# Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease:

## Cochrane Systematic Review and Meta-Analysis

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**Brief Title:** Exercise for coronary heart disease: systematic review

**Total Word Count:** 4326

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LA is funded by the University of Exeter Medical School, UK. RST is partly funded by the UK National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula at the Royal Devon and Exeter NHS Foundation Trust, and KR is supported by the NIHR Collaboration for Leadership in Applied Health Research and Care West Midlands at University Hospitals Birmingham NHS Foundation Trust, UK. RST, KR, NO and DRT were authors of the original Cochrane review. RST, KR and ADZ are authors on a number of other Cochrane CR reviews. RST is currently the co-chief investigator on the programme of research with the overarching aims of developing and evaluating a home-based CR intervention for people with heart failure and their carers (PGfAR RP-PG-0611-12004) and ADZ is Principal Investigator of an included (DAHREHAB) and ongoing CR trials (CopenHeart trials). All authors have reported that they have no relationships with industry relevant to the contents of this paper to disclose. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health in England.

# Abstract

**Background:** While recommended in guidelines for the management of coronary heart disease (CHD), concerns have been raised about the applicability of evidence from existing meta-analyses of exercise-based cardiac rehabilitation (CR).

**Objective:** To update the Cochrane systematic review and meta-analysis of exercise-based CR for CHD.

**Methods:** Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL and Science Citation Index Expanded were searched to July 2014. Retrieved articles, systematic reviews, and trial registries were hand-searched. We included randomised controlled trials with at least six months follow-up, comparing CR to no exercise control in individuals following myocardial infarction or revascularisation, or with a diagnosis of angina pectoris or CHD defined by angiography. Two authors screened titles for inclusion, extracted data and assessed risk of bias. Stratified meta-analysis was undertaken to examine potential treatment effect modifiers.

**Results:** Sixty three studies in 14,486 participants with median follow-up of 12 months, were included. Overall, CR led to a reduction in cardiovascular mortality (relative risk 0.74, 95% CI: 0.64 to 0.85) and the risk of hospital admissions (relative risk 0.82, 0.70 to 0.96). There was no significant impact on total mortality, myocardial infarction or revascularisation. The majority of studies (13/20) showed higher levels of health-related quality of life in one or more domains following exercise-based CR compared to control.

**Conclusions:** This study confirms that exercise-based CR reduces cardiovascular mortality and provides important data showing reductions in hospital admissions and improvements in quality of life. These benefits appear to be consistent across patients and intervention types and were independent of study quality, setting and publication date.



# Keywords

Rehabilitation, myocardial infarction, revascularisation, percutaneous coronary intervention, coronary artery bypass graft, angina, exercise training, exercise therapy

# Abbreviations

**CHD = coronary heart disease**

**CR = cardiac rehabilitation**

**HRQL = health-related quality of life**

**CABG = coronary artery bypass grafting**

**PCI = percutaneous coronary intervention**

**CV = cardiovascular**

**MI = myocardial infarction**

**RCT = randomised controlled trial**

**RR =relative risk**

**CI = confidence interval**

# Introduction

With increasing numbers of people living longer with symptomatic coronary heart disease (CHD), the effectiveness and accessibility of health services for people with CHD have never been more important. Cardiac rehabilitation (CR) programmes are recognised as integral to comprehensive care of CHD patients and have been given a Class I recommendation from the American Heart Association, and the American College of Cardiology, and the European Society of Cardiology, with exercise therapy consistently identified as a central element (1-4). While exercise training remains a cornerstone intervention, international guidelines consistently recommend the provision of comprehensive rehabilitation that includes education and psychological input focusing on health and lifestyle behaviour change, risk factor modification, and psychosocial well-being (1-3).

The first systematic reviews and meta-analyses of exercise-based CR by Oldridge and O'Connor were published more than 20 years ago, showing a 20-25% reduction in all-cause and cardiovascular mortality based on data from 22 randomised controlled trials (RCTs) in over 4,300 patients (5,6). Although there have been more recent updates to these meta-analyses (7-9), concerns have been raised about the applicability of their results to policy planning and the provision of CR services (10,11). It has been argued that major advances in CHD medical management may have led to a reduction in the incremental effect on mortality of exercise-based CR compared to usual care alone. Other concerns have included the inclusion of small, poor quality RCTs which may have resulted in overestimation of the benefits of CR, and the almost exclusive recruitment of low-risk, middle-aged post-myocardial infarction (MI) men in early trials, thereby reducing the generalisability of their findings to the broader population of CHD patients (12). Our aim was to systematically update existing meta-analyses to reassess the effects of exercise-based CR in patients with CHD in terms of mortality, morbidity, health-related quality of life (HRQL), and cost-effectiveness. We also sought to explore if effects vary with patient case mix, the nature of CR programmes, and study characteristics.

