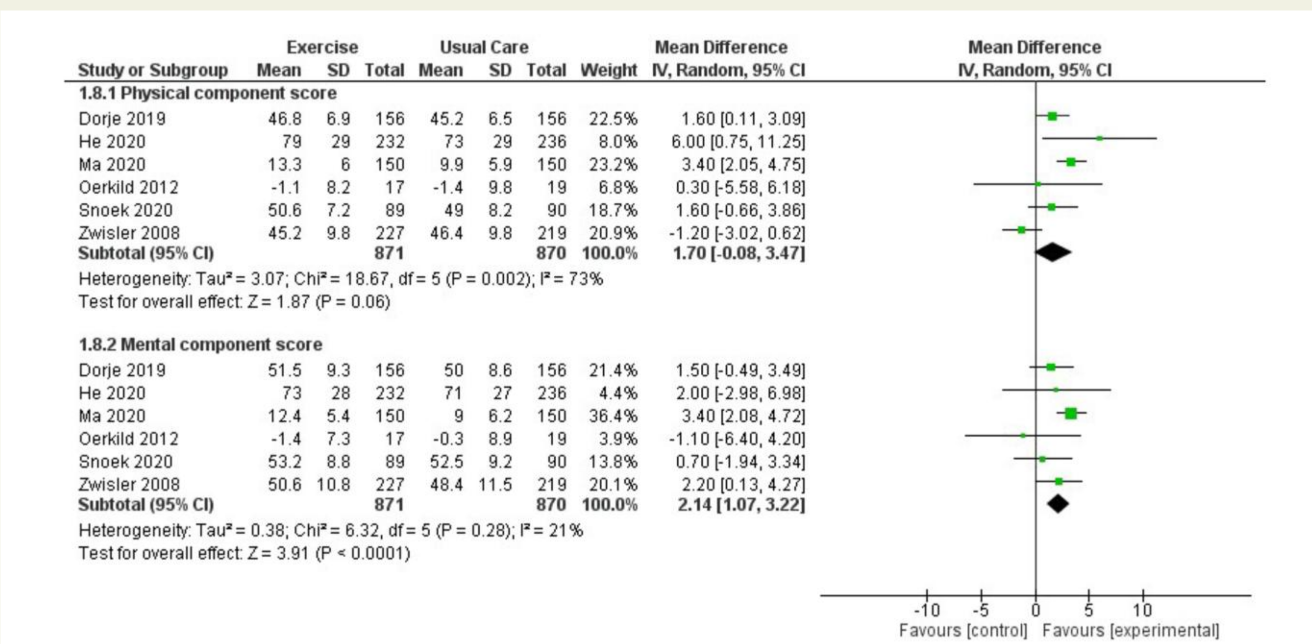


Figure 9 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (short-form-36 summary component scores).

methodologies. Second, this update sought to combine evidence across a range of CHD indications and studies that employed exercise-based CR interventions with varying doses of exercise, delivery settings, and durations of follow-up. However, we applied random-effect meta-analysis to take account of this potential clinical heterogeneity across studies. Furthermore, the GRADE assessment framework also

