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

Grace O. Dibben 1*, James Faulkner 2, Neil Oldridge 3, Karen Rees 4, David R. Thompson 5, Ann-Dorthe Zwisler 6,7,8, and Rod S. Taylor 1,9

1MRC/CSO Social and Public Health Sciences Unit, Institute of Health and Well Being, University of Glasgow, Glasgow, UK; 2School of Sport, Health and Community, Faculty Health and Wellbeing, University of Winchester, Winchester, UK; 3College of Health Sciences, University of Wisconsin-Milwaukee, Milwaukee, WI, USA; 4Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK; 5School of Nursing and Midwifery, Queen’s University Belfast, Belfast, UK; 6REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital, Nyborg, Denmark; 7Department of Clinical Research, University of Southern Denmark, Odense, Denmark; 8Department of Cardiology, Odense University Hospital, Odense, Denmark; and 9Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow, Glasgow, UK

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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.

* Corresponding author. Tel: +441413537500, Email: grace.dibben@glasgow.ac.uk

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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.

This updated Cochrane systematic review and meta-analysis of 85 RCTs in 23,430 patients with CHD (post-MI/PCI/CABG, or stable angina) found that CR was associated with:

1. **Better**
   - Health-related quality of life
   - Cost-effectiveness

2. **Reduced risk of**
   - Cardiovascular mortality
   - Myocardial infarction
   - Hospitalization

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**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

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**Introduction**
Coronary heart disease (CHD) is the most common cause of death globally.\(^1\) 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,\(^5\)\(^\text{-}^8\) 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.\(^7\)\(^\text{-}^9\)

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
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) 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.
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, 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), 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>
<thead>
<tr>
<th>Outcome follow-up time point</th>
<th>n participants</th>
<th>n studies</th>
<th>n events/participants</th>
<th>RR (95% CI)</th>
<th>Statistical heterogeneity I²</th>
<th>GRADE assessment of certainty</th>
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<tbody>
<tr>
<td>Overall mortality</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Longest follow-up</td>
<td>16 829</td>
<td>47</td>
<td>919/8608</td>
<td>0.96 (0.89–1.04)</td>
<td>0%</td>
<td>Moderate</td>
</tr>
<tr>
<td>6–12 months</td>
<td>8823</td>
<td>25</td>
<td>228/4590</td>
<td>0.87 (0.73–1.04)</td>
<td>35%</td>
<td>Moderate</td>
</tr>
<tr>
<td>13–36 months</td>
<td>11 073</td>
<td>16</td>
<td>467/5611</td>
<td>0.90 (0.80–1.02)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>&gt;36 months</td>
<td>3828</td>
<td>11</td>
<td>476/1902</td>
<td>0.91 (0.75–1.10)</td>
<td>35%</td>
<td></td>
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<tr>
<td>CV mortality</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Longest follow-up</td>
<td>7762</td>
<td>26</td>
<td>296/3997</td>
<td>0.74 (0.64–0.86)</td>
<td><strong>P &lt; 0.001</strong></td>
<td>Moderate</td>
</tr>
<tr>
<td>6–12 months</td>
<td>5360</td>
<td>15</td>
<td>109/2799</td>
<td>0.88 (0.68–1.14)</td>
<td>0%</td>
<td></td>
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<tr>
<td>13–36 months</td>
<td>3614</td>
<td>5</td>
<td>199/1861</td>
<td>0.77 (0.63 to 0.93)</td>
<td>5%</td>
<td></td>
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<tr>
<td>&gt;36 months</td>
<td>1392</td>
<td>8</td>
<td>56/690</td>
<td>0.58 (0.43–0.78)</td>
<td><strong>P &lt; 0.01</strong></td>
<td></td>
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<tr>
<td>Fatal and/or non-fatal MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Longest follow-up</td>
<td>14 151</td>
<td>39</td>
<td>383/7181</td>
<td>0.82 (0.70–0.96)</td>
<td>9%</td>
<td>Moderate</td>
</tr>
<tr>
<td>6–12 months</td>
<td>7423</td>
<td>22</td>
<td>140/3820</td>
<td>0.72 (0.55–0.93)</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>13–36 months</td>
<td>9565</td>
<td>12</td>
<td>264/4830</td>
<td>1.07 (0.91–1.27)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>&gt;36 months</td>
<td>1560</td>
<td>10</td>
<td>65/776</td>
<td>0.67 (0.50–0.90)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest follow-up</td>
<td>5872</td>
<td>29</td>
<td>211/3028</td>
<td>0.96 (0.80–1.15)</td>
<td>0%</td>
<td>High</td>
</tr>
<tr>
<td>6–12 months</td>
<td>4473</td>
<td>20</td>
<td>125/2324</td>
<td>0.99 (0.78–1.27)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>13–36 months</td>
<td>2826</td>
<td>9</td>
<td>123/1413</td>
<td>0.97 (0.77–1.23)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>&gt;36 months</td>
<td>675</td>
<td>4</td>
<td>19/333</td>
<td>0.66 (0.34–1.27)</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest follow-up</td>
<td>3878</td>
<td>17</td>
<td>171/1960</td>
<td>0.84 (0.69–1.02)</td>
<td>0%</td>
<td>Moderate</td>
</tr>
<tr>
<td>6–12 months</td>
<td>3465</td>
<td>13</td>
<td>91/1743</td>
<td>0.86 (0.63–1.19)</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>13–36 months</td>
<td>1983</td>
<td>6</td>
<td>114/996</td>
<td>0.96 (0.69–1.35)</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>&gt;36 months</td>
<td>567</td>
<td>3</td>
<td>28/281</td>
<td>0.76 (0.48–1.20)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest follow-up</td>
<td>7802</td>
<td>21</td>
<td>504/3958</td>
<td>0.77 (0.67–0.89)</td>
<td><strong>P &lt; 0.01</strong></td>
<td>Moderate</td>
</tr>
<tr>
<td>6–12 months</td>
<td>2030</td>
<td>14</td>
<td>130/1054</td>
<td>0.58 (0.43–0.77)</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>13–36 months</td>
<td>5995</td>
<td>9</td>
<td>392/3017</td>
<td>0.92 (0.82–1.03)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>CV hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest follow-up</td>
<td>1730</td>
<td>8</td>
<td>152/871</td>
<td>0.85 (0.67–1.08)</td>
<td>12%</td>
<td>Low</td>
</tr>
<tr>
<td>6–12 months</td>
<td>1087</td>
<td>6</td>
<td>40/546</td>
<td>0.8 (0.41–1.59)</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>13–36 months</td>
<td>943</td>
<td>3</td>
<td>129/470</td>
<td>0.92 (0.76–1.12)</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**Downgraded by one level due to evidence of publication bias.