# Methods

We conducted and reported this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (13) and the Cochrane Handbook for Interventional Reviews (14). The protocol was published on the Cochrane Database of Systematic Reviews (2001) (15).

**Data Searches and Sources**

Search terms from the 2011 Cochrane review (9) were updated and CENTRAL, DARE, HTA, MEDLINE & Medline in Process (OVID), EMBASE (OVID) and CINAHL Plus (EBSCO) were searched to July 2014. Conference proceedings were searched on Web of Science Core Collection (Thomson Reuters) (1970 to June 2014) and bibliographies of systematic reviews and trial registers (WHO's ICTRP and Clinicaltrials.gov) were hand-searched. No language or other limitations were imposed (see online supplementary material).

**Study Selection**

Randomised controlled trials of exercise-based CR compared to a control with a follow-up period of at least six months were sought. Exercise-based CR was defined as a supervised or unsupervised inpatient, outpatient, community- or home-based intervention which includes some form of exercise training, either alone or in addition to psychosocial and/or educational interventions. The comparator could include standard medical care, and psychosocial and / or educational interventions, but not any structured exercise training. We included patients irrespective of gender or age, who have had an MI, or who had undergone revascularisation (coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)) or who have angina pectoris or CHD defined by angiography. Finally, studies needed to report one or more of the following outcomes: total or cardiovascular mortality; fatal or non-fatal MI; revascularisations (CABG or PCI); hospitalisations; HRQL assessed using validated instruments; or costs and cost-effectiveness. Two reviewers (LA and RST) independently assessed all identified titles/abstracts for possible inclusion,

with any disagreements resolved by discussion. Where necessary, studies were translated into English.

**Data Extraction and Management**

One reviewer (LA) extracted study and patient characteristics, intervention and comparator details and outcome data from included studies using a standardised data collection form. A second author (RST) checked for accuracy and disagreements were resolved by consensus. Duplicate publications of the same study were assessed for additional data and authors were contacted where necessary to provide additional information.

**Assessment of Risk of Bias and Overall Quality of Evidence**

Risk of bias of included studies was assessed using the Cochrane Collaboration's core risk of bias items (14) and three further items deemed relevant to this review. GRADEProfiler software (16) was used to assess the overall quality of evidence for each outcome collected (17) (see eMethods for full details).

**Data Synthesis and Analysis**

Dichotomous outcomes were expressed as relative risks (RR) with 95% confidence intervals (CI). HRQL scores were expressed as mean differences. Heterogeneity amongst included studies was explored qualitatively and quantitatively (using the chi-squared test of heterogeneity and $I^2$ statistic). Data from each study were pooled using a fixed effect model, except where substantial heterogeneity was associated with an effect estimate (i.e. chi-squared test P value < 0.10, $I^2$ > 30%), when a random effects model was applied.

The meta-analysis of each outcome was stratified according to the duration of study follow-up i.e. 6 to 12 months ('short-term'); 13 to 36 months ('medium- term'); and > 36 months ('long- term'). Using the longest follow-up, we stratified meta-analyses to explore heterogeneity and examine potential treatment effect modifiers. We tested nine *a priori* hypotheses that there may be

differences in the effect of exercise-based CR on outcomes at longest follow-up across the following subgroups: (1) CHD case mix (MI-only trials versus other trials); (2) type of CR (exercise-only CR versus comprehensive CR); (3) 'dose' of exercise intervention [dose = number of weeks of exercise training x average number of sessions/week x average duration of session in minutes] (dose ≥ 1000 units versus dose < 1000 units); (4) follow-up period; (5) year of publication; (6) sample size; (7) setting (home- or centre-based CR); (8) risk of bias (low risk of bias in < 5 out of 8 domains); and (9) study location (continent).

The funnel plot and Egger test were used to examine small study bias (18). All statistical and analyses were performed using Review Manager 5.3 Software (19) and STATA V.13.0 (StataCorp, College Station, Texas) (20).

# Results

**Selection and Inclusion of Studies**

The 2011 Cochrane review provided 47 RCTs (81 publications). Our searches for this update yielded 11,028 titles of which 91 full papers were considered for inclusion. Sixteen new RCTs (21 publications) were included giving a total of 63 studies (102 publications) (see Figure 1 for a summary of the study selection process and eTable 1 for a list of included studies).

