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META-ANALYSIS
Ischaemic heart disease

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

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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

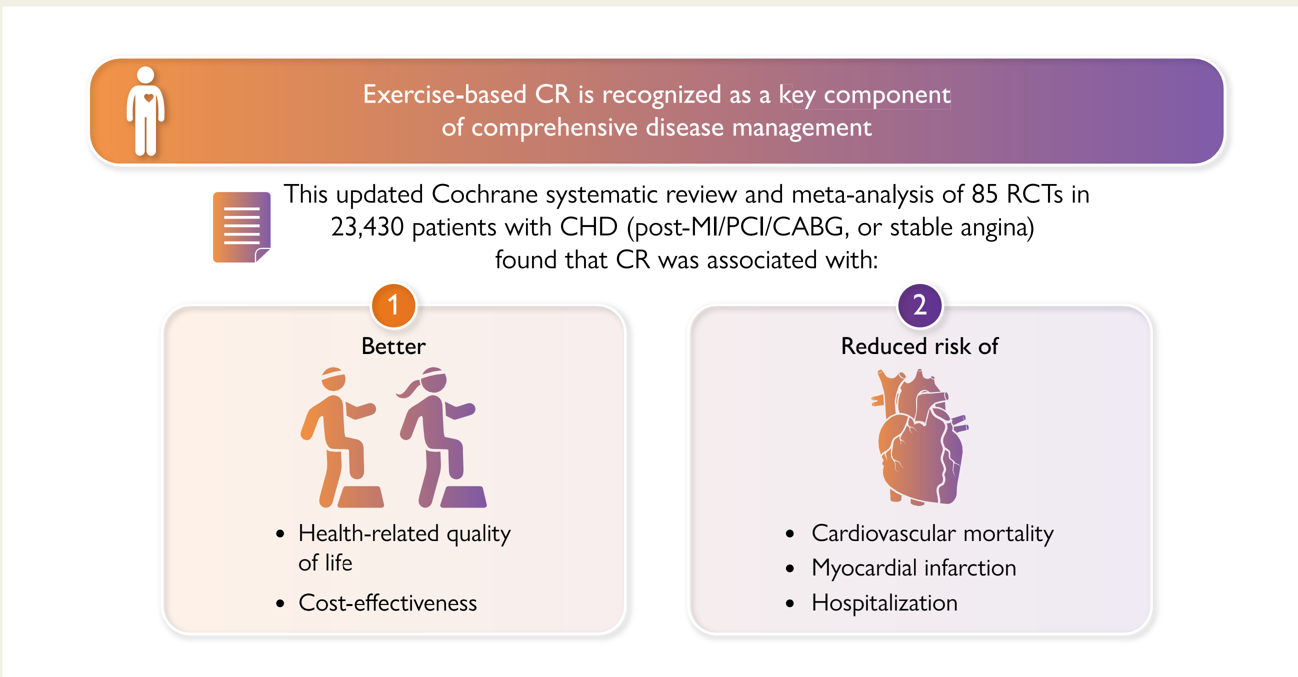
Compared to no exercise control, what are the clinical benefits of exercise-based cardiac rehabilitation (CR) for patients with coronary heart disease (CHD)?

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

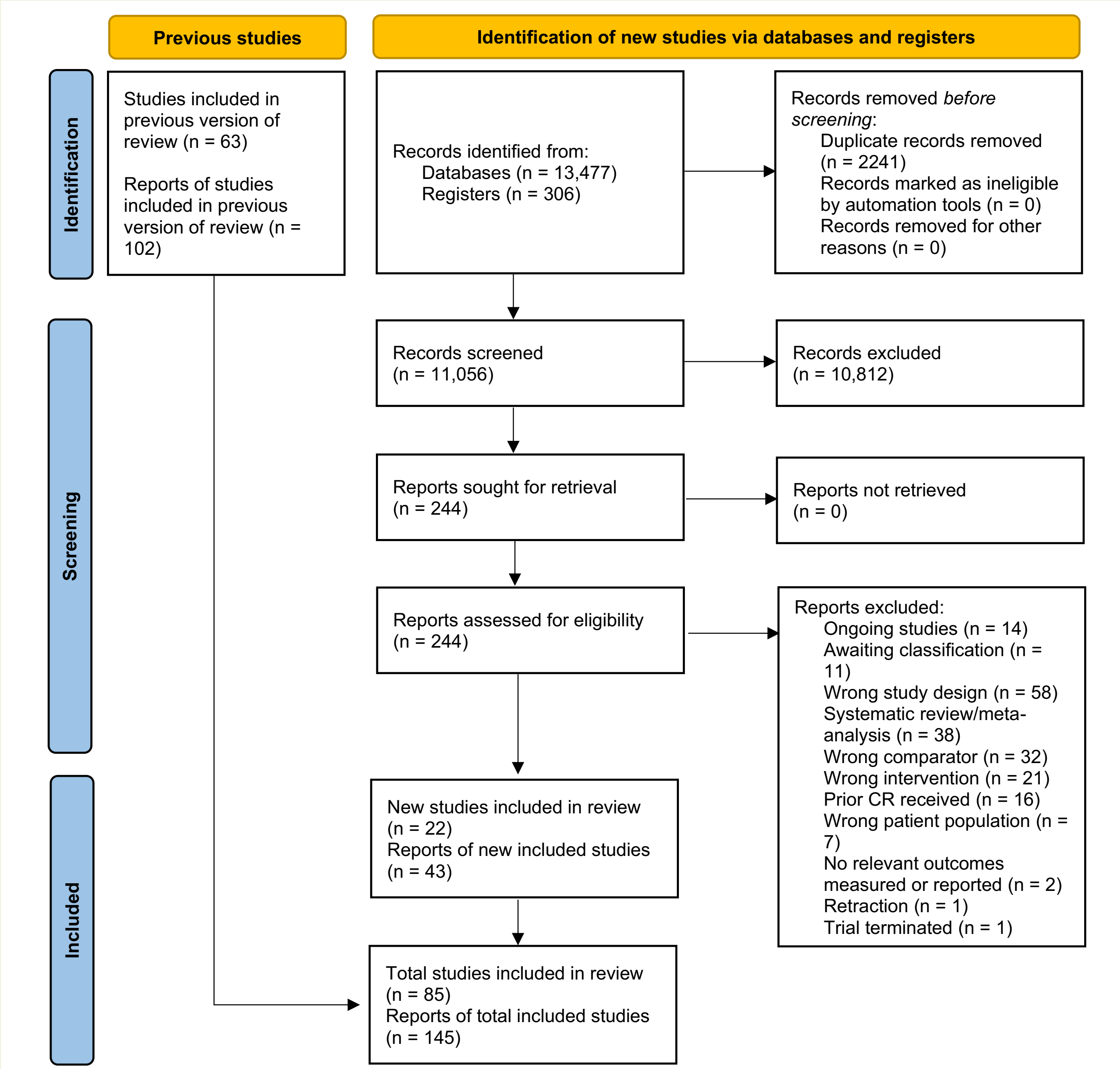


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection process.

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

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		RR (95% CI)	Statistical heterogeneity I^2 statistic χ^2test	GRADE assessment of certainty
			Intervention	Comparator			
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.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

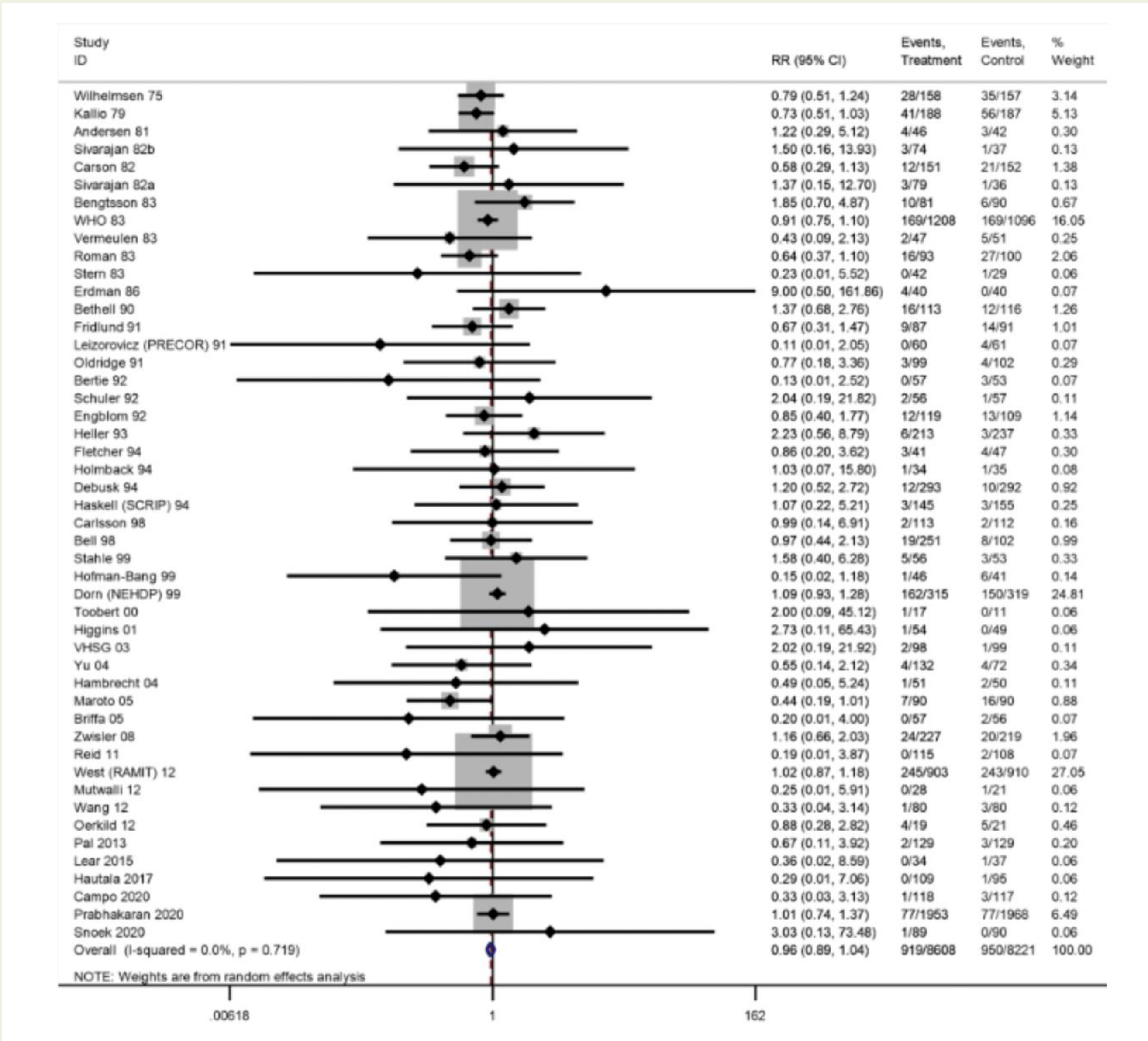


Figure 2 Forest plot: exercise-based cardiac rehabilitation vs. control for overall mortality.

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

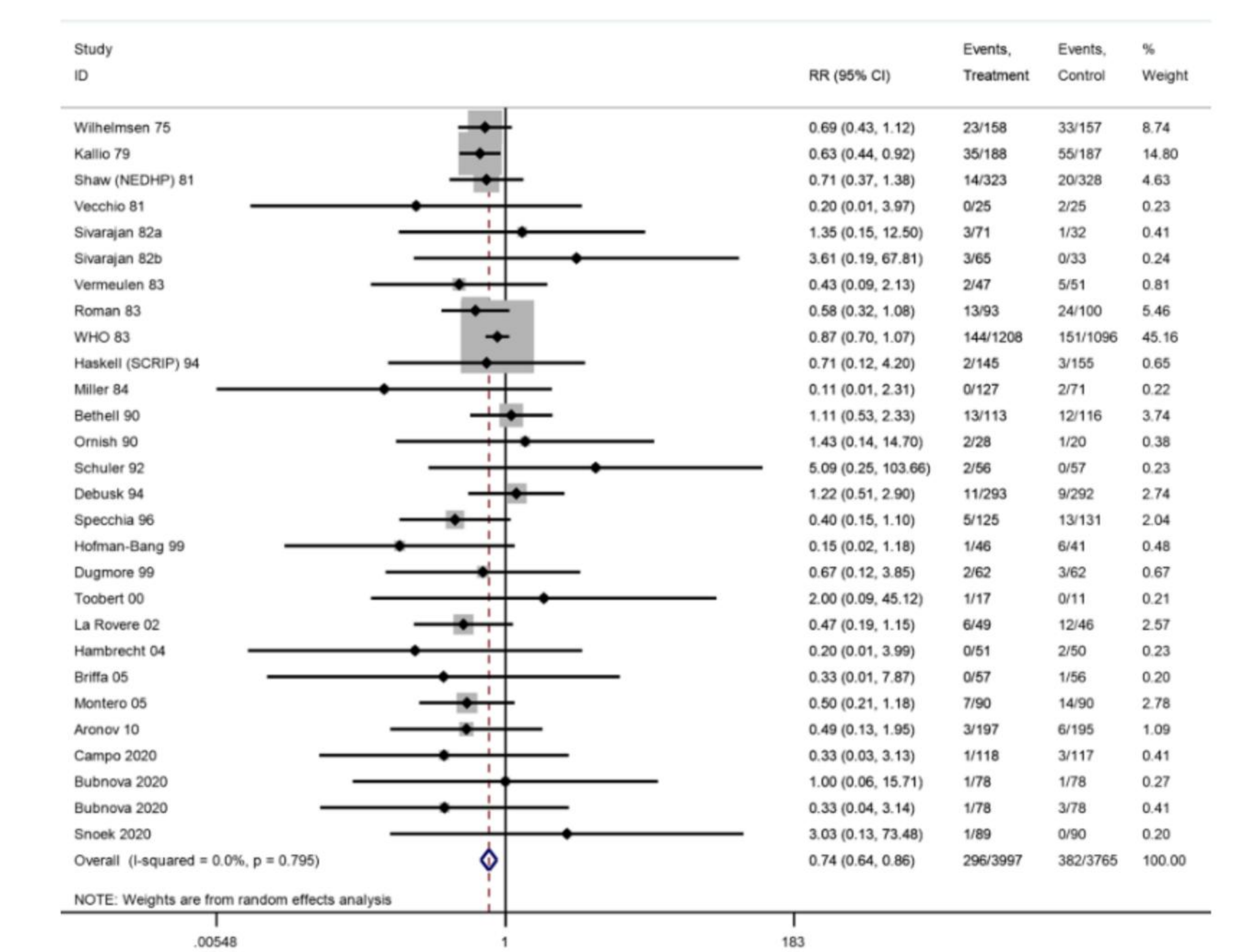


Figure 3 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular mortality.

