Cardiac rehabilitation for people with heart disease: an overview of Cochrane systematic reviews

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Abstract

Introduction: Overviews are a new approach to summarising evidence and synthesising results from related systematic reviews.

Objectives: To conduct an overview of Cochrane systematic reviews to provide a contemporary review of the evidence for cardiac rehabilitation (CR), identify opportunities for merging or splitting existing Cochrane reviews, and identify current evidence gaps to inform new review titles.

Methods: The Cochrane Database of Systematic Reviews was searched to identify reviews that address the objectives of this overview. Data presentation is descriptive with tabular presentations of review- and trial-level characteristics and results.

Results: The six included Cochrane systematic reviews were of high methodological quality and included 148 randomised controlled trials in 97,486 participants. Compared to usual care alone, exercise-based CR reduces hospital admissions and improves patient health related quality of life (HRQL) in low to moderate risk heart failure and coronary heart disease (CHD) patients. At 12 months or more follow-up, there was evidence of some reduction in mortality in patients with CHD. Psychological- and education-based interventions appear to have little impact on mortality or morbidity but may improve HRQL. Home- and centre-based programmes are equally effective in improving HRQL at similar costs. Selected interventions can increase the uptake of CR programmes but evidence to support interventions that improve adherence is weak.

Conclusions: This overview confirms that exercise-based CR is effective and safe in the management of clinically stable heart failure and post-MI and PCI patients. We discuss the implications of this overview on the future direction of the Cochrane CR reviews portfolio.

Keywords: systematic reviews, cardiac rehabilitation, exercise training, heart disease

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Highlights:

- This overview provides a contemporary review of the evidence for cardiac rehabilitation, summarising the findings of six Cochrane systematic reviews of a total of 148 randomised controlled trials in 97,486 participants.
- We conclude that exercise-based cardiac rehabilitation is an effective and safe therapy to be used in the management of clinically stable patients following myocardial infarction or percutaneous coronary intervention or who have heart failure.
- A number of recommendations for the design and conduct of future RCTs and systematic reviews of cardiac rehabilitation are presented.

1. Introduction

Cardiac rehabilitation (CR) can be defined as “The coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease” [1].

The gold standard level of evidence to inform clinical and policy decisions on the use of new and existing therapeutic interventions is the systematic review of randomised controlled trials (RCTs), which can include a meta-analysis. The largest single producer of systematic reviews in health care is the Cochrane Collaboration, with more than 8400 published at the time of writing. Compared with systematic reviews published in paper-based journals, studies have consistently shown Cochrane systematic reviews to have greater methodological quality [2-4]. In the first two systematic reviews and meta-analyses of CR published more than 20 years ago, Oldridge and O’Connor reported a 20-25% reduction in all-cause and cardiovascular mortality, pooling data from ten and 22 RCTs respectively, comparing rehabilitation and control in over 4,300 post-myocardial infarction patients [5, 6]. In 2001, Jolliffe et al published the first Cochrane review of exercise-based CR, updating the evidence to 32 RCTs in 8,440 post-myocardial infarction and revascularisation patients, and confirming a similar 27% mortality benefit of exercise-based CR [7].

With funding support of the National Institute of Health Research (NIHR) in the United Kingdom, over the last 10 years the portfolio of published cardiac rehabilitation Cochrane reviews has grown to six systematic reviews/meta-analyses: Exercise-based rehabilitation for heart failure [8] ; Home-based versus centre-based cardiac rehabilitation [9]; Exercise-based cardiac rehabilitation for coronary heart disease [10]; Psychological interventions for coronary heart disease [11]; Patient education in the management of coronary heart disease [12] and Promoting patient uptake and adherence in cardiac rehabilitation [13]. The development of the portfolio of Cochrane reviews has

reflected many of the key areas of evolution in the provision of CR and how this model of service delivery can differ across international healthcare jurisdictions These include, the shift from emphasis on exercise training alone to comprehensive secondary prevention, including risk factor and dietary education and management of psychological factors; the broadening of the population of patients receiving CR services to include those with heart failure; the development of alternative settings of CR delivery that include home provision in addition to the traditional supervised hospital or centre-based programmes and the need to focus the outcomes of CR to inform the needs of healthcare policy makers (e.g. impacts on hospital admission, health-related quality of life (HRQL), and healthcare costs). The Cochrane CR review portfolio remains dynamic, with three reviews having undergone an update in the last 12-months [8, 9, 13].