**Study, Patient and Intervention Characteristics**

Fourteen studies were published before 1999 and 49 published since 2000 (Table 1). The median follow-up was 12 months, with 50 studies reporting at least 12-months follow-up and 18 reporting follow-up of 36 months or more. The majority of studies were conducted in Europe (37 studies) or North America (12 studies). Although we included 14,486 patients, most studies were small in sample size (median 126, range: 28-2304), with two large multicentre centre trials (WHO and RAMIT) (12,21) contributing a total of 4,177 patients (about 30% of all participants).

The median age of participants across studies was 56.0 years. Although 42 studies (66%) included women, they accounted for less than 15% of all patients recruited. Studies published since 2005 were less dominated by post-MI patients, included other CHD diagnoses including revascularisation and angina, and were more likely to include older (average mean age 61.7 years vs 56.3 years) and female (20.0% vs 12.5%) participants.

Exercise-based CR programmes were typically delivered in a supervised hospital/centre-based setting either exclusively, or in combination with some maintenance home exercise sessions. Fifteen studies were conducted in an exclusively home-based setting (22-36)(31,35). While the primary mode of exercise training across all studies was aerobic, the overall or average duration, frequency and intensity of sessions, varied considerably across studies. Twenty four studies were exercise-only programmes, 38 were comprehensive CR, and one trial included both exercise-only and comprehensive CR arms (37).

**Risk of Bias and GRADE assessment**

The overall risk of bias across domains was judged to be low or unclear (see eTable 2). Quality of reporting was generally higher in more recent studies. Overall, the GRADE quality of evidence for each outcome was assessed to be low to moderate (Table 2).

**Outcome results**

As there was no difference in the impact of exercise-based CR on clinical outcomes across length of follow-up (Table 2), the following results focus on pooled findings across all trials at their longest follow-up (median 12 months).

***Mortality***

Forty seven studies (12,455 participants) reported total mortality (Table 2; eFigure 1). There was no statistically significant reduction in total mortality with exercise-based CR (relative risk (RR): 0.94, 0.87 to 1.02, fixed effects) compared with no exercise control. Twenty seven studies (7469 participants) reported cardiovascular mortality (Table 2; eFigure 2) and a statistically significant reduction in this outcome was seen compared with no exercise control (RR: 0.74, 0.64 to 0.85, fixed effects).

***Morbidity***

Thirty six studies (9717 participants) reported the risk of fatal or non-fatal MI (Table 2; eFigure 3), and no statistically significant difference in the risk of total MI was found with exercise based CR (RR: 0.89, 0.78 to 1.02). Twenty nine (5891 participants), and 16 (4012 participants) studies reported the risk of CABG and PCI, respectively (Table 2, eFigure 4 and eFigure 5). There was no difference between exercise-based CR and usual care for either CABG or PCI (CABG: RR: 0.94, 0.78 to 1.12; PCI: RR: 0.86, 0.71 to 1.04, fixed effects). Fifteen studies (2865 participants) reported hospital admissions (Table 2; eFigure 6). Risk of admissions was reduced with exercise-based CR compared with usual care (RR: 0.82, 0.70 to 0.96, random effects). There was no evidence of statistical heterogeneity

across trials in either mortality or morbidity outcomes (with exception of hospitalisations ($I^2$ statistic =35%).

**Stratified meta-analyses**

There was with no evidence of difference in CR vs control treatment effects across mortality and morbidity outcomes across any patient, intervention or study characteristics (Table 3).

***Health-Related Quality of Life***

Twenty studies (5,060 participants) assessed HRQL using a range of validated generic or disease-specific outcome measures (eTable 3). Given both the heterogeneity in outcome measures and methods of reporting the findings, we did not undertake meta-analysis. Thirteen out of the 20 studies (65%) reported a higher level of HRQL in one or more sub-scale following exercise-based CR compared with control (23,27,29,31,33,35,36,38-43), and in five studies (25%) there was a higher level of HRQL in half or more of the sub-scales (23,33,35,36,38).

**Costs and Cost-Effectiveness**

Seven studies reported data on costs (31,40,44-48) (eTable 4). Three studies showed no difference in total healthcare costs between CR and control groups, (40,44,46), one reported lower healthcare costs for CR compared with usual care (reduction of US$2378/patient) (47) while another reported higher healthcare costs for CR (increase of $US4,839 /patient) (45), and two studies did not report total healthcare costs (31,48). Cost-effectiveness ranged from an additional $US42,535 per quality adjusted life year (QALY) (40) for CR to a reduction of US$650 per QALY (46) for CR compared to control.