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

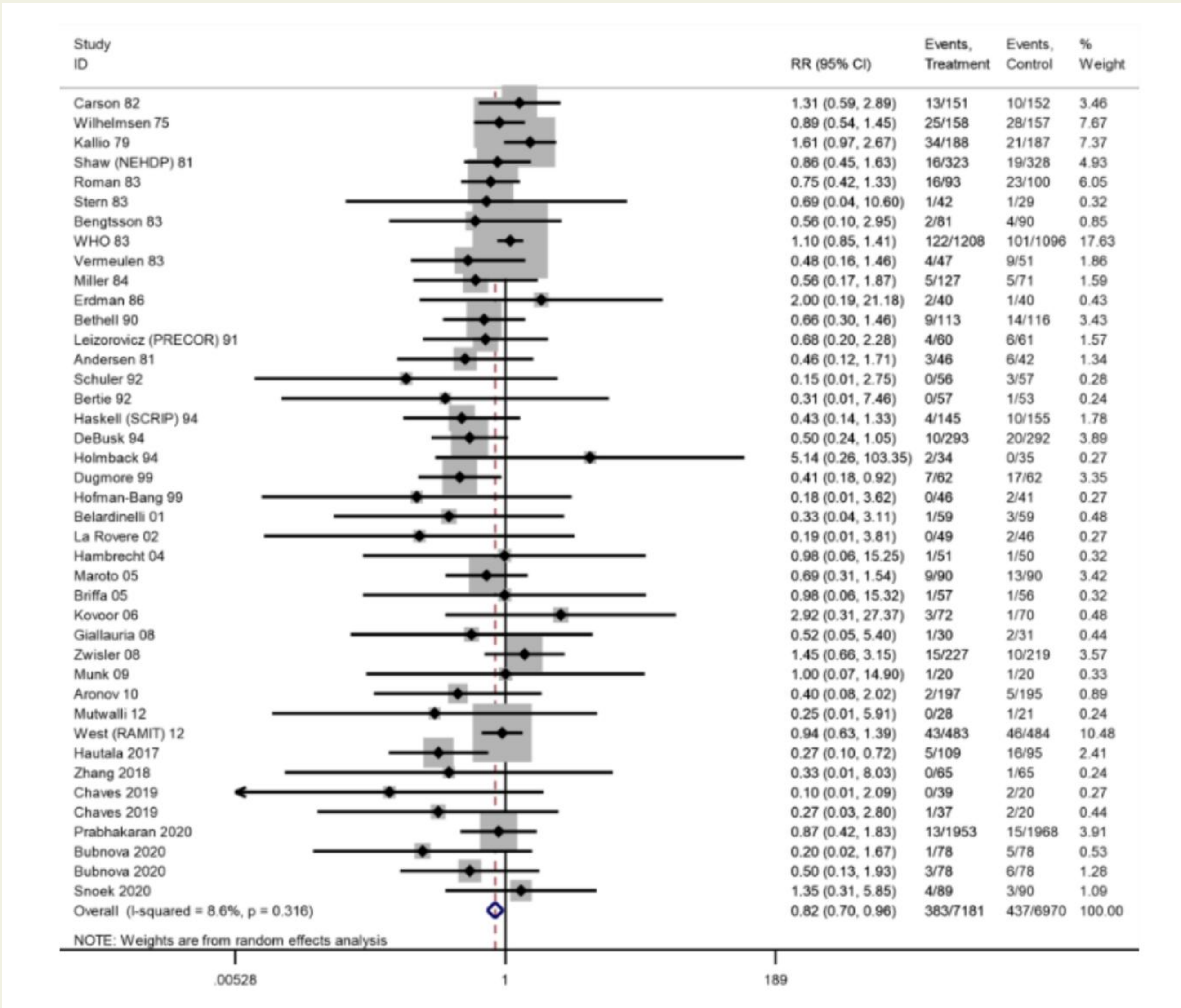


Figure 4 Forest plot: exercise-based cardiac rehabilitation vs. control for myocardial infarction.

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.

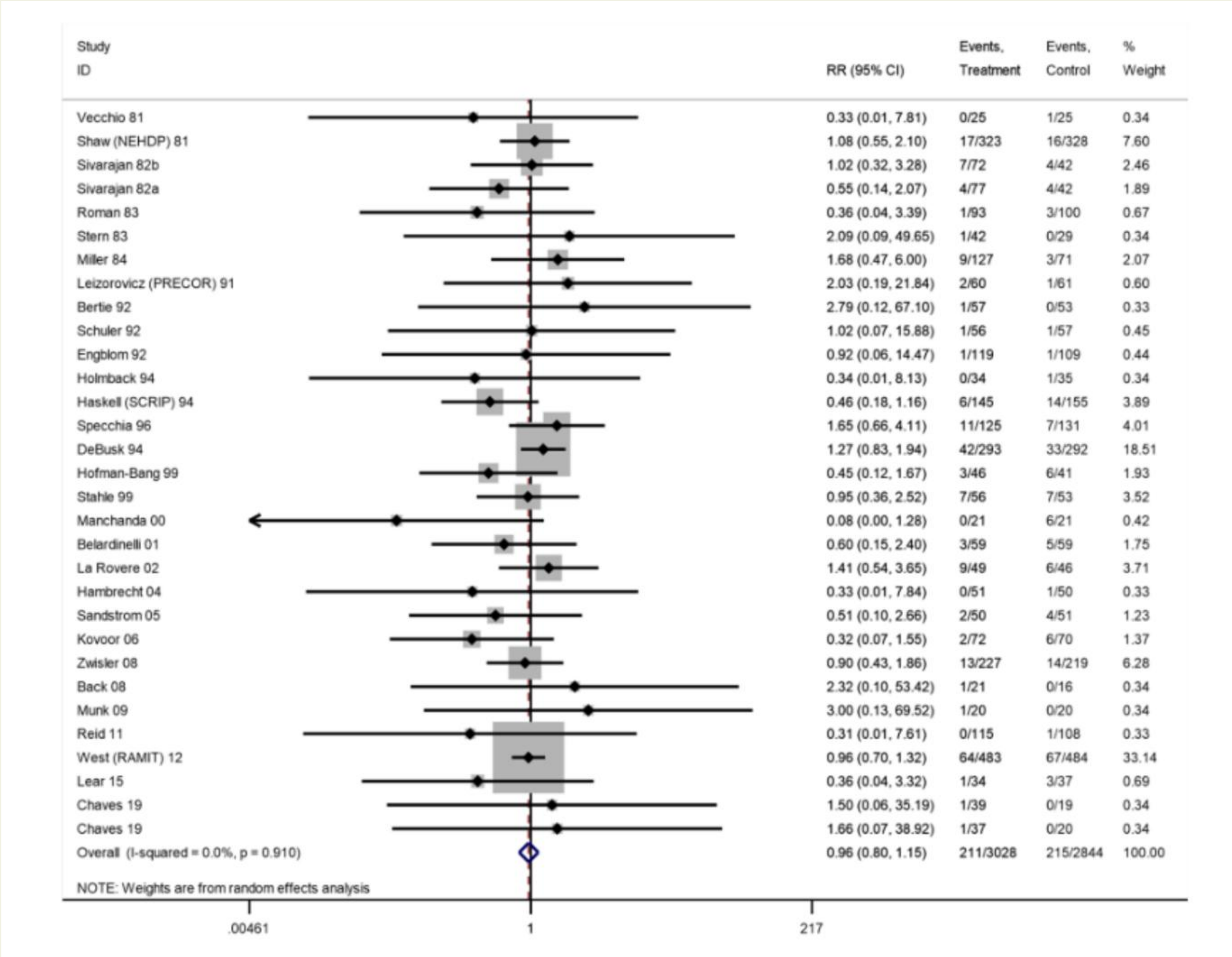


Figure 5 Forest plot: exercise-based cardiac rehabilitation vs. control for coronary artery bypass graft.

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

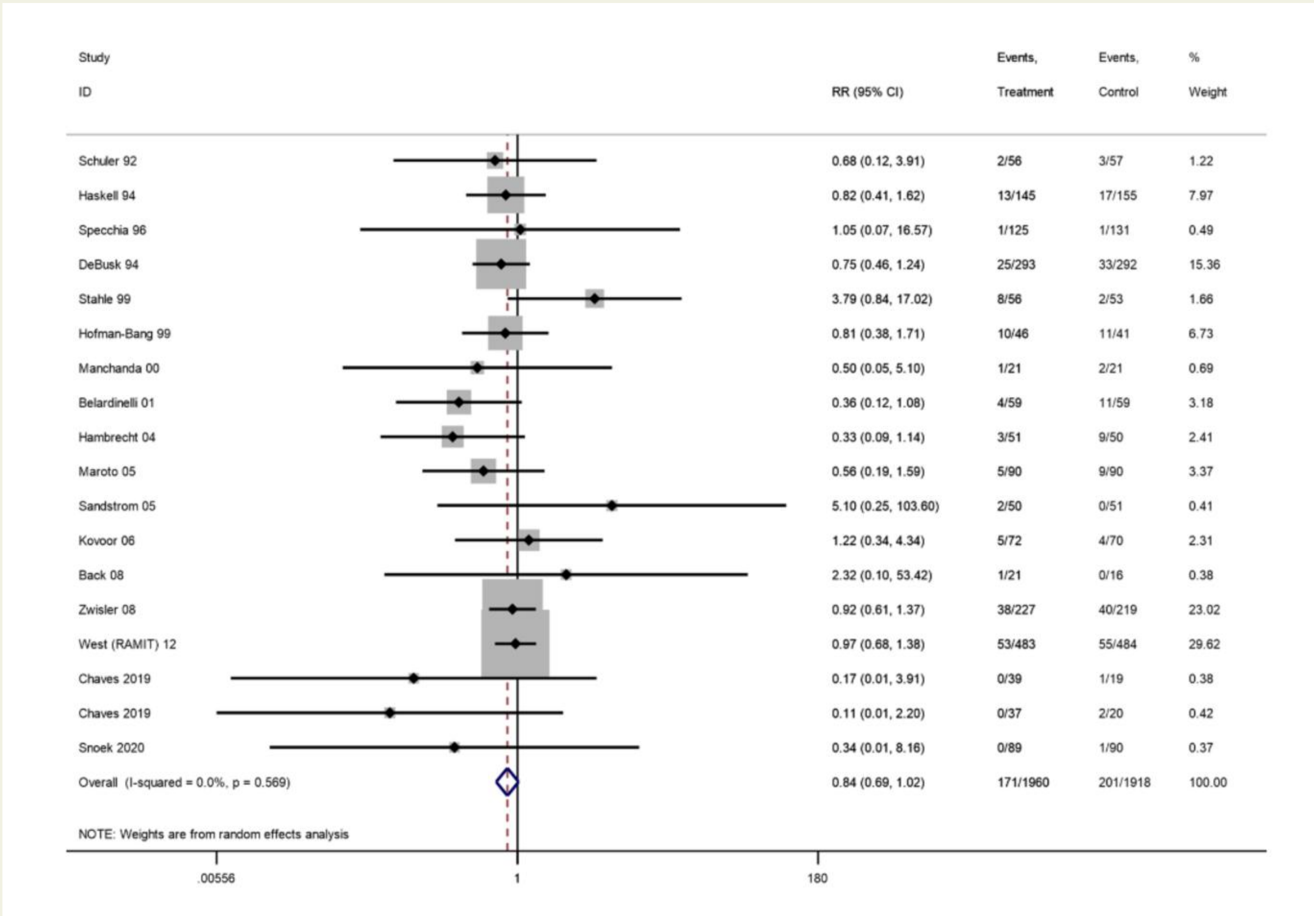


Figure 6 Forest plot: exercise-based cardiac rehabilitation vs. control for percutaneous coronary intervention.