*Downgraded by one level due to substantial heterogeneity.

*P < 0.05.

**P < 0.01.

***P < 0.001.
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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). 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 I² 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. 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. Given the number of statistical

Figure 2 Forest plot: exercise-based cardiac rehabilitation vs. control for overall 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), 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. 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), one study using quasi randomization methods, and one cluster RCT. Sixteen of the 22 new trials identified were undertaken in LMICs, resulting in a total of 21 RCTs in LMICs. Three large multicentre trials contributed a total of 8956 participants (~40% overall). 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, with 47 (55%) involving multiple components including education (20 trials), psychosocial (seven trials), or other components (i.e. controlled diet, risk factor management, smoking cessation, relaxation; four trials). Exercise was typically aerobic, with the inclusion of resistance training reported in 27% trials (23 out of 85). 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
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rate, 50%–95% of aerobic capacity, or at a rating of perceived exertion between 11 and 16. Of the 21 home-based exercise programmes, 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 generation21–25,28–32,34–37,40,42,45,49,50,54,59,60,67,69,70,72,73,75,77,79,83,84,86,95,97,98,101,103 and 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,19,23–25,29,34–36,40–41,68,70–72,74–78,80,82–89,91,92,94–99,101–103 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.
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 CABB, two trials reported zero events in both arms. There was no difference in risk of CABB 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
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, €1083,72 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 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).

**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), CAGB (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...
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.

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, but increases in EQ-5D VAS scores could be clinically meaningful. 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. 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
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

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Year of costs (currency)</td>
<td>1998 ($AUD)</td>
<td>NR</td>
<td>NR (€; Euros)</td>
<td>1999 ($AUD)</td>
<td>NR (€; Euros)</td>
<td>2000 ($USD)</td>
<td>1991 ($USD)</td>
<td>2003 ($USD)</td>
</tr>
<tr>
<td>Cost of rehabilitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean cost/patient</td>
<td>$694</td>
<td>NR</td>
<td>€299</td>
<td>$394</td>
<td>€127</td>
<td>$524</td>
<td>$670</td>
<td>NR</td>
</tr>
<tr>
<td>Costs considered</td>
<td>Details of costed elements not provided</td>
<td>NR</td>
<td>Estimated according to the average monthly fees in Finnish gyms where individual guidance in exercise training is led by a healthcare professional</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>space, equipment, staff, literature resources, operating costs, parking, patients costs</td>
<td>NR</td>
</tr>
<tr>
<td>Total healthcare costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehabilitation mean cost/patient</td>
<td>$4937</td>
<td>$3708 ± 156</td>
<td>€1944</td>
<td>NR</td>
<td>NR</td>
<td>$17272</td>
<td>NR</td>
<td>$15292</td>
</tr>
<tr>
<td>Usual care mean cost/patient</td>
<td>$4541</td>
<td>$6086 ± 370</td>
<td>€3027</td>
<td>NR</td>
<td>NR</td>
<td>$12433</td>
<td>NR</td>
<td>$15707</td>
</tr>
<tr>
<td>Absolute difference in mean cost/patient</td>
<td>$395</td>
<td>−$2378*</td>
<td>−€1083</td>
<td>NR</td>
<td>NR</td>
<td>$4839</td>
<td>$480</td>
<td>−$415</td>
</tr>
<tr>
<td>P-value for cost difference</td>
<td>0.74</td>
<td>P &lt; 0.001</td>
<td>NR</td>
<td>P &gt; 0.05 (see below)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Additional healthcare costs considered</td>
<td>Hospitalizations, pharmaceuticals, tests, consultations, rehabilitation, patient expenses, ambulance</td>
<td>Rehospitalizations, revascularization, cycle ergometers, training facilities, and supervising staff</td>
<td>Primary healthcare costs, secondary healthcare costs, occupational healthcare service costs</td>
<td>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)</td>
<td>NR</td>
<td>NR</td>
<td>Service utilization, physician costs, emergency costs, in-patient days, allied health, other rehabilitation visits</td>
<td>Hospitalizations; revascularizations; private clinic visit; cardiac clinic visits; public non-cardiac visits; casualty visits; drugs</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Rehabilitation mean healthcare benefits</td>
<td>Utility-Based Quality of life–Heart questionnaire: 0026 (95% CI, 0.013–0.039)</td>
<td>NR</td>
<td>Average change in 15D utility: 0.013</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</table>

*Continued*
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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106. Briggs A, Lloyd A, Pickard SS. Minimal clinically important difference in EQ-5D: we can calculate it, but does that mean we should? www.ispor.org/docs/default-source/presentations/1066.pdf?sfvrsn=25feff6d_1 (20 December 2022, date last accessed).

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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.