**Small Study Bias**

There was no evidence of funnel plot asymmetry or significant Egger tests for mortality or revascularisation outcomes (eFigures 7, 8, 10, and 11). However, Egger tests were significant for MI (P = 0.009) and hospitalisation (P = 0.001) indicating funnel plot asymmetry. This asymmetry

appeared to be due to an absence of small to medium size studies with negative results for exercise-based CR (eFigures 9 and 12).

# Discussion

We conducted an updated systematic review and meta-analysis of exercise-based CR in people with existing CHD. Our study shows a reduction in pooled cardiovascular mortality (10.4% to 7.6%; number needed to treat: 37), and hospital admission (30.7% to 26.1%; number needed to treat: 22) with exercise-based CR compared to no exercise control. There was no between group difference in total mortality or the risk of fatal or non-fatal MI, CABG, or PCI. Outcome effects were consistent across RCTs irrespective of patient case mix (i.e. % of MI patients), the nature of CR programme (i.e. exercise-only or comprehensive CR; dose of exercise training; or centre- or home-based settings), and study characteristics (i.e. sample size; risk of bias; location; length of follow-up or year of publication). There was evidence of higher levels of HRQL following exercise-based CR compared to control and that exercise-based CR can be a cost-effective use of healthcare resources.

In contrast to previous meta-analyses , we did not observe a statistically significant reduction in all-cause mortality with exercise-based CR and this may be explained by the inclusion of more recent studies that include a more mixed population of CHD patients, conducted in the era of optimal medical therapy for CHD. Our review included RCTs conducted over a period (1974 to 2014) during which there have been a number of major advances in medical CHD management, such as the increased use of statins. We found some support for this hypothesis in our meta-regression analysis that shows a trend of a linear reduction (slope: 0.0063, 95% CI: -0.00150 to 0.0141, P=0.08) in the all-cause mortality effect (log RR) of CR over time, i.e. study publication date (Figure 2). In spite of the observed improvements in cardiovascular mortality, in a context of contemporary CHD medical treatments, the opportunity for additional gains in overall mortality with exercise-based CR may be small. Nonetheless, the observation that exercise-based CR reduces the risk of cardiovascular mortality compared with no exercise control, but does not reduce the risk of MI or revascularization, suggests that while CR does not improve coronary vascular function or integrity, it does confer improved survival in patients post- MI.

**Limitations**

There are limitations to this systematic review. The generally poor level of reporting in the included RCTs made it difficult to assess their methodological quality and thereby judge their risk of bias. However, we did find some improvements in the quality of reporting in more recently published studies. Reassuringly our meta-analysis findings were consistent when limited to studies with a lower risk of bias. Nevertheless, the general paucity of reporting led to us downgrading the GRADE quality of evidence for outcomes to 'low' or 'moderate'. We acknowledge that the median outcome follow-up of 12 months is limited when assessing for impact on mortality and morbidity outcome measures. However, our results were consistent when pooling was limited to RCTs with a follow up > 12 months. Funnel plot asymmetry for the risk of MI and hospital admission is indicative of possible publication bias. Included RCTs did not consistently report all outcomes relevant to this review and events were often reported in study description of drop out or withdrawal. Reassuringly we found our overall meta-analysis results to be consistent in the subgroup of 20 studies reporting both mortality outcomes (all-cause mortality RR: 0.91, 95% CI: 0.82 to 1.01; CV mortality RR: 0.78, 95%: 0.67 to 0.90). The minority of trials reported non-cardiovascular causes of death. Only more recent studies have begun to consistently report data on hospitalisations, but still often fail to differentiate between new and recurrent admissions, while HRQL and cost data are still collected infrequently. Finally, we sought to categorise the diagnoses of study participants according to a more detailed framework based on Braunwald's classification of CHD (49) to study whether the effect of exercise-based CR differs according to the presentation i.e. acute coronary syndrome (MI, Non ST-segment elevation MI [NSTEMI], unstable angina pectoris) and stable angina pectoris or treatment modality (PCI, CABG or medication alone). The limited reporting by RCTs of inclusion and exclusion criteria and participant characteristics prevented us applying this categorisation. Nevertheless, we believe this to be the most comprehensive review of evidence to date and summarises the results of RCTs in >14000 patients.

# Conclusions

Among patients with established CHD, provision of exercise-based CR provides important health benefits that include reductions in cardiovascular mortality and hospitalisation (and associated healthcare costs), and improvements in HRQL. Based on a meta-analysis of RCTs, these results support the level I recommendation of current international clinical guidelines that CR should be offered to CHD patients. However, future trials need to pay increased attention to the recruitment of patients that are more representative of the broader CHD population, including those at higher risk and with major co-morbidities, plus those with stable angina, and also improve their quality of reporting, particularly in terms of risk of bias, details of the intervention and control, and clinical events, HRQL, and health economic outcomes.