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

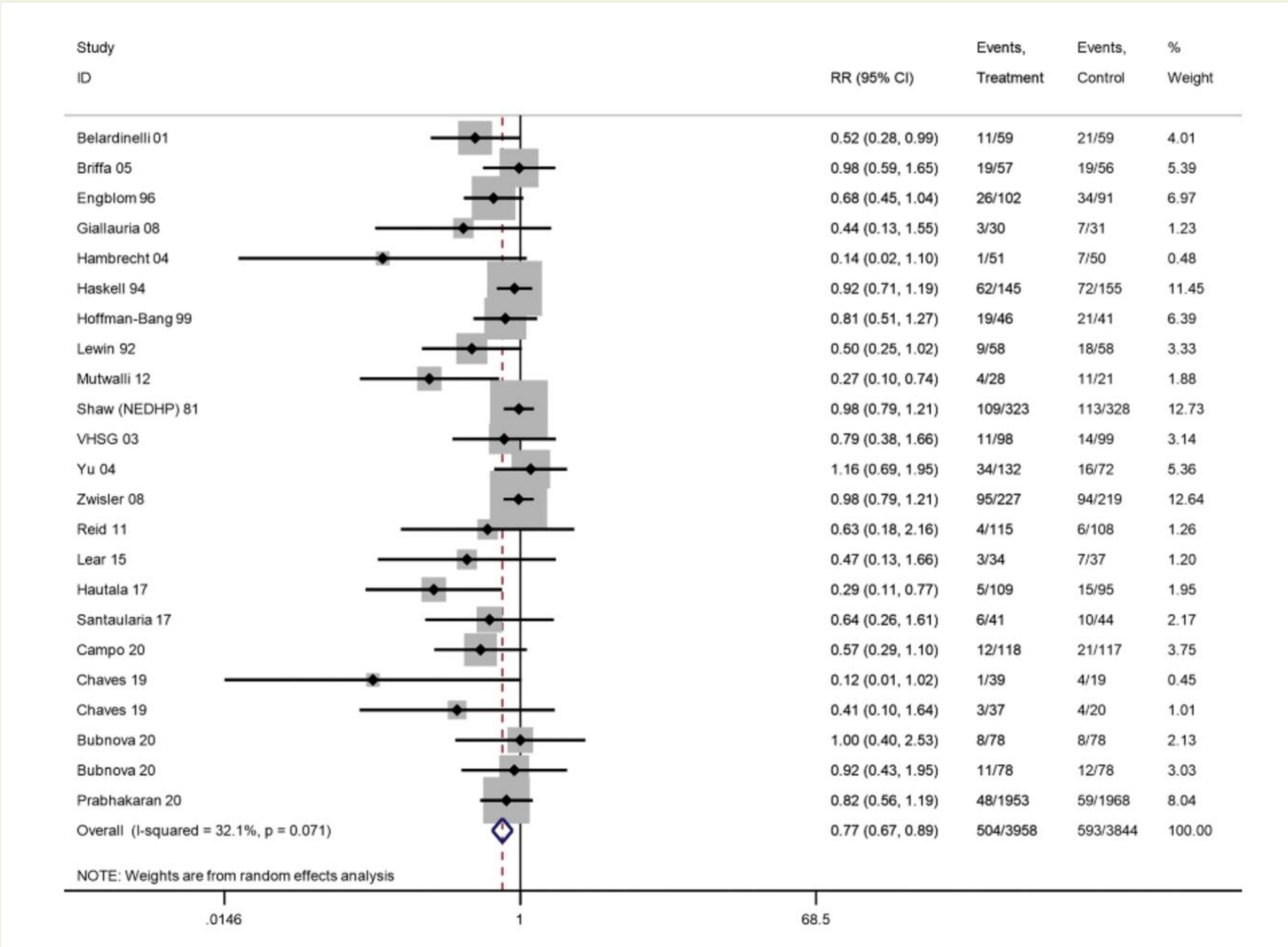


Figure 7 Forest plot: exercise-based cardiac rehabilitation vs. control for overall hospitalization.

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

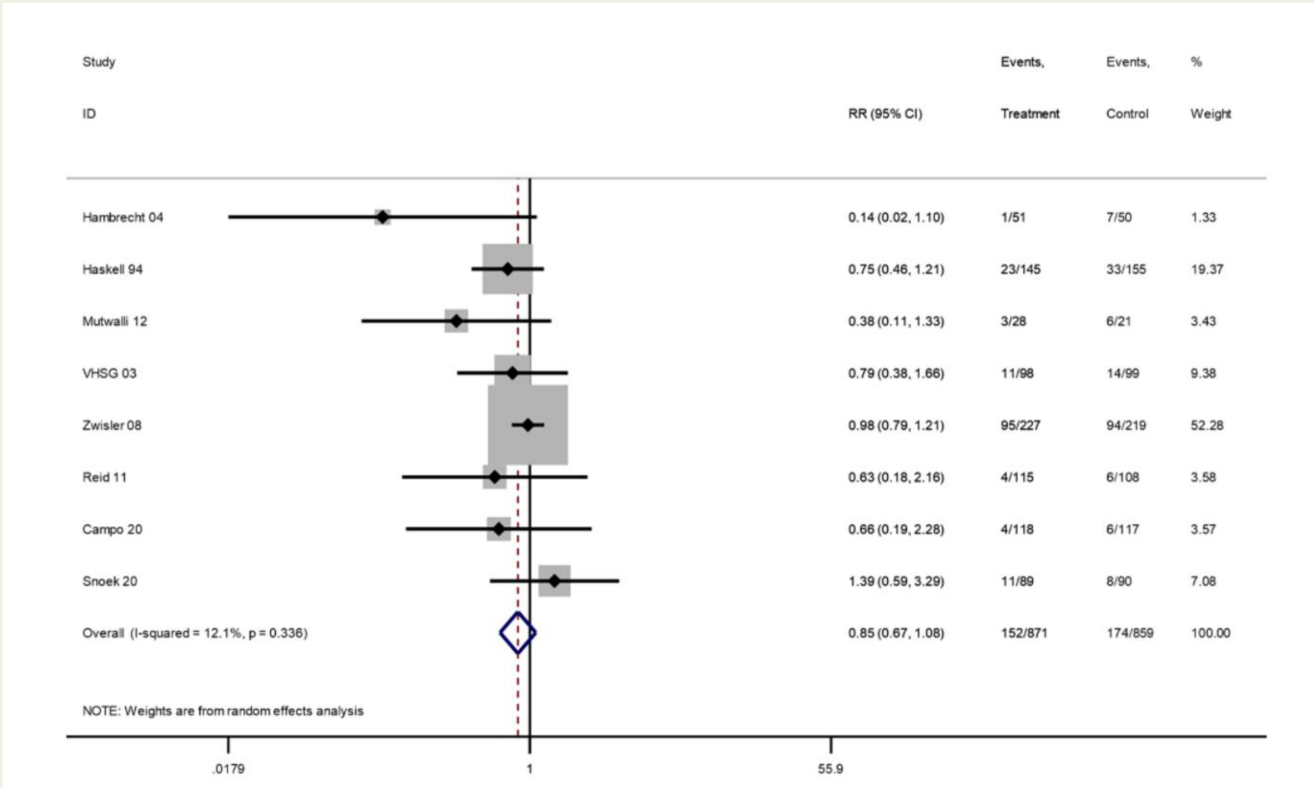


Figure 8 Forest plot: exercise-based cardiac rehabilitation vs. control for cardiovascular hospitalization.

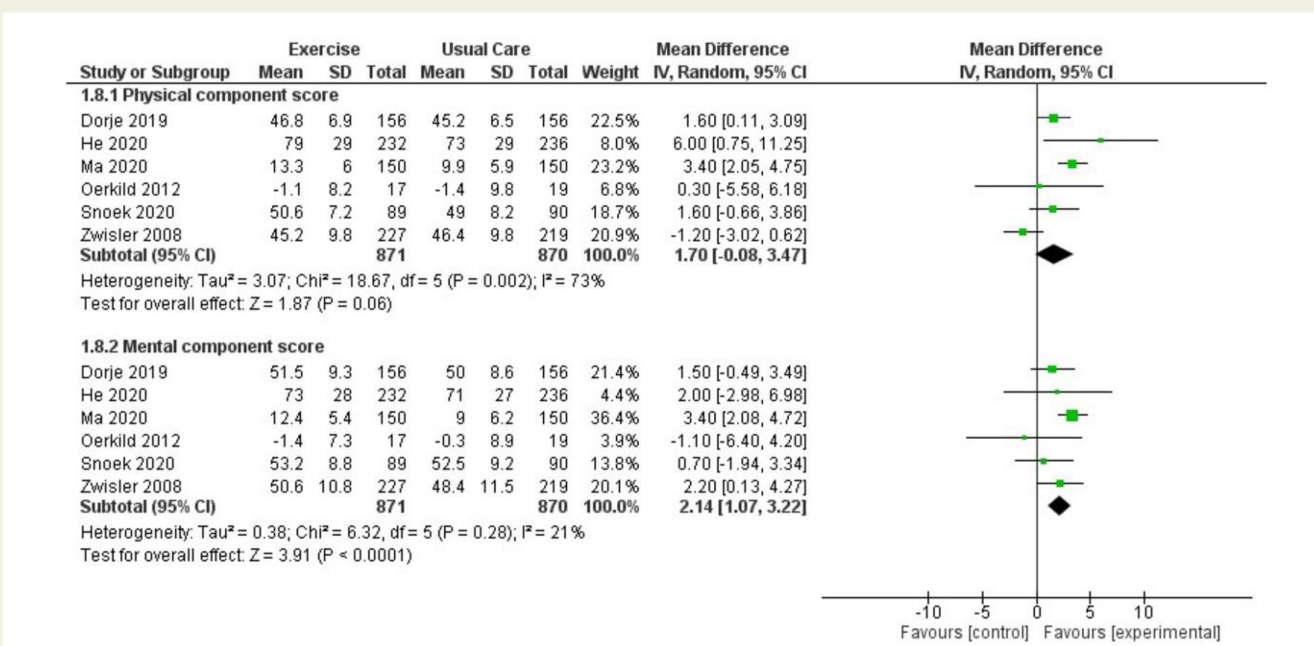


Figure 9 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (short-form-36 summary component scores).

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

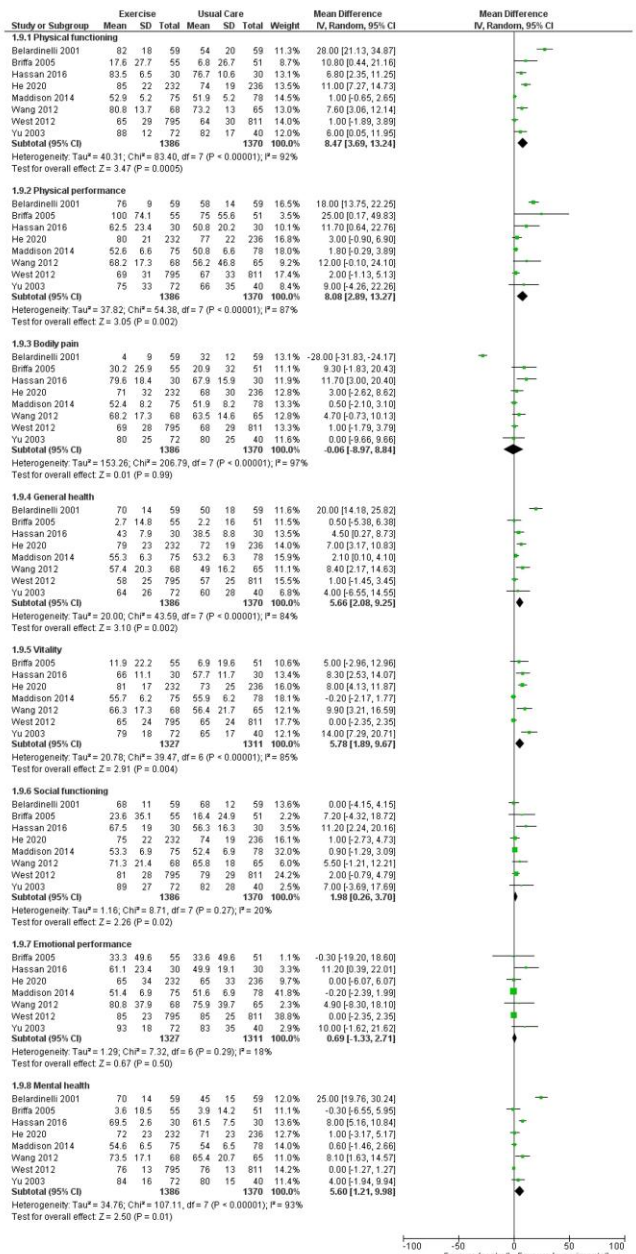


Figure 10 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (short-form-36 individual domain scores).

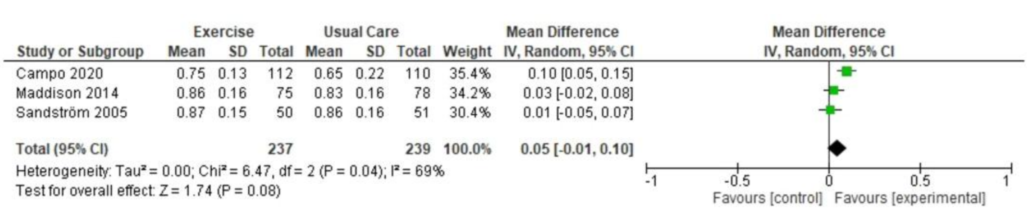


Figure 11 Forest plot: exercise-based cardiac rehabilitation vs. control for health-related quality of life (EQ-5D).

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.

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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

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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.