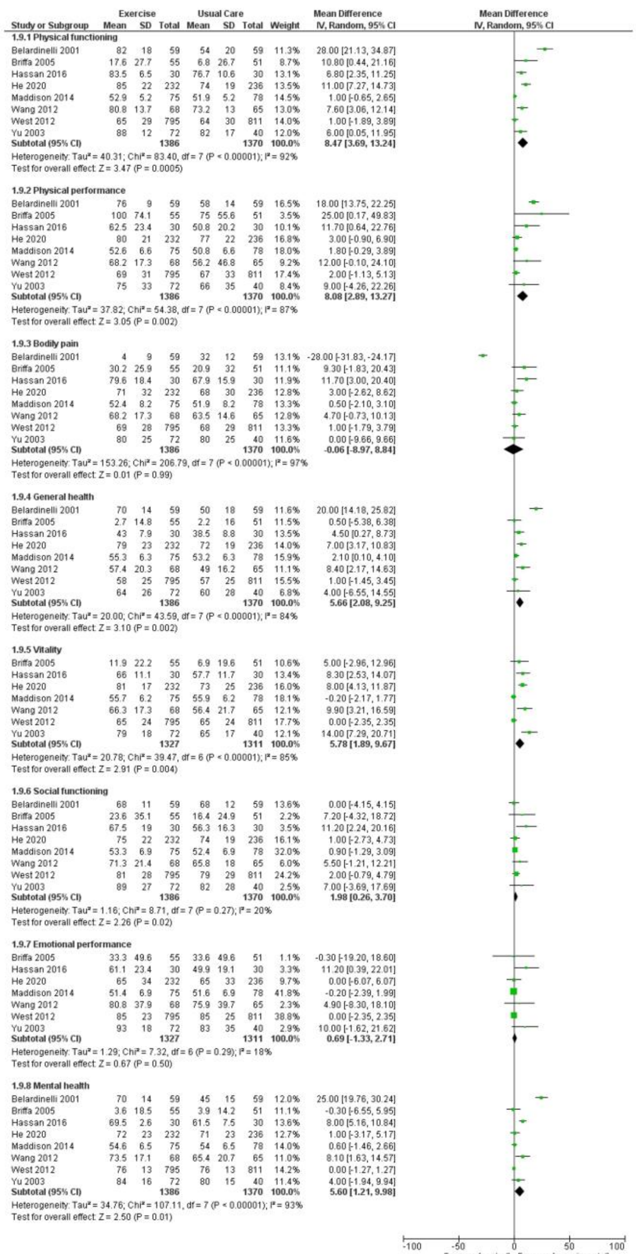


Figure 10 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (short-form-36 individual domain scores).

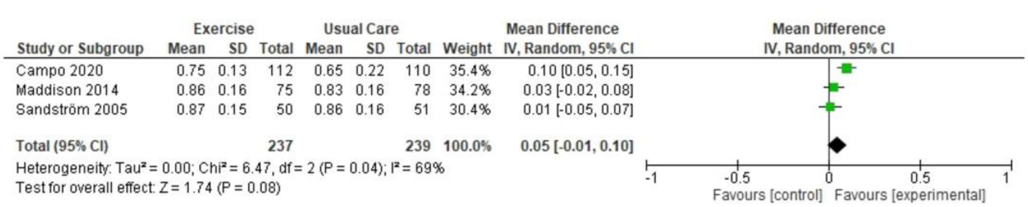


Figure 11 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (EQ-5D).

Table 3 Summary of costs of exercise-based rehabilitation and usual care

	Briffa (2005)	Hambrecht (2004)	Hautala (2017)	Kovoor (2006)/Hall (2002)	Maddison (2014)	Marchionni (2003)	Oldridge (1991/93)	Yu (2004)
Follow-up (months)	12	12	12	12	6	14	12	24
Year of costs (currency)	1998 ($AUD)	NR	NR (€; Euros)	1999 ($AUD)	NR (€; Euros)	2000 ($USD)	1991 ($USD)	2003 ($USD)
Cost of rehabilitation								
Mean cost/patient	$694	NR	€299	$394	€127	$5246	$670	NR
Costs considered	Details of costed elements not provided	NR	Estimated according to the average monthly fees in Finnish gyms where individual guidance in exercise training is led by a healthcare professional	staff, assessments, counselling, education, patient travel	NR	NR	space, equipment, staff, literature resources, operating costs, parking, patients costs	NR
Total healthcare costs								
Rehabilitation mean cost/patient	$4937	$3708 ± 156	€1944	NR	NR	$17 272	NR	$15 292
Usual care mean cost/patient	$4541	$6086 ± 370	€3027	NR	NR	$12 433	NR	$15 707
Absolute difference in mean cost/ patient	$395	−$2378*	−€1083	NR	NR	$4839	$480	−$415
P-value for cost difference	0.74	$P < 0.001$	NR	$P > 0.05$ (see below)	NR	NR	NR	$P > 0.05$
Additional healthcare costs considered	Hospitalizations, pharamaceuticals, tests, consultations, rehabilitation, patient expenses, ambulance	Rehospitalizations, revascularization, cycle ergometers, training facilities, and supervising staff	Primary healthcare costs, secondary healthcare costs, occupational healthcare service costs	Phone calls ($P = 0.10$); hospital admissions ($P = 0.11$); gated heart pool scan ($P = 0.50$); exercise stress test ($P = 0.72$); other diagnostics ($P = 0.37$); visits to general practitioner ($P = 0.61$), specialist doctor ($P = 0.35$), or healthcare professional ($P = 0.31$)	NR	NR	Service utilization, physician costs, emergency costs, in-patient days, allied health, other rehabilitation visits	Hospitalizations; revascularizations; private clinic visit; cardiac clinic visits; public non-cardiac visits; casualty visits; drugs
Cost-effectiveness								
Rehabilitation mean healthcare benefits	Utility-Based Quality of life–Heart questionnaire: 0.026 (95% CI, 0.013–0.039)	NR	Average change in 15D utility: 0.013	NR	NR	NR	NR	NR