## Perspectives

COMPETENCIES IN MEDICAL KNOWLEDGE: Exercise-based CR reduces the risk of cardiovascular mortality and hospital admissions, and improves HRQL in patients with established CHD. These benefits appear to be independent of setting, intervention, study risk of bias, and patient characteristics.

COMPETENCY IN PATIENT CARE: Exercise-based CR is effective and safe in the management of low- to moderate-risk post-MI or revascularisation patients, or those with stable angina.

TRANSLATIONAL OUTLOOK: Future RCTs of CR need to be better reported and recruit a broader population of CHD patients, including those at higher risk and with major co-morbidities.

# Acknowledgements

We would like to thank Zhivko Zhelev, Shenqiu Zhang and Oriana Ciani for their translation services, and Harriot Hunt for her assistance with screening. We thank all the authors who provided additional information about their trials. Finally we would like to acknowledge the support of co-authors on the two previous versions of this review.

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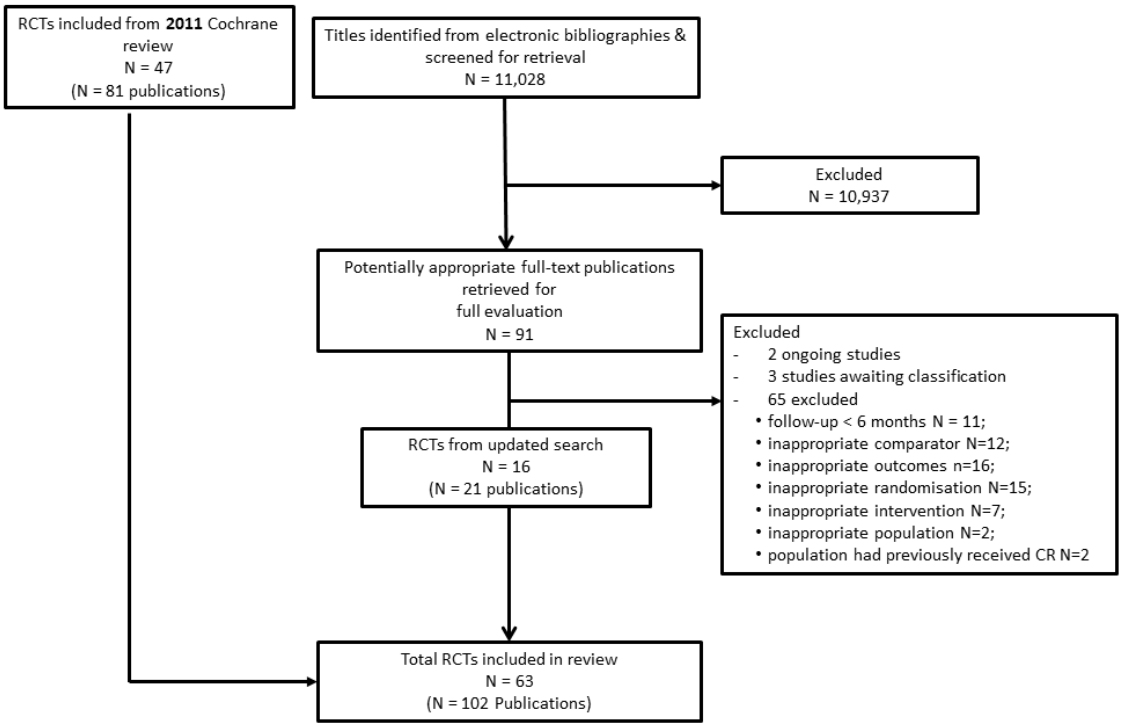
**Figure 1. Summary of study selection process**




**The 63 studies in this review included 47 studies (81 publications) from the 2011 version of the review, and a further 16 studies (21 publications) identified from the updated searches.**

**Figure 2. Meta-regression analysis of effect of CR on total mortality over time**


**Plot of treatment effect (log RR) of exercise-based CR on total mortality effect versus study publication year. The straight line indicates the treatment effect (log RR) of exercise-based CR on total mortality effect versus study publication year. The area of each data point is inversely related to the standard error of log RR.**