ESC European Society of Cardiology

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元分析

缺血性心脏病

冠心病以运动为基础的心脏康复:一项荟萃分析

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2022年4月26日;2022年10月31日修订;已接受2022年11月30日

请参阅这篇文章的社论评论:“心脏康复提供健康益处和减少事件的证据是无可争辩的:为政策行动提供时间”，作者s.l. Grace, https://doi.org/10.1093/eurheartj/ehac690。

摘要

目标 在全球范围内，冠心病是转诊到以运动为基础的心脏康复(CR)的最常见原因。然而，以前的随机对照试验(rct)荟萃分析的可泛化性受到质疑。因此，进行了一项当代更新的元分析。

方法以及结果 截至2020年9月，研究人员对数据库和试验注册进行了检索，寻找以运动为基础且随访时间≥6个月的干预措施的随机对照试验(rct)，与无运动对照的心肌梗死、心绞痛或后续患者进行比较冠状动脉搭桥术，或经皮冠状动脉介入治疗。采用随机效应荟萃分析对死亡率、复发临床事件和健康相关生活质量(HRQoL)的结果进行汇总，并对成本-效果数据进行叙述综合。使用元回归来检验效果修正。使用Cochrane偏倚风险工具评估研究质量。共纳入85项随机对照试验，涉及23430名参与者，中位随访12个月。总的来说，基于运动的CR与心血管死亡率的显著风险降低相关[风险比(RR): 0.74, 95%可信区间(CI): 0.64-0.86，治疗次数(NNT): 37]，住院次数(RR: 0.77, 95% CI: 0.67-0.89, NNT: 37)和心肌梗死(RR: 0.82, 95% CI: 0.70-0.96, NNT: 100)。有证据表明参与CR可显著改善HRQoL，且CR具有成本效益。对总死亡率(RR: 0.96, 95% CI: 0.89-1.04)、冠状动脉旁路移植术(RR: 0.96, 95% CI: 0.80-1.15)和经皮冠状动脉介入治疗(RR: 0.84, 95% CI: 0.69-1.02)没有显著影响。在不同的患者中，效果没有显著差异组，CR交付模式，剂量，随访，或偏倚风险。

结论 这篇综述证实了被轻蔑的冠心病患者参与以运动为基础的CR多样化的医疗管理可降低心血管死亡率、心脏再发事件和住院率，并提供额外的证据支持HRQoL的改善和CR的成本效益。

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结构化图形摘要

关键问题

心脏病? ...rcise control, what are the clinical benefits of exercise-based cardiac rehabilitation (CR) for patients with coronary

关键发现

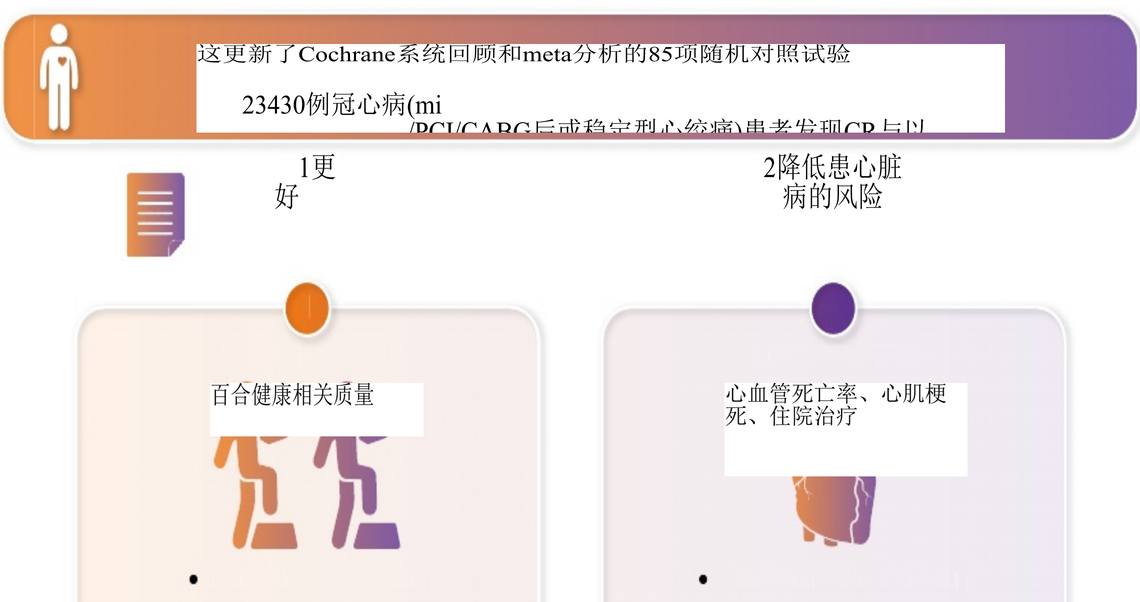
在这项对23430名冠心病患者的85项随机对照试验的荟萃分析中，基于运动的CR降低了心血管疾病的风险

...ic events, and hospitalizations, improved health-related quality of life and was cost-effective.

带回家的信息

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.

以运动为基础的CR被认为是全面综合疾病管理的重要组成部分



以运动为基础的CR被认为是全面疾病管理的一个关键组成部分。CABG，冠状动脉搭桥术;CHD，冠心病;MI，心肌梗死;PCI，经皮冠状动脉介入治疗;rct，随机对照试验。

关键词冠心

简介

冠心病(CHD)是全球最常见的死因。[1,2]
随着冠心病患者寿命的延长，提供有效的保健服务对冠心病的治疗至关重要。基于运动的心脏康复(CR)被公认为全面冠心病管理的关键组成部分，是国际指南中的一级a级推荐。[3,4]

尽管随机对照试验(rct)的荟萃分析已经显示CR对冠心病患者的有益效果，[5–7]
这一证据基础受到质疑的理由是:(1)对死亡率的影响不确定;(ⅱ)缺乏与健康有关的生活质量数据;(iii)纳入限制于低风险患者的随机对照试验(4)缺乏在现代冠心病治疗时代进行的试验。[7–9]

为了解决这些不确定性，我们对最新的Cochrane系统回顾和随机对照试验的meta分析进行了评估，以评估基于运动的CR对冠心病患者的死亡率、临床事件、HRQoL和成本效益的影响。我们还寻求探讨干预效果是否因患者病例组合、研究和干预特点以及CR交付设置而不同。

方法

我们根据《Cochrane介入评价手册》和《首选手册》进行并报道了本荟萃分析

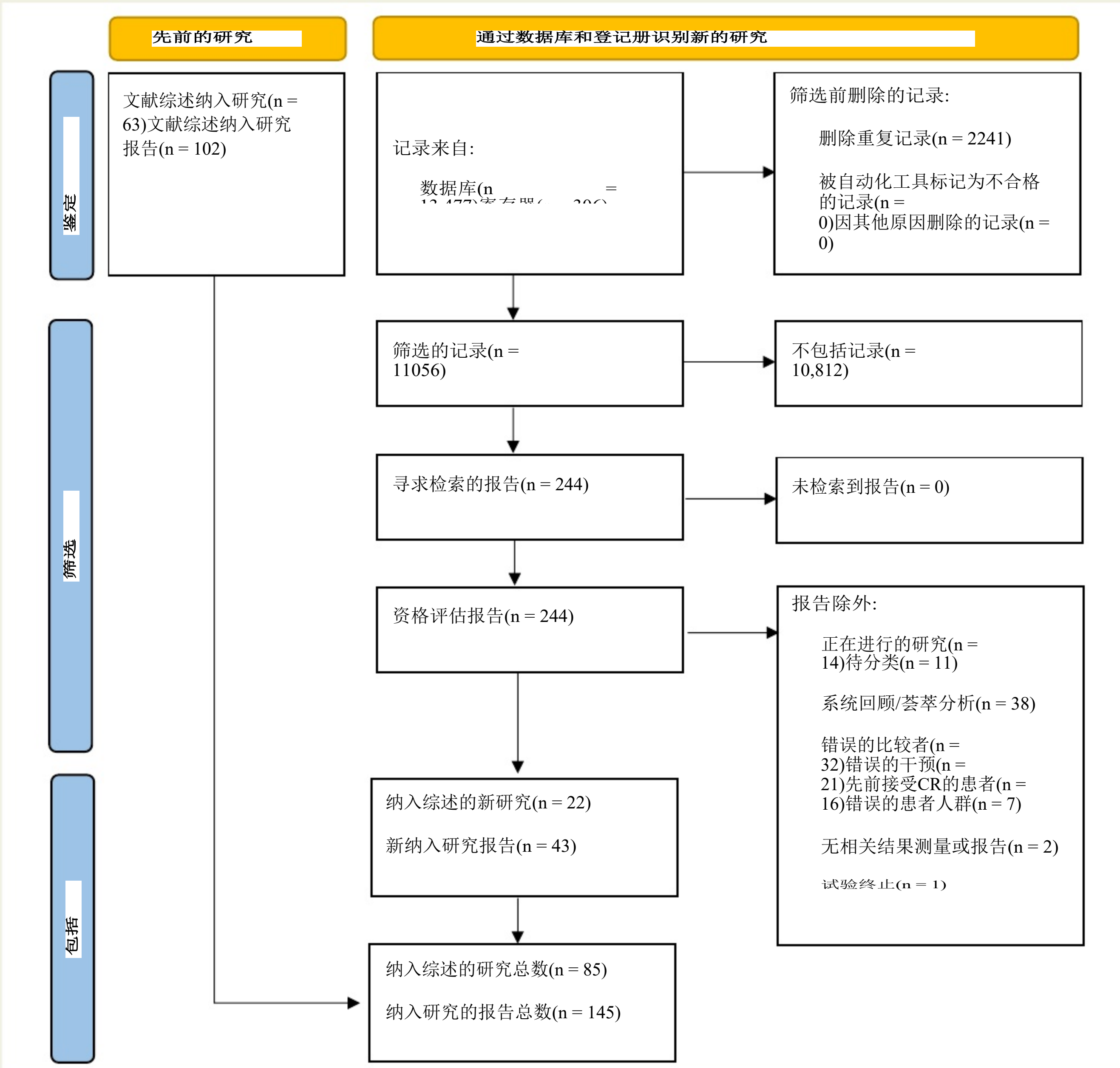


图1系统回顾和meta分析的首选报告项目研究选择过程流程图。

分别为系统评价和元分析的报告项目和不含元分析报表的综合报告项目。[10–12]

搜索策略和研究选择

我们对Cochrane中央对照试验登记(Central)、MEDLINE、Embase、CINAHL和2014年6月(Cochrane 2016综述的搜索结束日期)以来的科学引文索引进行了更新文献检索[5])至2020年9月(策略见在线补充材料，文件S1)。我们还搜索了两个临床试验注册表(世界卫生组织的国际临床试验注册平台和ClinicalTrials.gov)，并手工搜索了检索文章和最近的系统综述的参考列表。从试验注册表搜索中收集的记录被用来识别数据库搜索中没有发现的试验，以及正在进行的研究。我们寻求基于运动的CR的随机对照试验(单独运动训练或结合心理社会训练或教育干预)与不运动或常规护理对照组进行比较，并进行至少6个月基线后随访结果测量。干预组和对照组的所有患者通常报告接受(当地或国家)指南推荐的医疗治疗。

两位审稿人(G.O.D.和J.F.)独立确认了试验的资格。如有必要，异议通过讨论或由第三个审查员(R.S.T.)解决。

患者群体

我们的研究对象包括医院或社区中≥18岁的成年人，有心肌梗死(MI)，接受过血管重建(冠状动脉搭桥术(CABG)或经皮冠状动脉介入治疗(PCI))，或有心绞痛或血管造影确定的冠状动脉疾病。

表1研究总结、人群、干预措施和比较国特征

研究数量(%)或研究平均值中位数(范围)	
出版年份	
1970 - 1992年	2 (2%)
1980-9	12 (14%)
1990 - 2009年	20 (24%)
2000-9	21 (25%)
2010-9	23 (27%)
2020年以后	7 (8%)
研究大陆	
欧洲，北美，亚洲	48 (56%) 13 (15%) 16 (19%)
澳大利亚及其他	5 (6%) 3 (4%)
lmic	21 (25%)
单中心	61 (72%)
样本量	137 (25-3959)
随访时间 几个月	12 (6-228)
人口特征	
仅限男性	21 (25%)
仅限女性	1 (1%)
包括男性和女性	61 (72%)
年龄，年龄	2 (2%)
	56 (44-77)
诊断	
仅心肌梗死后	40 (47%)
仅血管重建	14 (16%)
仅心绞痛	5 (6%)
混合冠心病人群	25 (29%)
	1 (1%)
干预特点	
干预类型	
单纯运动项目	38 (45%)
综合项目	47 (56%)
干预剂量	6个月(0.75-42)
频率	1-7次/周

继续

表1继续

研究数量(%)或研究平均值中位数(范围)	
长度	20 - 90分钟/次
强度	•50%-90%最大/峰值HR或HRR •50%-95% vo_2 马克斯 •Borg RPE 11-16
设置	
中心为本	40 (47%)
中心与家庭为本的组合	21 (25%)
	21 (25%)
	3 (3%)
通常/标准护理	50 (59%)
通常护理加“无运动”	24 (28%)
	8 (9%)
其他	3 (4%)

CHD，冠心病;HR:心率;HRR，心率储备;LMIC，低收入国家;RPE，感觉用力程度评分;vo_2最大，最大摄氧量。

[a] 2020年他招募了无阻塞性冠状动脉疾病的心肌梗死患者。

[b]

数据抽象和质量评估

两位审稿人(G.O.D.和J.F.)独立完成了数据提取并使用Cochrane偏倚风险(ROB)工具评估了研究质量，[13] 由第三个审查员(R.S.T.)检查。试验的评估基于随机序列生成、分配隐蔽、结果评估的盲法、不完整的结果数据和选择性报告。获得了研究方法(国家、设计、随访和设置)、参与者特征(数字随机化、年龄、性别、诊断和纳入/排除标准)、干预(运动模式、持续时间、频率、强度)和对照(描述，即通常护理、不运动)、结果、资金来源和显著作者利益冲突等信息。

结果和证据的确定性

临床事件结局包括整体和心血管(CV)死亡率、致命性和/或非致命性心肌梗死(有研究报告)、CABG、PCI、整体住院和心血管住院。其他结果包括HR QoL和CR成本，以及每个质量调整生命年(QALY)的成本效益。一位审查员(G.O.D.)使用“建议分级评估、发展和评估”(GRADE)来评估证据的确定性，[14,15] 并让另一位审查员(R.S.T.)检查。分级评估应用于6-12个月随访时的临床事件结局(总体和CV死亡率、致命性和/或非致命性MI、冠脉搭桥、PCI、总体住院和CV住院)，这是所有试验中报道最多的随访时间点。根据以下几个领域，证据从高确定性下降了一个级别:研究设计或执行的局限性(ROB)、结果的不一致性、证据的间断性、不精确性和发表偏倚。