Overviews of systematic reviews (overviews) are a new approach to summarising evidence, synthesising results from multiple systematic reviews into a single usable document [14]. By providing a single synthesis of all relevant evidence in a particular area, overviews may be useful for therapeutic and policy decision-making, providing a comprehensive ‘‘friendly front end’’ to the evidence, so that the reader does not have to assimilate data from separate systematic reviews. Overviews can also help inform the strategic direction of conduct and structuring of future systematic reviews. For example, the latest version of the Cochrane review of exercise-based CR for coronary heart disease (CHD) includes 47 RCTs in over 10,000 patients and may therefore benefit from being organised into sub-reviews (“splitting”) according to CHD indications i.e. post-MI, revascularisation and angina. Finally, overviews provide an opportunity to identify potential “evidence gaps” and therefore inform areas where new Cochrane reviews should be prioritised.

This overview seeks to present a concise summary of the research question, methods and findings of the Cochrane reviews on CR. We also seek to identify the opportunities for merging or splitting across future Cochrane reviews, identify evidence gaps to inform de novo Cochrane CR review titles; and to provide recommendations to encourage uniformity of future reporting systematic reviews and RCTs of CR. While it is currently recognised that 'comprehensive' CR programmes should contain

exercise, education and psychological components, for clarity in this overview, we will pre-fix “CR” with the focus of the intervention where we feel it might help the reader in interpreting the evidence, e.g. exercise-based CR or education-based CR.

2. Methods

This overview was conducted in accordance with the recommendations for Cochrane overviews [14].

2.1 Search methods for identification of reviews

We initially included the six Cochrane CR reviews cited above [8-13]. In addition, we sought to include other Cochrane reviews that may inform the aims of this overview.

The Cochrane Database of Systematic Reviews on *The Cochrane Library* (issue 4 of 12, April 2014) was searched using the search strategy listed in appendix A. No date or language restrictions were applied. Where reviews had been updated, only the most recent version was sought. We sought full cochrane reviews or protocols currently published in *The Cochrane library* of systematic reviews that: (1) examine the impact or delivery of CR; (2) include adults with heart disease, regardless of aetiology; and (3) include exercise training interventions either alone or in combination with an educational or psychological intervention or both, delivered in a hospital community or a home-based setting.

Two authors (LJA, RST) independently screened titles and abstracts from the searches and full-text articles were retrieved for all potentially includable full reviews or protocols. Any disagreements were resolved through discussion.

2.2 Data extraction and management

The following information was extracted from included Cochrane reviews: review objective/question, search time frame, inclusion criteria (study design, population, intervention,

comparator and outcomes), study limitations, source of funding, and stated conflicts of interest of review authors. The following outcome data were sought: (i) mortality: all cause and disease specific; (ii) morbidity: fatal and non-fatal MI; percutaneous coronary intervention (PCI); hospitalisation: overall and disease specific; (iii) HRQL assessed using validated instruments (e.g. SF-36, EQ5D); (iv) measures of uptake of, or adherence to, CR; (v) costs and cost-effectiveness.

We also extracted characteristics and outcome data for the RCTs included in each of the systematic reviews: number of included RCTs, year of publication, population, intervention and comparator, primary and secondary outcomes specified and collected, total duration of follow up, and number and location of study centres.

Standardised data collection forms were used to extract characteristics of reviews and included studies. These forms were piloted on one review included in the overview. One author (LJA) extracted review and study characteristics from included reviews and a second author (RST) checked all extracted data for accuracy. If study level information within a published review was unclear or missing, we clarified this by reference to the published reports of the individual RCT.

2.3 Assessment of methodological quality of reviews and included studies

2.3.1 Quality of included Cochrane reviews

A single reviewer (LJA) assessed the methodological quality of the included reviews using the 'Revised Assessment of Multiple Systematic Reviews' (R-AMSTAR) measurement tool [15], where the 11 domains of the original AMSTAR tool [16] were scored between 1 and 4 and the R-AMSTAR total score ranged from 11 to 44. The assessment was checked by a second reviewer (RST).