**Table 1. Summary of Trial and Patient Characteristics (63 included studies)**

| | **Number of studies (%) or Median* (Range)** |
|---|---|
| **Study Characteristics** | |
| Publication year | |
| 1970–1979 | 2 (3) |
| 1980–1989 | 12 (19) |
| 1990–1999 | 20 (32) |
| 2000–2009 | 21 (33) |
| 2010 onwards | 8 (13) |
| Study location | |
| Europe | 37 (59) |
| North America | 12 (19) |
| Asia | 6 (10) |
| Australasia | 5 (8) |
| Other | 2 (3) |
| Not reported | 1 (2) |
| Single centre | 45 (71) |
| Sample size | 126 (28 to 2304) |
| Duration of follow-up | 12 months (6 to 120) |
| **Population Characteristics** | |
| Gender | |
| Males only | 18 (29) |
| Females only | 1 (2) |
| Both males and female | 41 (65) |
| Not reported | 3 (5) |
| Age (years) | 56.0 (49.3 to 71.0) |
| Diagnosis | |

| | |
|---|---|
| Post-myocardial infarction only | 31 (49) |
| Revascularization only | 2 (3) |
| Angina only | 5 (8) |
| Mixed CHD population | 25 (40) |
| **Intervention Characteristics** | |
| Intervention type | |
| Exercise-only programmes | 25† (38) |
| Comprehensive programmes | 39† (60) |
| Duration of intervention (months) | 6 (1 to 48) |
| Dose of intervention | |
| Duration | 6 months (1 to 48) |
| Frequency | 1 to 7 sessions/week |
| Length | 20 to 90 minutes/session |
| Intensity | • 50% to 85% of maximal heart rate<br>• 50% to 95% of maximal oxygen uptake ($VO_2$ max)<br>• Borg rating of 11 to 15 |
| Setting | |
| Centre-based only | 33 (52) |
| Combination of Centre- and home-based | 13 (21) |
| Home-based only | 15 (24) |
| Not reported | 2 (3) |

* Median of study means; †one study includes both exercise only and comprehensive CR arms

**Table 2. Summary of meta-analysis effects of exercise-based CR on clinical event outcomes**

| Outcome | Number of participants (Number of Studies) | Number of Events/ Participants | | Relative risk (95% CI) | Statistical Heterogeneity $I^2$ statistic $Chi^2$-test (P value) | GRADE Quality of the Evidence |
|---|---|---|---|---|---|---|
| | | Intervention | Comparator | | | |
| **All-cause mortality (All Studies)** | **12455 (47)** | **838/6424** | **865/6031** | **0.94 [0.87 to 1.02]** | **0% (0.58)** | ⊕⊕⊕⊖ **moderate*** |
| Follow-up of 6 to 12 months | 8800 (29) | 226/4573 | 238/4227 | 0.87 [0.73, 1.03] | 0% (0.82) | |
| Follow-up of > 12 to 36 months | 6823 (13) | 338/3495 | 417/3328 | 0.89 [0.78, 1.01] | 0% (0.47) | |
| Follow-up longer than 3 years | 3828 (11) | 476/1902 | 493/1926 | 0.98 [0.88, 1.08] | 35% (0.12) | |
| **CV mortality (All Studies)** | **7469 (27)** | **292/3850** | **375/3619** | **0.74 [0.64 to 0.85]** | **0% (0.70)** | ⊕⊕⊕⊖ **moderate*** |
| Follow-up of 6 to 12 months | 4884 (15) | 105/2561 | 107/2323 | 0.89 [0.69, 1.15] | 0% (0.72) | |
| Follow-up of > 12 to 36 months | 3833 (7) | 199/1971 | 239/1862 | 0.78 [0.65, 0.93] | 5% (0.38) | |
| Follow-up longer than 3 years | 1392 (8) | 56/690 | 100/702 | 0.56 [0.42, 0.76] | 0% (0.91) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Fatal and/or non-fatal MI (All Studies)** | **971 (36)** | **356/4951** | **387/4766** | **0.89 [0.78 to 1.02]** | **0% (0.48)** | **⊕⊕⊖⊖ low*,†** |
| Follow-up of 6 to 12 months | 6911 (20) | 126/3543 | 139/3368 | 0.86 [0.68, 1.09] | 0% (0.58) | |
| Follow-up of > 12 to 36 months | 5644 (11) | 251/2877 | 222/2767 | 1.08 [0.91, 1.28] | 0% (0.72) | |
| Follow-up longer than 3 years | 1560 (10) | 65/776 | 102/784 | 0.65 [0.49, 0.87] | 0% (0.67) | |
| **CABG (All Studies)** | **5891 (29)** | **208/3021** | **212/2870** | **0.94 [0.78 to 1.12]** | **0% (0.86)** | **⊕⊕⊕⊖ moderate*** |
| Follow-up of 6 to 12 months | 4563 (21) | 123/2351 | 121/2212 | 0.95 [0.75, 1.20] | 0% (0.83) | |
| Follow-up of > 12 to 36 months | 2755 (98) | 122/1379 | 123/1376 | 0.99 [0.78, 1.25] | 0% (0.93) | |
| Follow-up longer than 3 years | 675 (4) | 19/333 | 29/342 | 0.65 [0.37, 1.13] | 18% (0.30) | |
| **PCI (All Studies)** | **4012 (16)** | **171/2013** | **197/1999** | **0.86 [0.71 to 1.04]** | **0% (0.59)** | **⊕⊕⊕⊖ moderate*** |
| Follow-up of 6 to 12 months | 3564 (13) | 90/1778 | 99/1786 | 0.92 [0.70, 1.20] | 16% (0.30) | |
| Follow-up of > 12 to 36 months | 1983 (6) | 114/996 | 116/987 | 0.96 [0.76, 1.22] | 26% (0.24) | |
| Follow-up longer than 3 years | 567 (3) | 28/281 | 37/286 | 0.75 [0.48, 1.19] | 0% (0.81) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Hospital admissions (All Studies)** | **3030 (15)** | **407/1556** | **453/1474** | **0.86 [0.77 to 0.95]** | **34.5% (0.10)** | ⊕⊕⊖⊖ **low*,†** |
| Follow-up of 6 to 12 months | 1120 (9) | 82/574 | 116/546 | 0.65 [0.46, 0.92] | 37% (0.14) | |
| Follow-up of > 12 to 36 months | 1916 (6) | 322/984 | 330/932 | 0.95 [0.84, 1.07] | 0% (0.50) | |
| Follow-up longer than 3 years | 0 (0) | 0/0 | 0/0 | Not estimable | Not estimable | |