表2基于运动的心脏康复对最长随访、短期随访(6-12个月)、中期随访(13-36个月)、长期随访(>36个月)临床事件结局的meta分析总结

结果	n	n	事件/参与者		RR (95% CI)	I2	评估
结果n n n事件/参与者RR (95% CI)统计级别随访时间参与者研究...干预比较器的I2评估							
点统计量x ²测试确定性...							
总死亡率							
最长随访	16 829	47	919/8608	950/8221	0.96 (0.89-1.04)	0%	
6-12个月	8823	25	228/4590	242/4233	0.87 (0.73-1.04)	35%	⊕⊕⊕⊖温和[a]
13-36月	11 073	16	467/5611	498/5462	0.90 (0.80-1.02)	0%	
>36个月	3828	11	476/1902	493/1926	0.91 (0.75-1.10)	35%	
CV死亡率							
最长随访时间	7762	26	296/3997	382/3765	0.74 (0.64-0.86)***	0%	
6-12个月		15	109/2799	114/2561	0.88 (0.68-1.14)	0%	⊕⊕⊕⊖温和[a]
13-36个月		5	199/1861	39/1753	0.77 (0.63 - 0.93)	5%	
1392年		8	56/690	100/702	0.58 (0.43-0.78)***	0%	
致命和/或非致命MI							
最长随访	14 151	39	383/7181	437/6970	0.82 (0.70-0.96)*	9%	
6-12个月	7423	22	140/3820	174/3603	0.72 (0.55-0.93)*	7%	⊕⊕⊕⊖温和[b]
13-36个月	9565	12	264/4830	237/4735	1.07 (0.91-1.27)	0%	
>36个月	1560	10	65/776	102/784	0.67 (0.50-0.90)**	0%	
cabg							
最长随访时间	5872	29	211/3028	215/2844	0.96 (0.80-1.15)	0%	
6-12个月	4473	20	125/2324	232/2149	0.99 (0.78-1.27)	0%	⊕⊕⊕High
13-36个月	2826	. 9	123/1413	126/1413	0.97 (0.77-1.23)	0%	
>36个月	675		19/333	29/342	0.66 (0.34-1.27)	18%	
pci							
最长随访时间	3878	17	171/1960	201/1918	0.84 (0.69-1.02)	0%	
6-12个月	1983年	13	91/1743	104/1722	0.86 (0.63-1.19)	7%	⊕⊕⊕⊖温和[a]
13-36个月		6	114/996	116/987	0.96 (0.69-1.35)	26%	
3 i don ' t know		3	28/281	37/286	0.76 (0.48-1.20)	0%	
全因住院							
最长随访时间	7802	21	504/3958	593/3844	0.77 (0.67-0.89)**	32%	
6-12个月	2030	14	130/1054	209/976	0.58 (0.43-0.77)***	42%*	⊕⊕⊕⊖温和[b]
13-36个月	5995	9	392/3017	417/2978	0.92 (0.82-1.03)	0%	
CV住院							
最长随访	1730	8	152/871	174/859	0.85 (0.67-1.08)	12%	
6 - 12月	1087	6	40/546	42/541	0.8 (0.41-1.59)	53%	⊕⊕⊖⊖低[a,c]
13-36月	943	3	129/470	141/473	0.92 (0.76-1.12)	0%	

CABG，冠状动脉搭桥术;CI，置信区间;CR，心脏康复;CV，心血管;MI，心肌梗死;PCI，经皮冠状动脉介入治疗;RR，风险比率

因不精确而被下调一级，且置信区间较大。由于发表偏倚的证据，降级一级。

c由于显著的异质性降低了一个等级。

$* p < 0.05$。

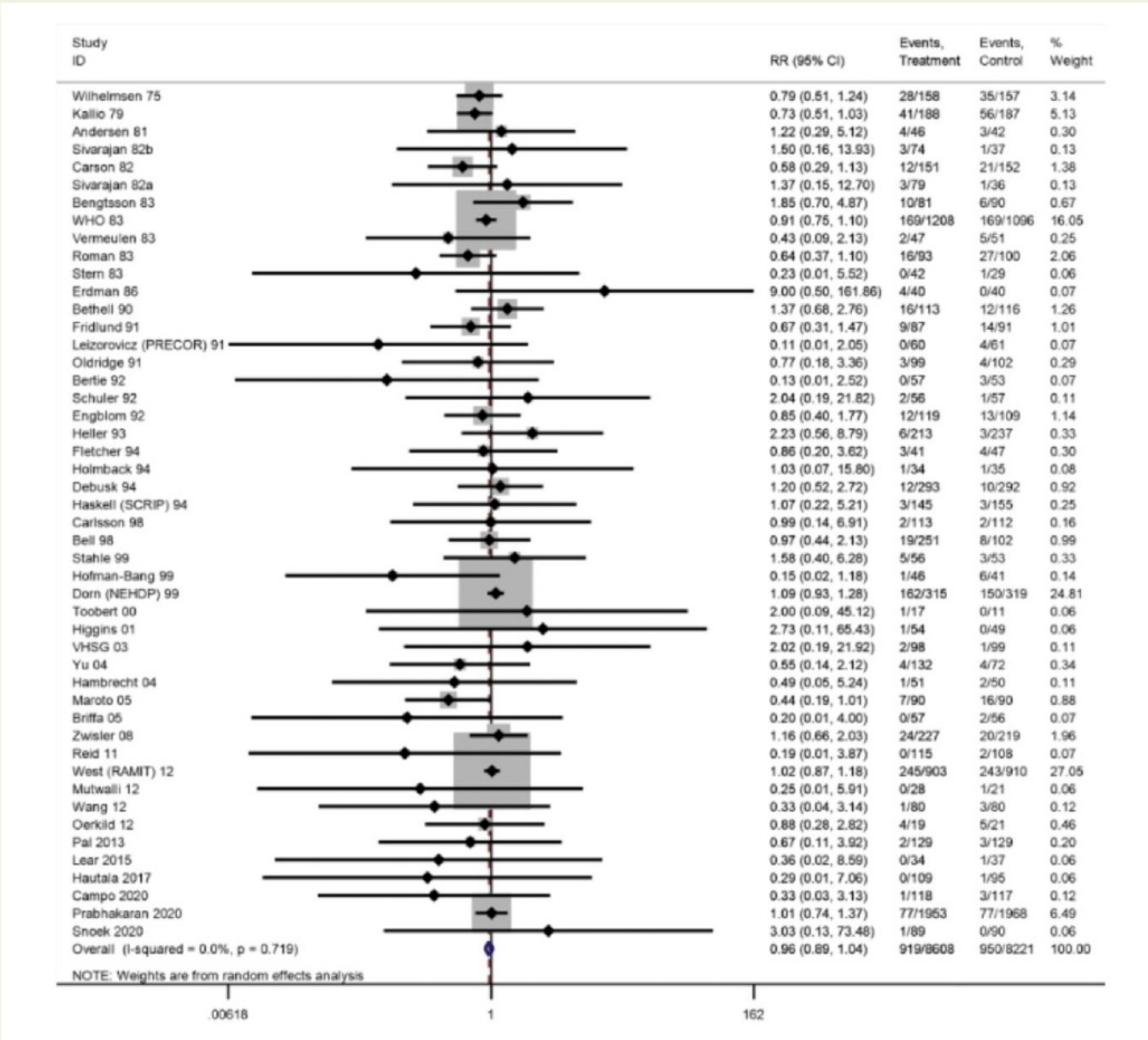


图2森林图:基于运动的心脏康复与对照组的总死亡率。

统计分析

结果数据汇总在最长随访时间和三个不同时间段:“短期”(6-12个月)、“中期”(13-36个月)和“长期”(>36个月)随访。鉴于临床异质性水平(CR干预和人群的差异)，我们有目的地采用了随机效应meta分析，使用DerSimonian和Laird随机效应meta分析方法，假设每个研究估计了不同的潜在干预效应。二分结局(总死亡率和CV死亡率、MI、CABG、PCI、全因住院率和CV住院率)表示为具有95%置信区间(ci)的风险比(RRs)。对于那些风险显著降低的临床事件结果，我们计算了需要治疗的额外有益结果(NNT)的数量。[16] 如果≥2个试验报告了相同的验证的HRQoL测量和域[即。Short-Form-36 (SF-36)，EuroQol-5D (EQ-5D))，连续结果按每个量表分别汇总，并报告为平均差异(MD)和95% CI。考虑到HRQoL结果测量和报告的异质性，为了全面，我们使用了投票计数方法来综合荟萃分析，其中阳性、阴性和非显著结果的数量被总结。成本-效果数据的综合叙述。统计异质性被认为是实质性的^2 统计数字是50%。对于纳入meta分析的试验≥10个的结果，我们使用漏斗图和Egger’s检验来检查小的研究偏倚。[17] 双侧p值<0.05认为有统计学意义。采用单变量随机效应meta回归来探讨异质性，并仅在临床事件结果中检查以下预定义的治疗效果修正因子:(i)病例组合(出现MI的患者百分比)，(ii)运动“剂量”[剂量(单位)=运动训练的周数×每周平均会话×每次会话的平均持续时间在min内]，(iii) CR类型(仅运动vs.综合CR)，(iv)随访时间长度(评估多个时间点的最长随访时间)，(v)发布年份，(vi)样本大小，(vii) CR设置(家庭或中心)，(viii) ROB(5个领域中低于3个领域)，(ix)研究大陆(欧洲，欧洲)(x)根据世界银行集团研究国家地位[中低收入国家(LMICs)或高收入国家][18]。给出了统计数字

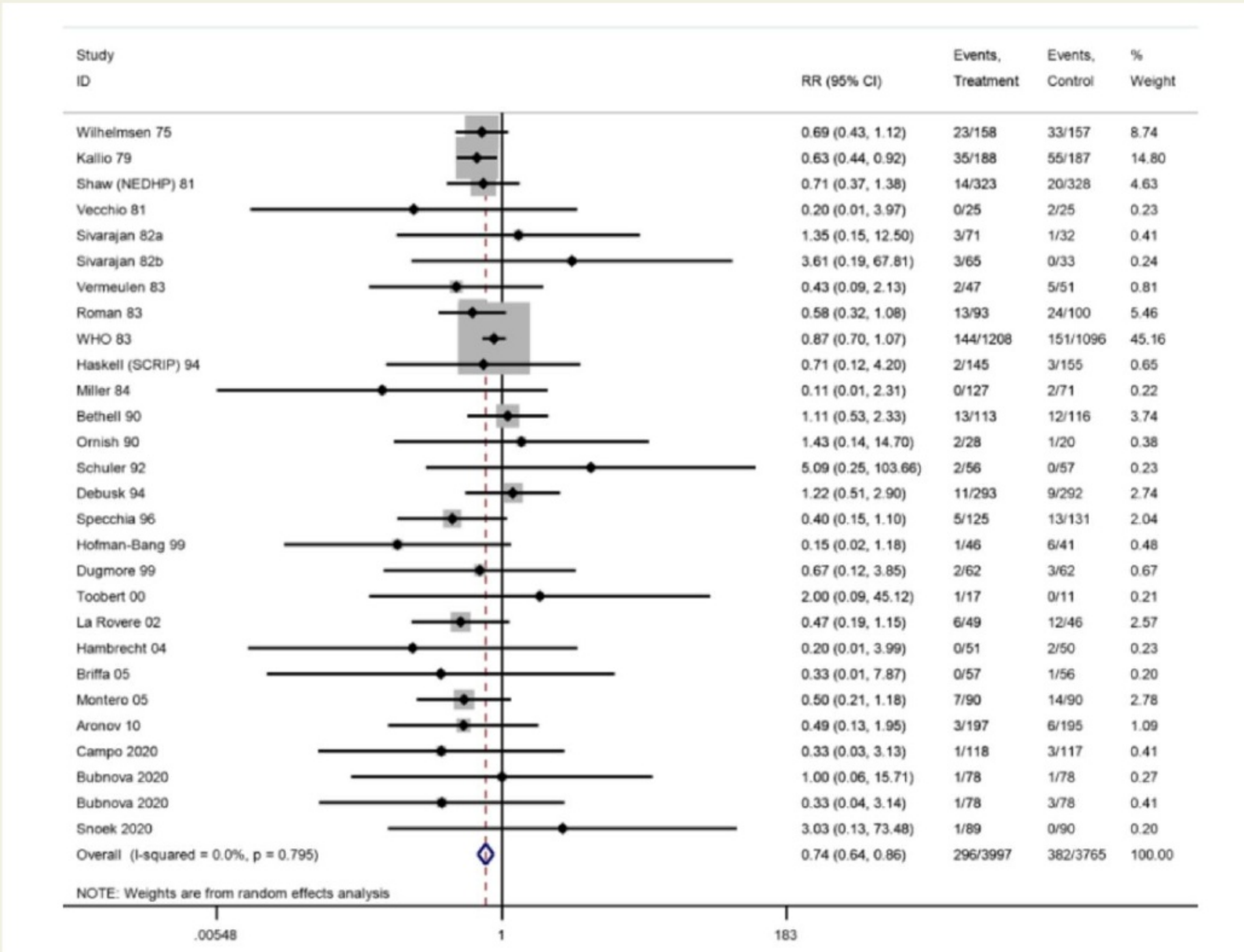


图3森林图:基于运动的心脏康复与对照组的心血管死亡率。

在本综述中进行的比较中，结果的解释主要是基于95%的CIs而不是p值。统计分析在RevMan Web版本3.12.1和STATA版本16.1中进行。

结果

研究的搜索和选择

图1总结了搜索选择过程。更新的数据库和试验注册表搜索结果总共有13 783次，其中11 056条唯一的记录被识别，其中244条被选中进行全文审查。排除的主要原因是研究设计(例如，非rct，随访<6个月)，或使用运动比较器。22项新的随机对照试验(7795名参与者;43种出版物)，[19–40] 该研究提供了85项随机对照试验(145篇论文，23430名参与者)的总证据基础，比较了基于运动的CR和不运动的冠心病患者对照组。[19–103] 新纳入试验的参与者约占本研究所有参与者的三分之一(33%)。被纳入研究的主要和相关补充参考文献的完整列表在在线补充材料中提供，文件S2。