2.3.2 Quality of included RCTs

We have reported the quality of included studies as reported in reviews using the Cochrane risk of bias tool. The core risk of bias items include: the quality of random sequence generation and

allocation concealment, description of drop-outs and withdrawals, blinding of outcome assessment and presence of selective reporting [17]. We also assessed three further quality criteria: whether the study groups were balanced at baseline, if the study groups received comparable care (apart from the intervention), and whether an intention to treat analysis was undertaken. Where a risk of bias element was not reported within the review, the original included RCT publication was assessed by a single reviewer (LJA) and checked by a second reviewer (RST).

2.4 Data presentation and synthesis

The focus of the data presentation is descriptive with detailed tabular presentations of the extracted review and trial level information outlined above. We extracted review level summaries of the outcome findings detailed in each of the included reviews. No de novo data analysis of trial level outcomes was conducted for this overview. For each included review, we extracted all results for the outcomes listed above, and where outcomes were meta-analysed, we have reported pooled effect sizes. Where no quantitative pooling of effect sizes has been reported, or where outcomes are reported descriptively by single studies, we have reported these results by vote counting [18] or using standardised language indicating direction of effect and statistical significance. For continuous outcomes, data is summarised using the standardised mean difference (SMD) or weighted mean difference (WMD) with 95% confidence interval (95% CI) as reported in the included reviews. For dichotomous outcomes, relative risk (RR) or odds ratio (OR) and 95% CI are presented as appropriate. Due to the heterogeneity of populations, interventions and outcomes in the included systematic reviews, we deemed it inappropriate to indirectly compare either CR interventions across reviews (e.g. exercise-training versus education for CHD) or to indirectly compare interventions across review populations (e.g. exercise training for CHD versus exercise training for HF). This is in accord with the Cochrane Comparing Multiple Interventions Methods Group recommendations (http://cmimg.cochrane.org/methods-innovation-fund-stream-1) [19].

3. Results

3.1 Identification of reviews

The review selection process is summarised in the flow diagram in Figure 1. Our database search yielded 91 titles from which we identified one published Cochrane review (in addition to the previously identified six reviews) and three Cochrane review protocols which were judged to meet the inclusion criteria. On review of the full text we excluded the published Cochrane review [20] as while it evaluated physical therapy with an exercise component for elective cardiac surgery patients, only one included RCT compared cardiorespiratory exercise training with a non-exercise control. All other included RCTs assessed inspiratory muscle training. The three Cochrane protocols were judged to meet the inclusion criteria and are listed in Appendix B. The remainder of this overview focuses on presenting the six Cochrane CR reviews.

3.2 Description of included Cochrane reviews

The characteristics of the six included Cochrane reviews and included RCTs are summarised in Tables 1 and 2 respectively.

All included reviews were published between 2011 and 2014, with searches conducted from the inception of the electronic databases to 2013. In all reviews, searches were limited to an RCT design and in three cases the inclusion was limited to RCTs with follow up of 6 months or longer [8, 10, 12]. In total, the included reviews contained 148 RCTs and 97,486 participants. Four RCTs were included in more than one review [21-24]. The majority of included RCTs were published in the last two decades (1970-9: 4 RCTs; 1980-9: 16 RCTs; 1990-9: 40 RCTs; 2000-9: 72 RCTs, 2010 and later: 16 RCTs). The median sample size of RCTs ranged widely from only 16 participants [25] to 46,606 participants [26]. The majority of RCTs were undertaken either in Europe (69%) or North America (35%) and were mainly single centre (79%).

3.2.1 Search methods

All six reviews searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, and PsycINFO. Three reviews also undertook searches for ongoing RCTs using Trial registers (Controlled-trials.com and Clinicaltrials.gov) and all reviews searched for additional RCTs by manually checking the reference lists of included studies.

3.2.2 Participants

The types of participants included in this overview varied between reviews. The scope of two reviews included all adult heart disease patients, regardless of indication [9, 13], three reviews were limited to patients with coronary heart disease (post MI and PCI) [10-12] and one review was limited to heart failure [8]. Although 78% of the RCTs (which reported gender) included women, the median proportion of males included in RCTs ranged from 60 to 88% across reviews. The mean age of patients in RCTs ranged from 46 to 87 years.