Continued

Table 3 *Continued*

	Briffa (2005)	Hambrecht (2004)	Hautala (2017)	Kovoor (2006)/Hall (2002)	Maddison (2014)	Marchionni (2003)	Oldridge (1991/93)	Yu (2004)
Usual care mean healthcare benefit	Utility 0.010 (95% CI, −0.001 to 0.022)	NR	Average change in 15D utility: −0.012	NR	NR	NR	NR	NR
Incremental mean healthcare benefit	Utility 0.013 (95% CI, NR), $P = 0.38$;+0.009 QALY	NR	0.045 QALY (0.023–0.077)	NR	NR	NR	0.052 QALY (95% CI, 0.007–0.1)	0.06 QALY
Incremental cost-effectiveness ratio/patient	+$42 535 per QALY. Extensive sensitivity analyses reported	NR	−€24 511/QALY	NR	+€15 247 per QALY	NR	+$9200 per QALY	−$650 per QALY

*The healthcare costs within Hambrecht 2004 are reported with $, but currency not specified. NR, not reported; QALY, quality-adjusted life year.

considers heterogeneity in the evidence. For example, the outcomes all-cause mortality, CV mortality, PCI, and CV hospitalization were downgraded in GRADE due to wide CIs that crossed the boundary with no effect. Cardiovascular hospitalization was downgraded due to evidence of statistical heterogeneity (I^2 statistic >50%). Thirdly, while studies reported a prescribed dose of exercise, few, if any, reported the actual level of exercise undertaken by participants. So, we were not able to assess the impact of intervention adherence. Fourth, the number of trials reporting follow-up data beyond 12 months has decreased over the last decade, from 48% (between 2000 and 2009) to 23% (between 2010 and 2020). Consequently, the number of deaths and clinical events reported in several trials were low or zero, and these data were often reported within descriptions of trial loss to follow-up rather than as primary or secondary outcomes, which also means that trials would not have been powered for these outcomes. Additionally, hazard ratios were inconsistently reported across trials; therefore, no analyses using these data were possible. Finally, we also found evidence of reporting bias. For example, although 60 trials reported all-cause mortality, only 33 of these same trials reported CV mortality. Sensitivity analysis of the subgroup group of 16 trials that reported both mortality outcomes (see Supplementary material online, *Figures S8* and *S9*) showed improvements in both pooled overall (RR 0.85, 95% CI: 0.74–0.98) and CV mortality (RR 0.79, 95% CI: 0.68–0.92). This sensitivity analysis is in contrast with our main analysis, showing different effects of exercise-based CR on overall mortality and CV mortality.

Conclusions

The findings of this latest Cochrane review of 85 RCTs in 23 430 CHD patients confirm the clinical outcome benefits of reduced CV mortality, MI, and hospitalization with participation in exercise-based CR and also provide timely evidence that supports the generalizability of these benefits across patients, in the context of contemporary medical management, and across healthcare settings, including LMICs. This updated review also provides meta-analytic evidence that CR participation improves patient quality of life-based on validated HRQoL data. Our findings reinforce the need to improve access to CR for patients with CHD across the globe.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Acknowledgements

The authors thank Olga Utkina-Macaskill, Houra Haghpanahan, and Lili Wei (Institute of Health and Wellbeing, University of Glasgow) for their translation services. They also thank all the authors who provided additional information about their trials. Finally, the authors acknowledge the support of co-authors on the three previous versions of this review. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence [where permitted by UKRI, 'Open Government Licence' or 'Creative Commons Attribution No-derivatives' (CC BY-ND) licence may be stated instead] to any Author Accepted Manuscript version arising.

Funding

This work was supported by the Medical Research Council [grant number MC_UU_00022/1] and the Scottish Government Chief Scientist Office [grant number SPHSU16].

Conflict of interest: N.O. declares being an author of a study that is eligible for inclusion in the work (funding source: European Society of Cardiology & European Association of Preventive Cardiology). D.R.T. declares being an author of a study that is eligible for inclusion in the work. A.D.Z. declares being an author of a study that is eligible for inclusion in the work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Erratum

https://doi.org/10.1093/eurheartj/ehac800

Online publish-ahead-of-print 26 December 2022

Erratum to: Saving two hearts at once: How the 2014 ESC Congress inspired a revolution in maternal health in Iraq

This is an erratum to: Judith Ozkan, Saving two hearts at once: How the 2014 ESC Congress inspired a revolution in maternal health in Iraq, *European Heart Journal*, Volume 43, Issue 15, 14 April 2022, Pages 1447–1449, https://doi.org/10.1093/eurheartj/ehab740

In the originally published version, a redundant question mark appeared at the end of the article title. This has been removed in the version available online and in the citation above.