表1对85项纳入研究的研究、参与者、干预和比较者特征进行了总结。

85项研究中79项(93%)是双臂平行rct，有4项研究比较了两个以上的手臂(两种类型的CR vs. control)，[21,24,32,89] 一项使用准随机化方法的研究，[38] 和一组RCT。[62] 确定的22项新试验中，有16项是在中低收入国家进行的，[19–21,24–26,28,30–34,37–40] 在中低收入国家共进行了21项随机对照试验。三个大型多中心试验共贡献了8956名参与者(约占总参与者的40%)。[34,98,99] 研究参与者的中位年龄为56岁，在过去十年中，试验中女性患者的比例从11%上升到17%。平均CR干预时间和试验随访时间分别为6个月和12个月。85项干预措施中有38项(45%)仅涉及运动、20 - 24、28、31-33、35、39-44、48、49、52、59、60、65、69、73、76、77、82-84、88-92、94,100项，47项(55%)涉及教育(20项试验)、25、26、29、34、37、38、51、53、55、57、61、62、70、78、85 - 87、97、101、102项社会心理(7项试验)，[36,46,58,72,74,80,95] 或两者的结合(16项试验)，19、30、45、50、63、64、66-68、71、75、93、96、98、99,103或其他成分(即控制饮食、危险因素管理、戒烟、放松;四次试验)。[27,47,79,81] 运动通常是有氧运动，在27%的试验(85例中的23例)中报告了包括抵抗训练在内的运动。22、27、28、30、35、39、41、43、44、46、47、50、54、65、69、77、83、86、89、90、100 - 102运动干预的剂量差异很大，频率为每周1 - 7次，活动时长为20 - 90分钟，强度为最大或峰值心脏的50% - 90%

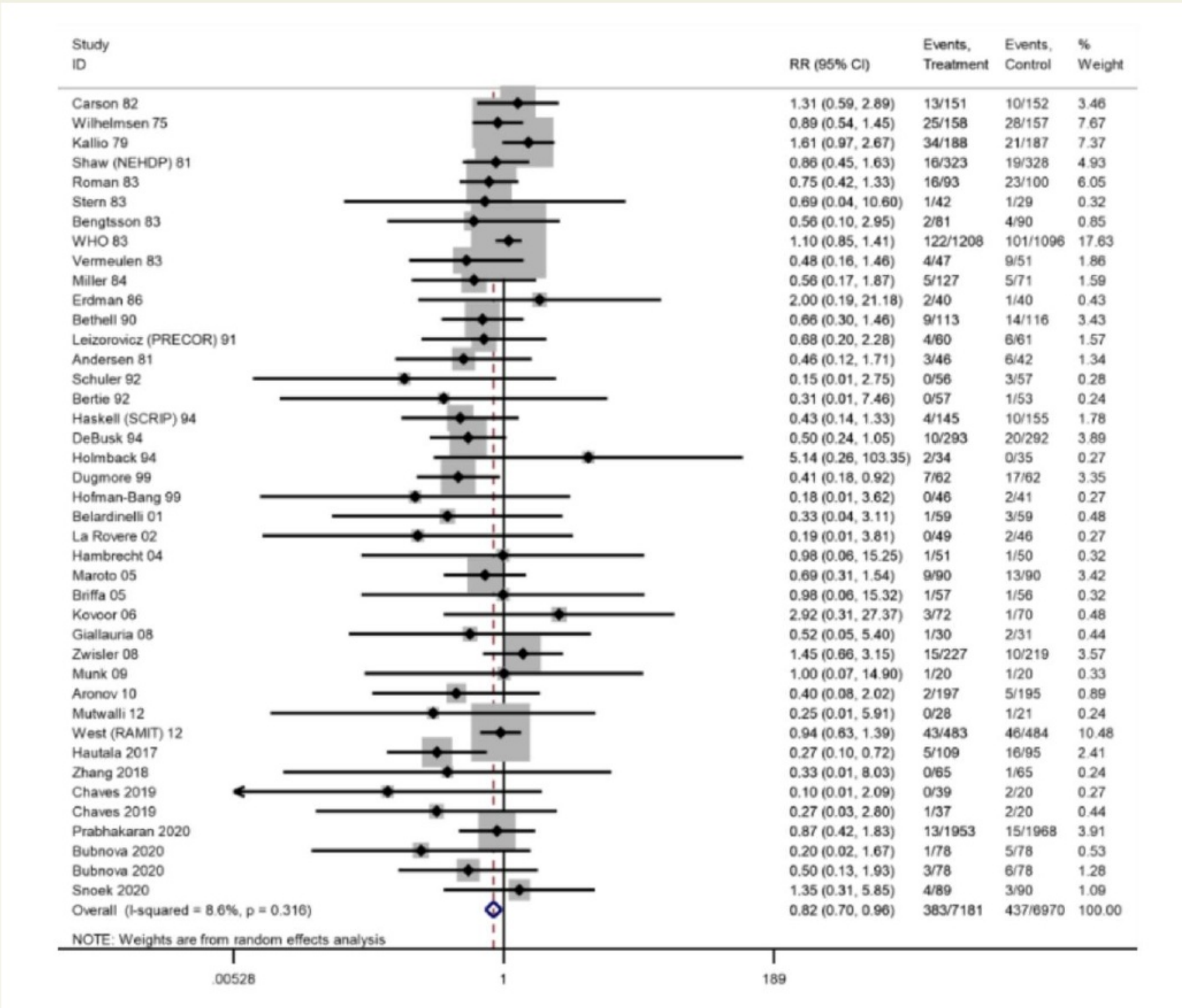


图4森林图:基于运动的心脏康复与心肌梗死对照组。

速率，50%-95%的有氧能力，或在11-16之间的感觉运动评分。在21个家庭锻炼项目中，25、29、30、36、38、43-45、53、57、61-63、66、71、72、76、78、79、82、97有4个是通过移动电话或互联网进行的。[25,29,72,82]

偏倚风险和GRADE评估

纳入试验的总体ROB被判定为低或不明确(见在线补充材料，图S1)，自2010年以来报告的质量有所提高(2010年前80%的研究有<3个low-ROB域，2010年后为55%)。30个试验(35%)报告了足够和适当的随机序列生成细节，21-25、28-32、34-37、41、45、48、50、56、60、61、65、66、72、77、79、82、97、100、103和23(27%)报告了适当的分配隐藏，[21–25,29–31、34、36、45、50、61、65、68、72、77、79、82、85、96、98、103]例(28%)报告了足够详细的结果评估盲法。[23–25,28,29,34–36,57,59,60,65,71–74,77,81,82,84,85,98,103]38项(44%)试验评估结果不完整，rob较低，[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]62例(73%)选择性报道rob较低。[19,23–25,29,34–36,40–68,70–72,74–78,80,82–89,91,92,94–99,101–103]

在短期随访中，对临床事件结果的GRADE评价从低到高(表2)，不精确(广泛ci)的降级，公开偏倚的证据，或显著的统计异质性。

结果

表2总结了所有四个随访时间点[最长随访，短期(6-12个月)，中期(13-36个月)，长期(>36个月)]的临床事件汇总。在短期(6-12个月)随访的临床事件结局中，证据确定性的等级评估从低确定性到高确定性不等。我们将总死亡率、CV死亡率、PCI和CV住院率降低了一个水平，因为较宽的ci重叠了边界，但没有效果。由于发表偏倚的证据，我们将心肌梗死和全因住院降低了一个水平。由于存在显著的异质性，我们将CV住院降低了一个额外的水平。

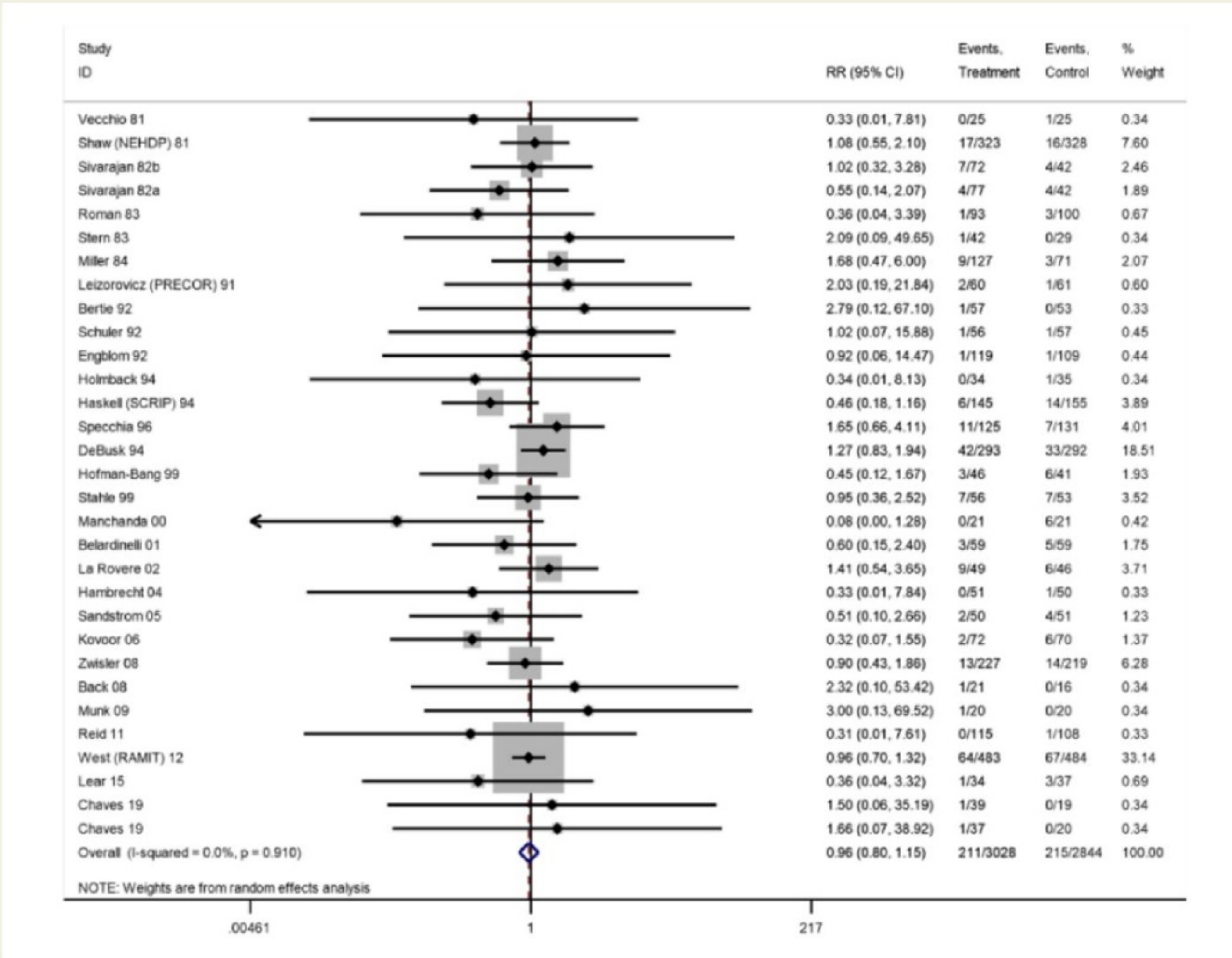


图5森林图:基于运动的心脏康复与冠状动脉旁路移植术对照。

死亡率

在报告总死亡率的60个试验(61个比较)中，有13个试验报告两组均无事件发生。在短期随访中(6-12个月;Rr: 0.87, 95% ci: 0.73-1.04, I^2 = 0%;中度确定性证据)或最长随访(47项试验，RR: 0.96, 95% CI: 0.89-1.04, I^2 = 0%;*图2)。*

在报告CV死亡率的33个试验(35个比较)中，有7个试验报告两组均无事件发生。在最长的随访报告中，CV死亡风险降低26%(26项试验，RR: 0.74, 95% CI: 0.64-0.86, I^2 = 0%;*图3)，NNT为37。*在短期(6-12个月)随访中，CV死亡率无显著差异(RR: 0.88, 95% CI: 0.68-1.14, I^2 = 0%，中等确定性)。

致命和/或非致命MI

在42个报告致死性和非致死性心肌梗死的试验(44个对比)中，有3个试验在两组均报告了零事件。在最长的随访期间(39个试验，RR: 0.82, 95% CI: 0.70-0.96, I^2 = 9%;*图4)，NNT为100。*总体风险是由短期内(6-12个月;Rr: 0.72, 95%可信区间:0.55 - 0.93^2 = 7%，高确定性证据)和长期(>36个月;Rr: 0.67, 95%可信区间:0.50-0.90,I^2 = 0%)中期随访(13-36个月;Rr: 1.07, 95%可信区间:0.91-1.27,I^2 = 0%)。

血管重建事件

在31个报告CABG的试验(33个比较)中，有2个试验报告两组均无事件发生。在最长的随访时间内，CABG的风险无差异(29个试验，RR: 0.96, 95% CI: 0.80-1.15, I^2 = 0%;*图5)。在报告PCI的20个试验(21个比较)中，有3个试验报告两组均无病例发生。*17项临床试验，RR: 0.84, 95% CI: 0.69-1.02, I^2 = 0%;*图6)。*

住院

在报告总住院率的22项试验(24个对比)中，有一项试验报告两组均无事件发生。在最长的随访中，参与基于运动的CR的总住院风险降低了23%(21项试验，RR: 0.77, 95% CI: 0.67-0.89, I^2 = 32%;*图7)，NNT为37。*9项试验报告了CV住院，1项试验报告了两组零事件。两组患者在最长随访时间内CV住院时间无显著差异(8项试验，RR: 0.85, 95% CI: 0.67-1.08, I^2 = 12%;*图8)。*