3.2.3 Interventions

Two of the reviews included exercise training or exercise training alongside other interventions that included education or psychological support or both [8, 10]. One review focused on psychological interventions [11], although it included a number of RCTs that also incorporated an educational component. One review included only RCTs with an educational focus [12], one included interventions to increase the uptake and adherence to CR [13] and one compared the delivery of CR in home- and centre-based settings [9].

3.2.4 Outcome measures

All reviews pre-specified outcome measures that consistently included all-cause mortality and HRQL. Although all reviews sought morbidity outcomes, the definition and breadth of these outcomes varied across reviews. For example, the review by Heran et al stated that they sought MI (total, fatal, non-fatal), revascularisations (total, CABG, PTCA, stenting) and hospitalisations [10], while the

review by Karmali et al reported “CHD event rates” [13]. Four reviews sought economic outcomes [8-10, 12] and two reviews reported uptake or adherence data [9, 13].

3.2.5 Data analysis

Five of the six reviews included meta-analyses of mortality and morbidity outcomes. The review by Karmali et al, pre-stated that heterogeneity (participants, interventions, and outcomes), together with the small number of studies identified, precluded undertaking meta-analysis [13]. Given the heterogeneity in measures, only one review used meta-analysis to pool HRQL data across RCTs [8], the other reviews using a descriptive and vote counting approach to summarise outcomes. This was also the case for uptake and adherence and economic outcomes. Two of the reviews undertook meta-regression analyses to explore how the impact of interventions varied across patient and RCT characteristics [8, 10].

3.2.6 Methodological quality of included reviews

Based on our assessments using the R-AMSTAR tool, all included reviews scored between 35 and 41 (out of a possible maximum of 44) and were deemed of high methodological quality (see Table 3). None of the reviews stated that journals were hand-, or manually-searched and only one stated that searches were supplemented by consulting books or experts in the field. Two reviews were marked down based on inadequate reporting of the publication status of their included studies. None of the reviews rated the quality of evidence based on a characterised instrument such as GRADE, and while all reviews used the Cochrane risk of bias tool, most were marked down as they failed to refer to the quality of included studies in formulating recommendations. The two weaknesses identified across reviews by R-AMSTAR were the lack of an explicit statement on the impact of findings on clinical practice guidelines and the failure to assess the sources of support or conflict of interest in the included RCTs.

3.2.7 Risk of bias of included RCTs

All six Cochrane reviews used the core items of the Cochrane risk of bias tool (see Table 4). A consistent finding across reviews was that the included RCTs often failed to give enough detail to assess the adequacy of their potential risk of bias. Where details were reported, the quality of RCTs appeared to vary considerably across the risk of bias items. Across all reviews, only a minority of RCTs were judged to be 'adequate' in terms of sequence generation (31%); sequence concealment (29%) and outcome blinding (24%). Other aspects of RCT quality (baseline balance, selective reporting, loss of follow up, intention to treat analysis and groups receiving same intervention) were judged to be better (> 50% of all included RCTs achieving adequacy).

3.3 Effect of interventions

The outcome results across included Cochrane reviews are summarised in Table 5.

3.3.1 Exercise-based cardiac rehabilitation for coronary heart disease [10]

This review undertook database searches up to December 2009 with the inclusion of RCTs with 6 or more months follow up comparing exercise-based CR to no exercise control. A total of 47 RCTs were included across 10,794 patients who were mainly post-MI or PCI, predominantly male (median 88%) and with a median mean age of 55.0 years (see Table 2). The exercise-based CR programmes differed considerably across RCTs in duration (range 1 to 30 months), frequency (1 to 7 sessions/week), and session length (20 to 90 minutes/session).