**Footnotes**

* Random sequence generation, allocation concealment or blinding of outcome assessors were poorly described in over 50% of included studies; bias likely

† Funnel Plots and / or Egger test suggest evidence of asymmetry

**GRADE Working Group grades of evidence**

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

**Table 3. Stratified meta-analysis by patient, intervention and study characteristics at longest follow up**

| | All-cause mortality | CV mortality | MI | CABG | PCI | Hospitalisation |
|---|---|---|---|---|---|---|
| | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** | **RR (95% CI)** |
| **All studies** | **0.94 (0.87 to 1.02)** | **0.74 (0.64 to 0.85)** | **0.89 (0.78 to 1.02)** | **0.94 (0.78 to 1.12)** | **0.86 (0.71 to 1.04)** | **0.86 (0.77 to 0.95)** |
| | | | | | | |
| **Stratified analyses** | | | | | | |
| **Case mix** | | | | | | |
| 100% MI | 0.91 (0.82 to 1.00) | 0.75 (0.64 to 0.87) | 0.91( 0.79 to 1.05) | 1.06( 0.86 to 1.30) | 0.87 (0.67 to 1.14) | 0.90 (0.73 to 1.09) |
| < 100% MI | 1.02 (0.88 to 1.18) | 0.616 (0.378 to 1.01) | 0.68 (0.42 to 1.10) | 0.63(0.43 to 0.93) | 0.84 (0.64 to 1.11) | 0.84 (0.74 to 0.96) |
| **Dose of exercise*** | | | | | | |
| < 1000 | 1.00 (0.49 to 2.04) | 0.47 (0.19 to 1.15) | 0.72 (0.32 to 1.62) | 0.96 (0.46 to1.99) | 1.22 (0.34 to 4.34) | 0.67 (0.45 to 0.99) |
| ≥ 1000 | 0.99 (0.87 to 1.13) | 0.71 ( 0.56 to 0.91) | 0.73 (0.59 to 0.91) | 0.96 (0.76 to 1.21) | 0.81 (0.63 to 1.03) | 0.88 (0.78 to 0.98) |
| **Type of CR** | | | | | | |
| Exercise only | 0.98 (0.86 to 1.13) | 0.63 (0.49 to 0.82) | 0.76 (0.60 to 0.97) | 0.91 (0.64 to 1.29) | 1.03 (0.54 to 1.97) | 0.85 (0.70 to 1.04) |
| Comprehensive CR | 0.92 (0.829 to1.02) | 0.78 (0.66 to 0.93) | 0.96 (0.81 to 1.13) | 0.95 (0.77 to 1.17) | 0.87 (0.71to 1.07) | 0.86 (0.76 to 0.98) |
| **Duration of follow months (months)** | | | | | | |
| ≤ 12 months | 1.06 (0.52 to 2.18) | 0.71 (0.61 to 0.83) | 0.60 (0.40 to 0.90) | 0.96 (0.70 to 1.32) | 0.85 (0.56 to 1.30) | 0.64 (0.49 to 0.83) |
| > 12months | 0.95 (0.86 to 1.02) | 0.98 (0.63 to 1.52) | 0.94 (0.81 to 1.09) | 0.92 (0.74 to 1.15) | 0.86 (0.69 to 1.07) | 0.92 (0.81 to 1.03) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Year of publication** | | | | | | |