与健康有关的生活质量

在长达12个月的随访中，6个试验报告了SF-36总成分评分(图9)

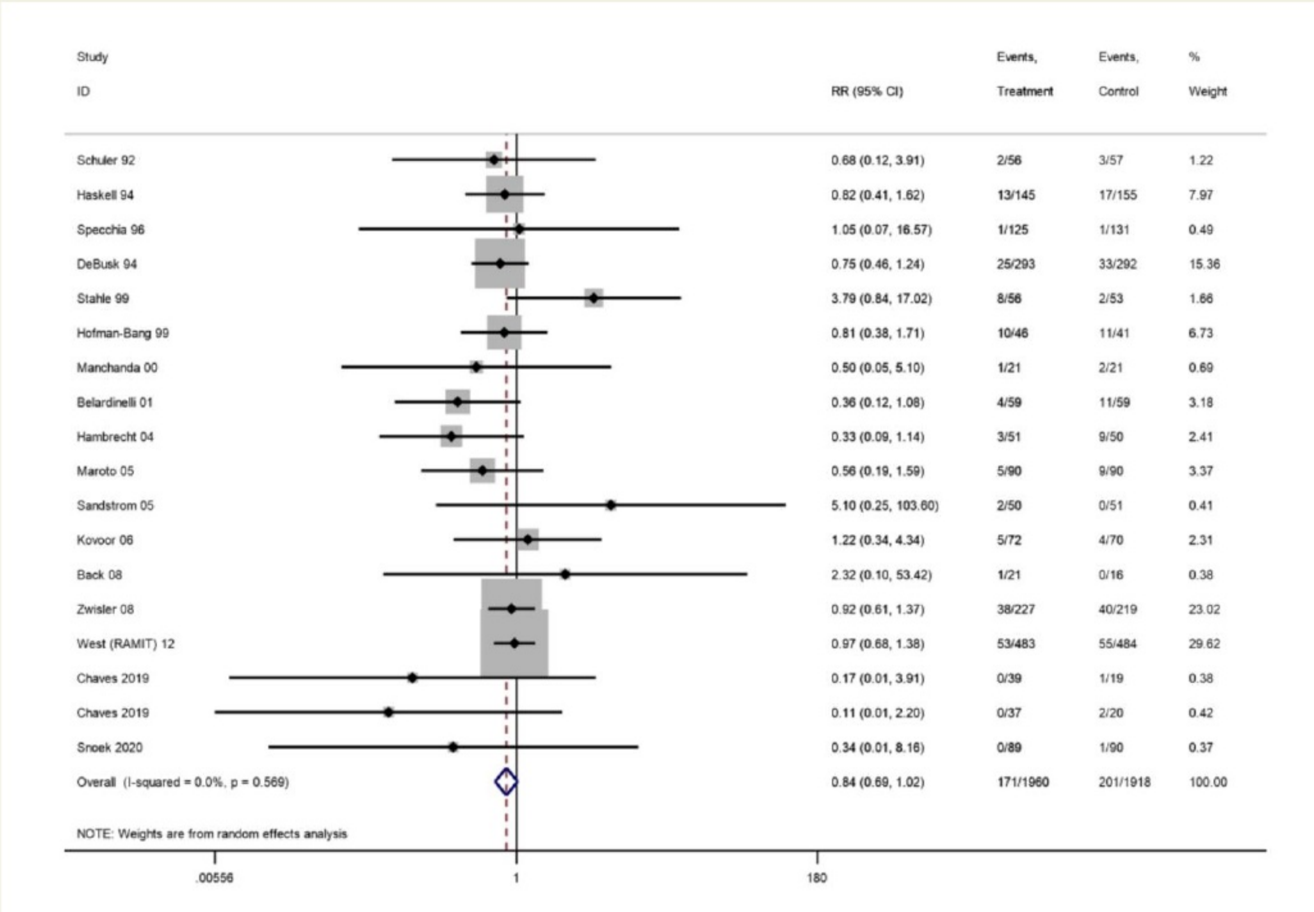


图6森林图:基于运动的心脏康复与经皮冠状动脉介入治疗对照。

心理成分得分(MD: 2.14, 95% CI: 1.07-3.22, I^2 = 21%)和身体成分得分(MD: 1.70, 95% CI:−0.08-3.47,I^2 这些发现得到了选定SF-36个人领域分数(图10)的改善的支持，该分数包括身体功能、身体表现、一般健康、活力、社会功能和心理健康。没有证据表明EQ-5D视觉模拟评分(VASs;Md 0.05, 95% ci−0.01-0.10,I^2 = 69%;*图11)。*

在32项使用一系列经过验证的通用或疾病特异性预后指标评估HRQoL的试验中，投票计数证实了CR的益处，其中20项(63%)试验在一个或多个分量表中报告了基于运动的CR与对照相比HRQoL水平更高，12项(38%)试验报告了50%的分量表>中HRQoL水平更高(见在线补充材料，表S1)。

成本和成本效益

在85项研究中，只有8项报告了CR的医疗成本数据，5项研究报告了两组的总体医疗成本(表3)。[60] 1083欧元，[27] 415美元[102] 在三项研究中，以运动为基础的CR比通常护理的医疗费用更高(平均395美元，[50] 4,839美元，[72] 480美元[80] 每个病人更多)，在一项研究中没有报告差异。然而，只有1例差异显著(平均2378美元/患者;*P* < *0.001)*。中每QALY可接受的成本效益比在3个试验中(42,535美元，[50] 15247欧元，[72] 9,200美元[80])。

研究偏倚小

Egger’s检验和漏斗图的目视检查表明，没有证据表明总体死亡率存在小的研究偏倚(Egger’s检验:P = 0.05;在线补充资料，图S2)，CV死亡率(Egger’s检验:P = 0.20;在线补充资料，图S3)， CABG (Egger’s检验:P = 0.12;在线补充资料，图S4)和PCI (Egger’s test: P = 0.39;在线补充资料，图S5)。然而，有证据表明，漏斗图不对称的研究偏倚较小，MI的Egger’s检验显著(P = 0.001;在线补充资料，图S6)和全因住院(Egger’s检验:P < 0.001;在线补充资料，图S7)。

元回归

对于所有临床事件的结果，没有证据表明在患者、干预和研究特征之间的治疗效果有显著差异(见在线补充材料，表S2)。

讨论

这项更新的Cochrane综述和rct荟分析纳入了> 23000名冠心病患者的数据，并证实了参与基于运动的CR的好处，包括CV风险的降低

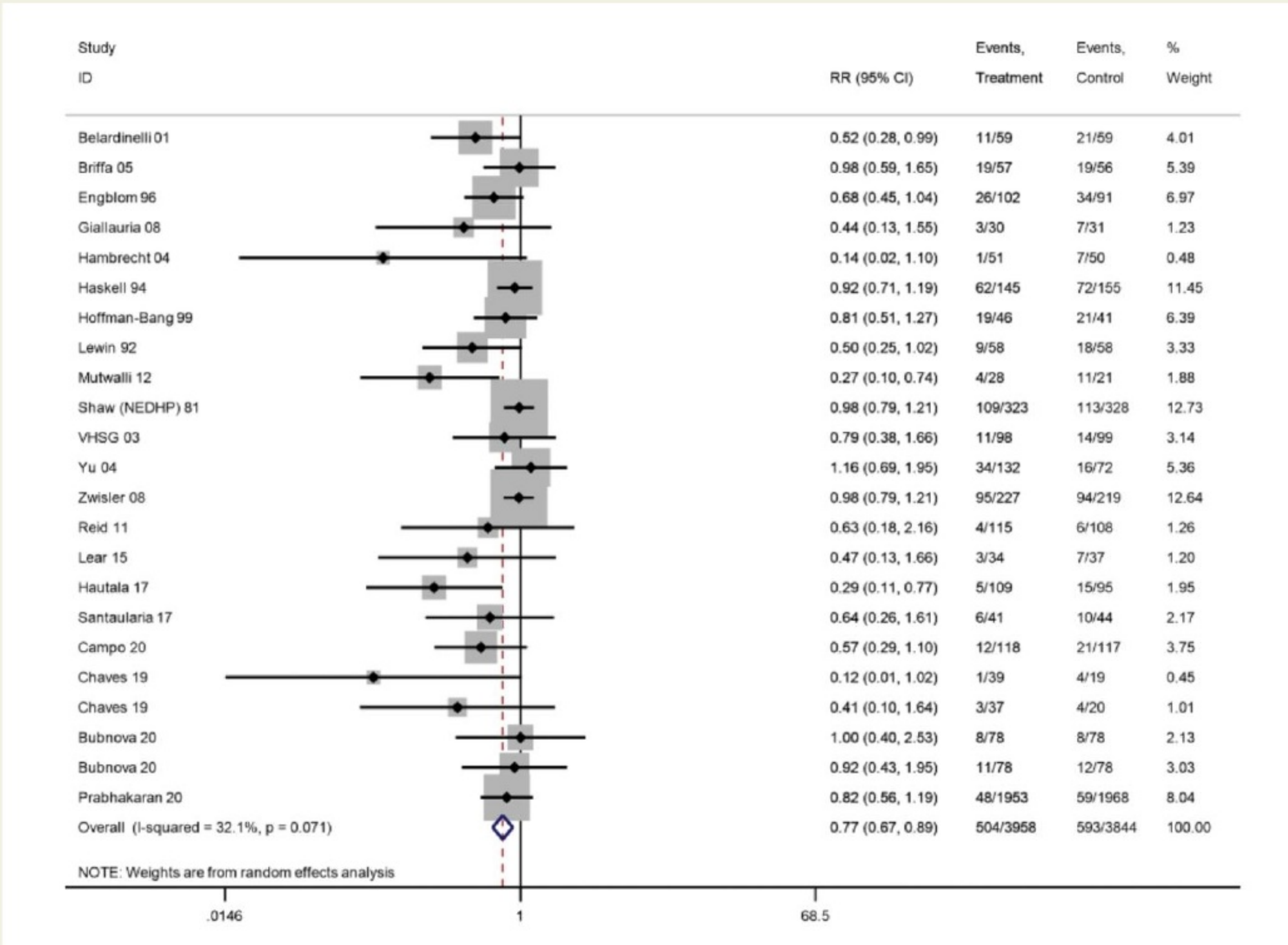


图7森林图:基于运动的心脏康复与总体住院率对照。

死亡率、心肌梗死和全因住院的中位随访时间为12个月(结构图摘要)。在患者的病例组合、CR计划的类型或组、规定的运动剂量、研究样本量、地点、随访时间、发表年份和ROB中没有发现显著差异。在卫生资源使用和相关成本方面，减少住院可能对医疗保健服务和患者都有好处，并使他们早日回到家庭和社区支持网络。重要的是，这篇更新的综述表明，CR的益处延伸到最近的试验中，这些试验更具有现代治疗方法在冠心病、扩大的冠心病人群和低收入和中等收入人群中的代表性(21项在中低收入国家进行的试验，共有7851名参与者)，这些地区的冠心病患病率持续上升。[104]

此外，我们发现HRQoL在8个SF-36领域中的6个得分、心理成分得分、EQ-5D VAS得分和32个报告HRQoL数据的综合综合分析中都有所增加。基于最小重要性的临床差异，个体领域得分的增加在临床上并不重要，[105] 但EQ-5D VAS评分的增加可能具有临床意义。[106] 对于冠心病患者，总结成分评分的最低重要临床差异尚未公布。尽管HRQoL对患者很重要，而且在通用的测量方法中已经证明了其改善，但如果采用通用的测量方法，这一发现可能会更有说服力

同时附加使用冠心病疾病特异性的HRQoL测量。为了提供更有说服力的证据，我们建议未来的试验考虑至少12个月的常规合并两种类型的HRQoL结果测量，以描述HRQoL的哪些方面(如果有的话)可能产生改善。基于试验的经济评估表明，与常规护理相比，CR是一种具有成本效益的医疗资源使用方式。

正如当前慢性冠状动脉综合征临床指南术语所反映的那样，冠心病在临床上正从一种危及生命的疾病转变为一种慢性疾病轨迹。[4] 这一关键转变强烈要求采取干预措施，以改善慢性病患者的再住院率、福祉和HRQoL。因此，最新的Cochrane rct综述仍然强调了以运动为基础的CR作为冠心病综合护理的一部分与现代侵入性和药理学治疗的重要性。

局限性

我们的综述有许多潜在的局限性。首先，尽管我们发现研究的方法学质量和报告在过去十年中得到了改善，而且糟糕的报告似乎没有改变审查结果，但试验中的几个ROB评估被认为是不清楚的，许多研究的报告不够充分