Up to 12-month follow up, there was a trend towards a reduction in total mortality (relative risk (RR) 0.82; 95% CI, 0.67 to 1.01) while no difference was seen between groups in cardiovascular mortality (RR 0.93; 95% CI, 0.71 to 1.21). At 12 or more months follow-up, exercise-based CR reduced overall (RR 0.87; 95% CI, 0.75 to 0.99) and cardiovascular mortality (RR 0.74; 95% CI, 0.63 to 0.87). There was no evidence of a difference in risk of reinfarcton or PCI between the exercise-based CR and control groups. Ten of the included studies (2,379 participants) reported hospital admissions. In the shorter term (< 12 months follow-up) hospital admissions were also reduced compared to control

(RR 0.69; 95% CI, 0.51 to 0.93) but no evidence of a reduction in the longer term (> 12 months follow-up) was found (RR 0.98; 95% CI, 0.87 to 1.11). No evidence of heterogeneity of effect across RCTs was found for any of the mortality or morbidity outcomes. Univariate meta-regression showed no differences in intervention effects across various patient and RCT characteristics in mortality or morbidity outcomes. In seven out of 10 RCTs there was evidence of a significantly higher level of HRQL with exercise-based CR than control. Three of the included studies reported data on patient costs, but direct comparison was limited by differences in currencies and the time when the studies were conducted.

3.3.2 Exercise-based rehabilitation for heart failure [8]

This review was recently updated with searches up to March 2013 and included 33 RCTs with 6 or more months follow up, comparing exercise-based CR to no exercise control in 4,676 patients with heart failure. Patients were predominantly male (median 80%) with a median mean age of 60.5 years, had a reduced ejection fraction (HFREF< 40-45%) and New York Heart Association classification I to III (see Table 2). The dose of exercise training ranged widely across RCTs from a session duration of 15 to 120 minutes, for one to seven sessions/week, and intensity an of 40 to 80% of maximal heart rate (or equivalent) over a period of one to 120 months.

There was no evidence of difference in pooled mortality between intervention and controls at up to 12 month follow-up (RR 0.93; 95% CI, 0.69 to 1.27). However, in the six RCTs with more than 12 months follow-up, a trend towards a reduction in all-cause mortality with exercise was seen (RR 0.88; 95% CI, 0.75 to 1.02). Compared to control, exercise training reduced the risk of overall (RR 0.75; 95% CI, 0.62 to 0.92) and heart failure-specific hospitalisation (RR 0.61; 95% CI, 0.46 to 0.80) although there was no difference in all hospital admissions beyond 12 month follow-up (RR 0.92, 95% CI, 0.66 to 1.29). Exercise resulted in a clinically important improvement in the Minnesota Living with Heart Failure (MLHF) questionnaire (WMD: -5.8 points, -9.2 to -2.4) although there was

evidence of high levels of statistical heterogeneity (I^2 = 70%). Univariate meta-regression analysis showed that these benefits in hospitalisation and HRQL were independent of patient characteristics, type and dose of CR, length of follow up, overall risk of bias, or RCT publication date. There was limited evidence to support CR for patients with heart failure with preserved ejection fraction (HFPEF; 3 RCTs, undefined participant number) and when exclusively delivered in a home-based setting (5 RCTs, 521 participants).

Three RCTs reported economic data. Although no group differences in costs or outcomes across these three studies achieved statistical significance, two studies indicated exercise-based CR to be cost-effective (US$ 1773 per life-year saved [27] and a mean gain in QALY of 0.03 at an additional mean cost of US$ 1161 per person [28]).

3.3.3 Psychological interventions for coronary heart disease [11]

This review undertook searches up to January 2009 with the inclusion of RCTs of psychological interventions compared to usual care in patients with a diagnosis of coronary artery disease. A total of 24 RCTs were included in 9,087 patients who were predominantly low risk post-MI or PCI, male (median 84%) with a median mean age of 57 years (see Table 2). The review authors reported substantial variability in the intensity of treatments offered across RCTs; the mean number of hours spent in treatment was 26.1 (2.4 hrs to 96 hrs).

The majority of the interventions were based on group therapy sessions or comprised a mix of group and individual session; only four RCTs used treatments that were delivered only on an individual basis. There was evidence of a trend towards a reduction in all-cause mortality (RR 0.89; 95% CI, 0.75 to 1.05) and fewer cardiac deaths with psychological intervention (RR 0.80; 95% CI 0.64 to 1.00). There were significant effects on occurrence of revascularisation (RR 0.95; 95% CI 0.80 to 1.13) and non-fatal reinfarction (RR 0.87; CI 0.67 to 1.13). One of seven studies reported superiority in HRQL with psychological intervention compared to usual care.