| Pre 1995 | 0.86 (0.75 to 0.98) | 0.78 (0.67 to 0.91) | 0.96 (0.82 to 1.13) | 0.87 (0.59 to 1.28) | 0.80 (0.42 to 1.51) | 0.88 (0.76 to 1.02) |
| Post 1995 | 1.00 (0.903 to 1.11) | 0.54 (0.37 to 0.80) | 0.75 (0.58 to 0.97) | 0.96 (0.78 to 1.18) | 0.87 (0.71 to 1.06) | 0.83 (0.71 to 0.97) |
| **Setting** | | | | | | |
| Centre | 0.94 (0.86 to 1.02) | 0.75 (0.65 to 0.87) | 0.96 (0.83 to 1.11) | 0.97 (0.77 to 1.22) | 0.93 (0.73 to 1.18) | 0.89 (0.78 to 1.02) |
| Centre plus home | 0.72 (0.39 to 1.36) | 0.63 (0.34 to 1.16) | 0.36 (0.13 to 0.99) | 0.74 (0.45 to 1.23) | 0.62 (0.35 to 1.08) | 0.86 (0.61 to 1.21) |
| Home | 1.01 (0.68 to 1.50) | 0.89 (0.43 to 1.81) | 0.48 (0.28 to 0.83) | 1.07 (0.75 to 1.53) | 0.79 (0.53 to 0.18) | 0.76 (0.60 to 0.95) |
| **Risk of bias** | | | | | | |
| Low (bias in <5 out of 8 domains) | 1.00 (0.87 to 1.16) | 0.91 (0.28 to 2.95) | 0.95 (0.69 to 1.31) | 0.91( 0.69 to 1.20) | 0.91(0.70 to 1.17) | 0.89 (0.73 to 1.08) |
| High (bias in > 5 out of 8 domains) | 0.91 (0.82 to 1.00) | 0.74 (0.64 to 0.85) | 0.75 (0.42 to 1.33) | 0.96 (0.76 to 1.21) | 0.80 (0.60 to 1.07) | 0.84 (0.74 to 0.96) |
| **Study location (continent)** | | | | | | |
| Europe | 0.91 (0.82 to 1.01) | 0.74 (0.63 to 0.86) | 0.93 (0.81to 1.08) | 0.91 (0.72 to 1.14) | 0.92 (0.73 to 1.15) | 0.77 (0.66 to 0.91) |
| North America | 1.10 (0.94 to 1.28) | 0.89 (0.57 to 1.40) | 0.62 (0.41 to 0.93) | 1.04 (0.77 to 1.39) | 0.78 (0.52 to 1.16) | 0.95 (0.80 to 1.11) |
| Australasia | NR | 0.33 (0.01 to 7.87) | 1.95 (0.36 to 10.49) | 0.32 (0.07 to 1.55) | 0.98 (0.33 to 2.93) | 1.07 (0.74 to 1.55) |
| Other | 0.61 (0.34 to 1.05) | 0.58 (0.32 to 1.08) | 0.25 (0.01 to 5.91) | NR | NR | 0.27 (0.10 to 0.74) |
| **Sample size** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≤ 150 | 0.95 (0.87 to 1.03) | 0.59 (0.35 to 0.98) | 0.56 (0.37 to 0.82) | 0.73 (0.50 to 1.06) | 0.82 (0.54 to 1.24) | 0.60 (0.46 to 0.78) |
| > 150 | 0.76 (0.50 to 1.15) | 0.76 (0.65 to 0.88) | 0.95 (0.82 to 1.10) | 1.02 (0.83 to 1.25) | 0.87 (0.70 to 1.08) | 0.93 (0.83 to 1.05) |

NR – not measurable; CV mortality – cardiovascular mortality; MI – myocardial infarction; CABG – coronary artery bypass graft; PI – percutaneous intervention; RR – relative risk

* number of weeks of exercise training x average number of sessions/week x average duration of session in min