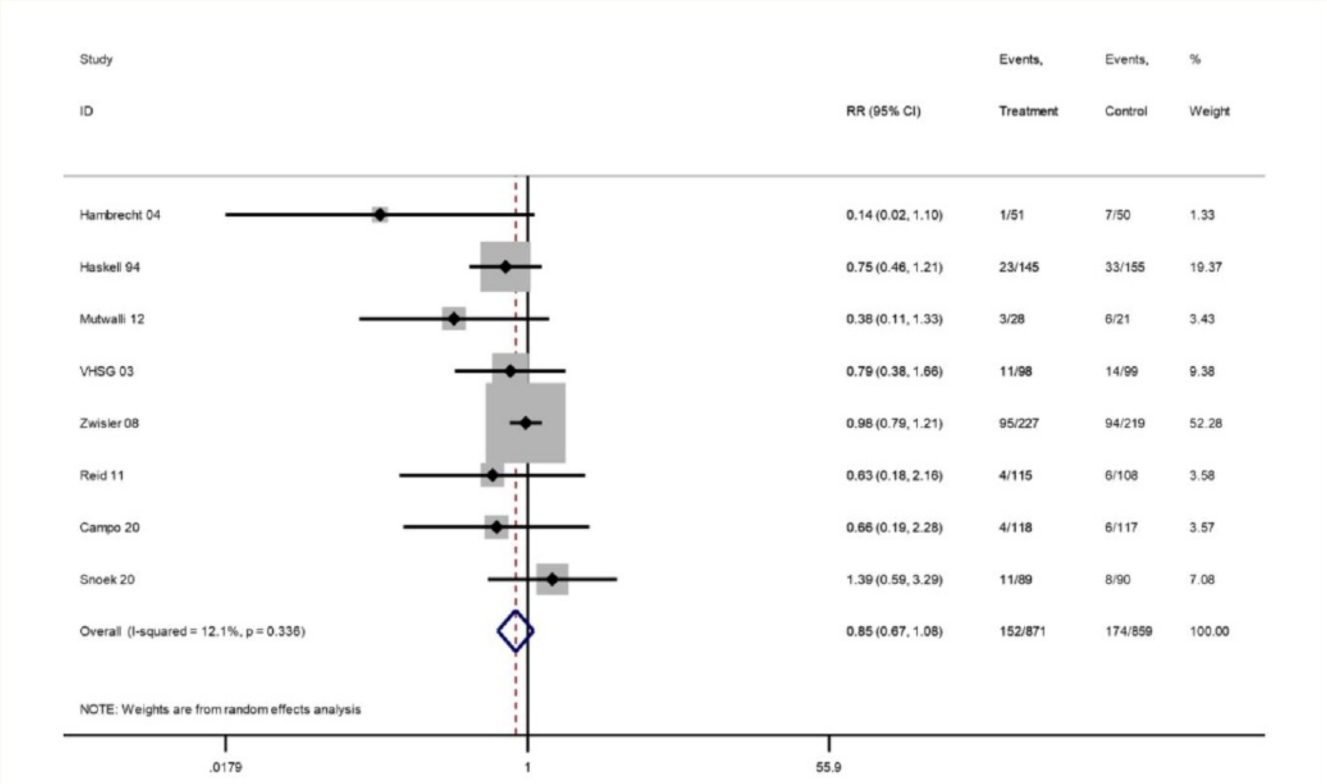


图8森林图:基于运动的心脏康复与心血管住院对照组。

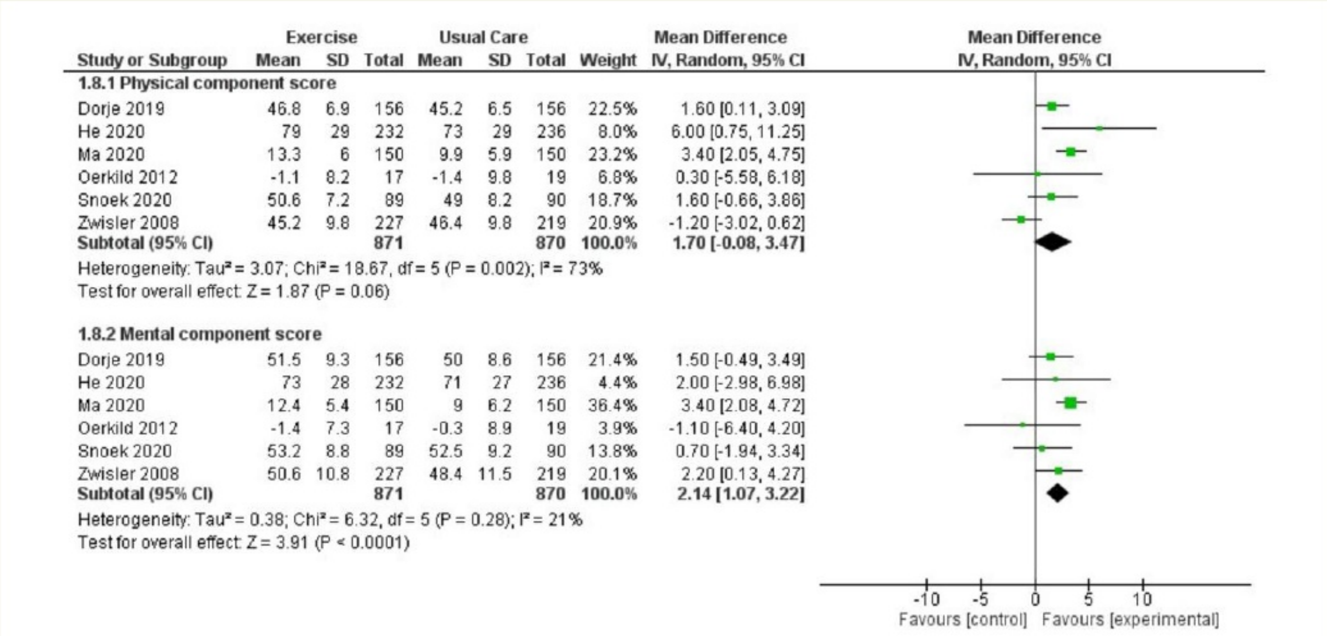


图9森林图:基于运动的心脏康复与健康相关生活质量对照(简表-36摘要成分得分)。

方法。第二，本次更新试图结合一系列冠心病适应症的证据，以及采用不同运动量、分娩环境的基于运动的CR干预的研究随访时间。然而，我们采用了随机效应荟萃分析来考虑这些研究之间潜在的临床异质性。此外，年级评估框架也

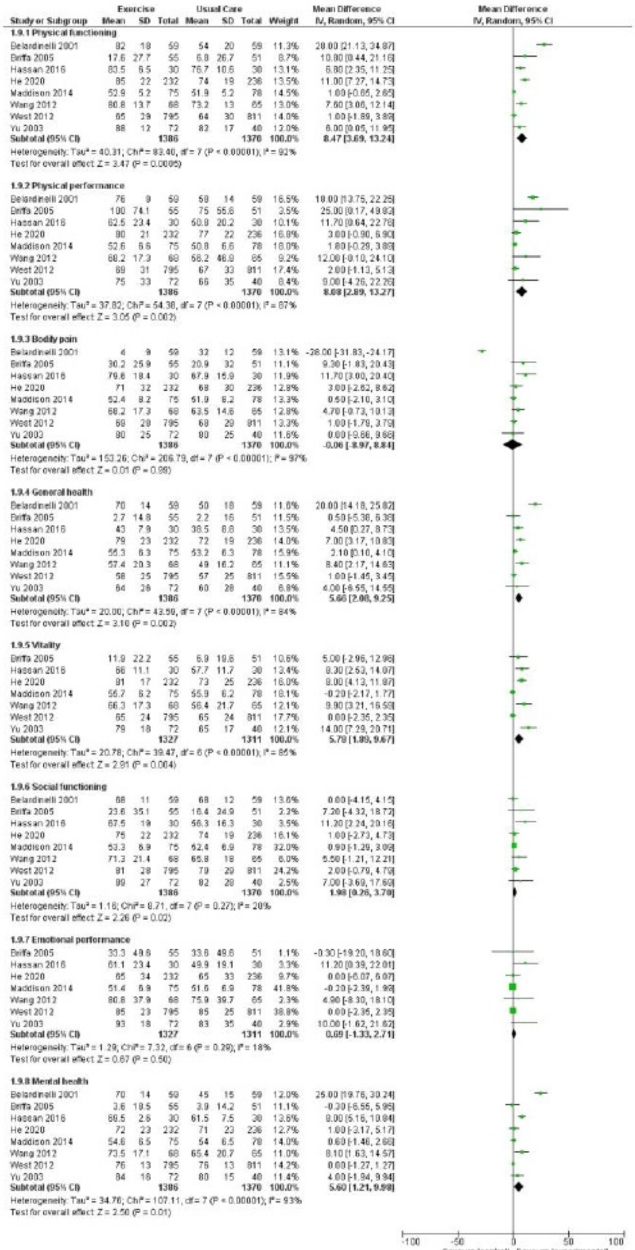


图10森林图:基于运动的心脏康复与健康相关生活质量对照(简式-36个体领域得分)。

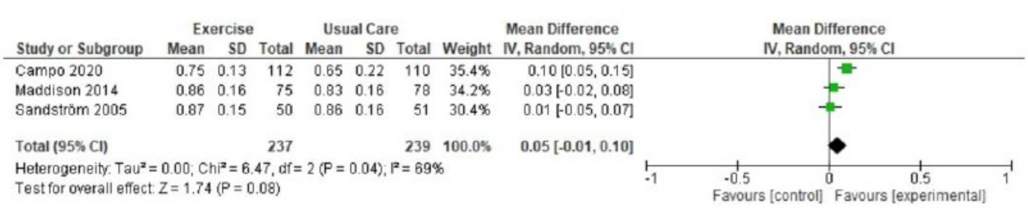


图11森林图:基于运动的心脏康复与健康相关生活质量对照(EQ-5D)。

表3以运动为基础的康复和日常护理费用汇总

	布里法(2005)	Hambrecht (2004)	Hautala (2017)	Kovoor (2006)/Hall (2002)	Maddison (2014)	Marchionni (2003)	Oldridge (1991/93)	Yu (2004)
随访(月)	12	12	6	14	12	24	12	12
(货币)	1998年($AUD)	NR	NR(€;1999年($AUD)	NR(€;欧元)2000(美元)	1991(美元)	2003(美元)		
康复费用 平均成本/患者	694美元	Nr	299 欧元 根据芬兰健身房每月的平均费用估计，在那里，运动训练的个人指导是由卫生保健专业人员领导的	$394 工作人员，评估，咨询，教育，病人旅行	€12 7 nr	5246 nr	$670 空间，设备，员工，文献资源，运营成本，停车，患者费用	Nr
康复指的是费用/病人	$4937	$6086±370−	€1944	nr	nr	$ 17272	nr	$ 15292
通常注意的意思 费用/病人	$4541	$2378*	€3027 -	nr	nr	$ 12433	nr	$ 15707
平均成本/的绝对差异 病人	395 美元		€1083	nr	nr	$4839	480 美元	−$415
成本p值	0.74	*P < 0.001*	nr	*P > 0.05(见下)*	Nr	Nr	nr	*P > 0.05*
差异 额外的	住院治疗，药物测试咨询 康复，病人费用，救护车	再住院，血运重建，骑行里程计，训练设施和监督 职员	初级保健费用，二级保健 费用，职业保健服务费用	电话(P = 0.10);住院次数(P = 0.11);门控心池扫描(P = 0.50);运动应激试验(P = 0.72);其他诊断(P = 0.37);拜访全科医生(P = 0.61)、专科医生(P = 0.35)或保健专业人员 (p = 0.31)			服务利用、医生费用、急诊费用、住院天数、联合保健等 康复探访	住院; 血管重建;私人诊所就诊;心脏门诊就诊;非心脏疾病的公众就诊;伤亡人员探访;药物
成本效益康复意味着医疗保健 利益	基于效用的生活质量-心脏问卷:0.026 (95% CI, 0.013 - 0.038)	nr	15D效用的平均变化:0.013	nr	nr	nr	nr	nr

继续

表3继续

布里法(2005)Hambrecht (2004) Hautala (2017) Kovoor (2006)/Hall Maddison Marchionni Oldridge Yu (2004)
(2002) (2014) (2003) (1991/93)

通常护理平均效

用0.010 (95% CI, NR 15D内的平均变化NR NR NR NR
医疗保健效益−0.001至0.022)效用:−0.012
增量平均效用0.013 (95% CI, NR 0.045 QALY) (0.023 - NR NR NR 0.052 QALY
保健效益NR)， P = 0.38;+0.009 0.077) 0.007-0.1)
qaly

* Hambrecht 2004年的医疗保健费用以美元报告，但没有具体说明货币。NR，未报;QALY，质量调整生命年。

考虑证据的异质性。例如，结果全因死亡率、心血管病死亡率、PCI和心血管病住院率在GRADE中被降低，这是由于宽的ci跨越边界而没有效果。心血管住院由于统计上的异质性而降低(I^2 统计数字是50%)。第三，虽然研究报告了规定的锻炼剂量，但很少(如果有的话)报告参与者的实际锻炼水平。因此，我们无法评估干预依从性的影响。第四，报告12个月以上随访数据的试验数量在过去十年中下降了，从48%(2000年至2009年)降至23%(2010年至2020年)。因此，在一些试验中报告的死亡和临床事件的数量很低或为零，这些数据通常是在随访试验失败的描述中报告的，而不是作为主要或次要结果，这也意味着试验不会为这些结果提供动力。此外，各个试验的危害系数报告不一致;因此，利用这些数据进行分析是不可能的。最后，我们还发现了报道偏见的证据。例如，尽管60个试验报告了全因死亡率，但在这些相同的试验中，只有33个试验报告了CV死亡率。对报告两种死亡率结果的16项试验的亚组敏感性分析(见在线补充资料，图S8和S9)显示，两种试验的汇总总体(RR 0.85, 95% CI: 0.74-0.98)和CV死亡率(RR 0.79, 95% CI: 0.68-0.92)均有改善。这一敏感性分析与我们的主要分析相反，显示了基于运动的CR对总死亡率和CV死亡率的不同影响。

结论

Cochrane对23430名冠心病患者的85项随机对照试验的最新研究结果证实，参与基于运动的CR可降低CV死亡率、MI和住院率，并提供及时证据，支持在当代医疗管理背景下，以及在包括中低收入国家在内的医疗保健机构中，这些益处在患者中具有普遍性。这篇更新的综述还提供了元分析证据，证明参与CR改善了基于HRQoL数据的患者生活质量。我们的发现强化了改善全球冠心病患者接受CR治疗的必要性。

补充数据

补充数据可在《欧洲心脏杂志》网站上找到。

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数据可用性

在合理的要求下，本文的数据将被共享给通信作者。

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