3.3.4 Patient education in the management of coronary heart disease [12]

This review undertook searches up to August 2010 with the inclusion of RCTs with follow up of 6 months or more, of patient education interventions compared to usual care. A total of 13 RCTs were included across 68,649 participants with heart failure, stable angina, and post-MI or PCI who were predominantly male (median 60%) with a median mean age of 62.0 years (see Table 2). Interventions varied considerably across RCTs, with some providing group sessions, some individualised education and others both. Educational 'dose' ranged from a total of two clinic visits to a four-week residential stay with 11 months of follow-up sessions. There was no evidence of a significant difference in total mortality (RR 0.79; 95% CI, 0.55 to 1.13) or morbidity. Across the eleven RCTs which reported HRQL, whilst there was no consistent difference in HRQL total or domain score at follow-up between intervention and control, five RCTs demonstrated statistically significant differences in some domains in favour of intervention. Five RCTs reported healthcare utilisation and costs.

3.3.5 Home-based versus centre-based cardiac rehabilitation [13]

This review was recently updated with searches up to November 2012 and sought to include RCTs comparing home-based and centre-based CR. Home-based CR was defined as 'a structured programme with clear objectives for the participants, including monitoring, follow up visits, letters or telephone calls from staff, or at least self-monitoring diaries' and centre-based CR was defined as 'based in a variety of settings (e.g. hospital physiotherapy department, university gymnasium, community sports centre)'. A total of 17 RCTs were included in 2,266 patients with stable angina, heart failure and post-MI and PCI who were predominantly male (median 80%) with a median mean age of 60 years (see Table 2). The majority of RCTs compared comprehensive programmes (i.e. exercise training plus education and/or psychological interventions) with the exercise components

differing considerably across RCTs in duration (range: 1.5 to 6 months), frequency (1 to 5 sessions per week) and session length (20 to 60 minutes per session).

A pooled analysis found no evidence of a significant difference in mortality up to 12 months follow-up between home and centre CR (RR 1.26; 95% CI, 0.68 to 2.33). Four studies reported cardiac events, but no pooling of data was possible due to differences in the varied nature of the reported events. There was no evidence of difference between the two settings in overall or domain HRQL scores in individual RCTs. Four out of the 14 studies reporting adherence found superior adherence in the home-based compared with centre-based CR setting. No consistent difference was seen in the healthcare costs of the two forms of CR.

3.3.6 Promoting patient uptake and adherence in cardiac rehabilitation [13]

This review was recently updated with searches up to January 2013 and sought to include RCTs of interventions to increase CR uptake (participants attendance or enrolment in CR programmes) or adherence (extent to which the participant's behaviour concurred with the advice given by health professional, e.g. to attend CR meetings or to undertake independent exercise) . A total of 18 RCTs were included in 2,266 participants with heart failure, stable angina, and post-MI and PCI who were predominantly male (median 84%). Meta-analysis was not undertaken due to heterogeneity in outcome definition across RCTs. Of the ten RCTs (1,658 participants) evaluating the effectiveness of interventions to increase uptake of cardiac rehabilitation, eight reported higher rates of CR uptake in the intervention group (range 11% to 46%). Interventions which improved uptake of CR included: structured nurse or therapist-led contacts; early appointments after discharge; motivational letters; gender-specific programmes; and intermediate phase programs for elderly patients. Three out of eight RCTs (1,167 participants) found significant improvements in adherence to CR although there was no evidence of an improvement in HRQL. Interventions which improved adherence included self-monitoring of activity, action planning, and tailored counselling by CR staff. Although data was

limited, there was no evidence of a difference in mortality or morbidity with uptake or adherence interventions. No RCTs reported on costs or cost-effectiveness.

4. Discussion

4.1 Summary of main results

CR programmes have become an integral part of the standard of care for patients with heart disease. The scope of contemporary CR has shifted from exercise interventions alone to more comprehensive secondary prevention programmes that include risk factor education and psychological support. This overview identified six Cochrane systematic reviews of RCTs that have assessed the outcomes of various aspects of the delivery of CR and its component interventions. The key outcome findings of our overview are: (i) Compared to a no exercise training control, exercise-based CR in low to moderate risk patients with heart failure and after MI or PCI is safe, with no increase in short-term mortality, and effective, in terms of reductions in the risk of hospital admission and improvements in patient HRQL, as well as some evidence of a reduction in total and cardiovascular mortality in CHD patients at 12 months or more follow-up. Whilst there was considerable evidence of heterogeneity across included primary studies in both the characteristics of the evaluated CR programmes and also across the included patients, the outcome benefits of CR in terms of HRQL and reduced hospitalisation appeared to be independent of these programme and patient characteristics; (ii) Psychological-based and education-based interventions alone appear to have little or no impact on mortality or hospitalisation, but may improve HRQL of CHD patients in comparison with usual care alone; (iii) Home based and centre-based programmes seem to be equally effective in improving the outcomes of exercise-based CR in low risk patients after MI or post-revascularisation or with heart failure. Healthcare costs of the two forms of CR are similar,

presumably as any cost reduction in delivering the intervention in the home is offset by the associated costs of delivering individual nursing care; and (iv) Uptake of CR programmes is only weakly supported by interventions designed to improve adherence to CR programmes.

4.2 Strengths and limitations

The included Cochrane systematic reviews were generally of high quality and three had been updated with a literature search within the past three years [8, 9, 13]. None of the reviews commented on the quality of the interventions or comparison groups described by the RCTs, although it is recognised that this would be restricted by limited reporting of the interventions in the RCTs. This limitation should be taken into consideration when interpreting the evidence presented. The quality of the primary RCTs in the included systematic reviews was variable. The main sources of bias in the primary studies were inadequate reporting of allocation concealment and randomisation methods and lack of outcome blinding. Another potential source of inconsistency which was not reported within reviews, was differential use of outcome data by RCTs i.e. some studies analysed only post interventional data while others measured pre-post change.

There are a number of published non Cochrane systematic reviews of CR [29-33]. Given our focus was Cochrane review we acknowledge that this overview cannot be regarded as an all-inclusive summary of the evidence base for CR. However, by focusing on high quality Cochrane reviews, we believe this overview provides a least biased estimate of the impact of CR.

This overview includes RCTs conducted between 1974 and 2013. During this time, there have been major advances in medical management, such as the increased use of statins since the mid-1990s. Indeed it has been hypothesised that major advances in post-MI medical management in the last decade has led to a reduction in the incremental effect on mortality of CR compared with usual care alone [34]. This decrement in mortality benefit of CR is supported by the rehabilitation after myocardial infarction (RAMIT) trial. This trial randomised 1,813 patients in 14 hospitals in England and Wales to receive either comprehensive CR or usual care and found no difference in all-cause

mortality at 2 years (RR 0.98, 95% CI 0.74 to 1.30) or after 7-9 years (0.99, 95% CI 0.85 to 1.15) [35]. This RCT was published after the search cut of the exercise-based CR for CHD Cochrane review.

A potential strength of an overview is that it can provide an opportunity to undertake indirect comparisons across interventions that might not be included in single systematic reviews using mixed treatment comparisons and network meta-analysis methods [14, 36]. In brief, an indirect comparison involves the comparison of two (or more) interventions via one or more common comparator. For example, we may seek to compare the impact of exercise-based interventions and psychological-based interventions via the combination of RCTs of exercise-based intervention versus usual care with RCTs of psychological-based intervention versus usual care. However, for the intervention effect determined using an indirect comparison to be valid and equivalent to the intervention effect measured using a direct comparison, the sets of RCTs used to obtain the indirect comparison need to sufficiently similar in their characteristics i.e. patient population, intervention, comparator and outcomes across trials need to similar – the transitivity assumption [37]. Given the substantial heterogeneity in the populations of the included RCTs, not only between, but also within the included CR systematic reviews, we deemed indirect comparisons as inappropriate in the case of this overview. Based on the same reasoning, readers of this overview need to apply considerable caution in taking an informal indirect comparison approach and comparing the results for a given outcome across reviews.

4.3 Agreements and disagreements with other overviews

Oldridge recently undertook an overview of meta-analyses of CR [38]. Given that this overview included both Cochrane and non-Cochrane meta-analyses published since 2000, there is considerable overlap in findings and conclusions with the present overview. However, an important difference between the two overviews is the conclusion of a reduction in all-cause and cardiovascular mortality with CR in the review by Oldridge. This mortality benefit was primarily seen in the two non-Cochrane meta-analyses [30, 39], while the Cochrane review found a statistically

significant reduction in all-cause and cardiac mortality only at follow-up of greater than 12 months (Heran 2011).

. 4.4 Implications for research

The central aim of this overview was to inform conduct and direction of the Cochrane systematic reviews of CR. In brief, we make the following recommendations for future CR systematic reviews:

(1) Scope of reviews: the scope of CR reviews needs to reflect current guidelines advising that CR should be based on an individually prescribed programme of exercise training with appropriate co-intervention including psychological or educational interventions.

(2) Handling clinical heterogeneity: a key challenge of CR systematic reviews is the substantive level of heterogeneity in the population and interventions across RCTs. A number of approaches can be used to handle heterogeneity in future reviews, including stratification of outcome results by patient indication or intervention type (i.e. exercise training only versus comprehensive CR interventions); reporting within RCT subgroup analyses; and use of meta-regression to explore the impact of patient and intervention characteristics on outcomes between trials.

(3) Effectiveness and costs of different CR interventions: broadening the inclusion criteria of reviews to include the active comparator arms of RCTs that allow comparisons of different CR interventions and consideration of the use of the indirect comparison methods [40].

(4) Consistency in review conduct and reporting: to facilitate comparison across CR systematic reviews and the efficient future update of this overview, future Cochrane CR reviews need to standardise their conduct, including improved reporting of included RCT characteristics, content and quality/fidelity of delivery of interventions, and risk of bias assessment criteria, and outcomes.

This overview also highlights several potential areas for consideration in the conduct of future RCTs of CR. RCT recruitment criteria need to better reflect the real world of CR delivery that includes patients at higher risk who are older, female and from a broader range of ethnicities and socio-

economic groups. Reporting of trial methods should be improved (e.g. details of the process of randomisation and outcome blinding) and consistency is needed in the collection and reporting of outcome measures, including the use of validated HRQL, cardiac-related events, re-admissions and costs. Finally, as noted by Clark and colleagues, future RCTs need to better "open the black box" of CR [41]. In other words, to determine the incremental benefits of the various components of CR requires future RCTs to provide more precise descriptions of their CR interventions so these comparisons can more explicitly and reliably undertaken in future systematic reviews. A recent publication provides researchers and clinicians with a framework to improved reporting of intervention detail [42]. Also, future RCTs should be designed to provide a 'head-to-head' comparison of different combinations of CR interventions (e.g. an 'exercise only' CR intervention compared versus 'exercise plus' CR intervention).

4.5 Implications for policy

The evidence compiled by this overview support current international clinical guidelines which state that the addition of exercise-based CR to medical management is effective, (improving HRQL and reducing the risk of future hospitalisations) and safe (with no increase in short-term mortality), compared to a no exercise training control, for clinically stable patients following MI or PCI or who have heart failure [43-46]. Future RCTs of CR need to improve their reporting methods and better reflect the real world practice including the recruitment of higher risk patients and consideration of contemporary models of CR delivery, and identify effective interventions for enhancing adherence to rehabilitation.

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Contributions of authors

Both authors were involved in the conception and design of the protocol and the review. LJA and RST undertook the study selection, data extraction and risk of bias assessment. The manuscript was drafted by both authors.

Declarations of interest

Lindsey Anderson declares that she has no conflicts of interest. RST was a co-author on five of the included systematic reviews.

Table 1. Summary of included Cochrane review characteristics

Short title Review Reference	Exercise for CHD Heran 2011 [10]	Exercise for HF Taylor 2014a [8]	Psychological for CHD Whalley 2011 [11]	Education for CHD Brown 2011 [12]	Home vs centre Taylor 2014b [9]	Uptake & adherence Karmali 2014 [13]
Main objective	To determine the effectiveness of exercise-based CR (exercise training alone or in combination with psychosocial or educational interventions) on mortality, morbidity and health-related quality of life of patients with CHD.	To determine the effectiveness of exercise-based interventions compared with usual medical care by focusing on the mortality, hospital admission rate, morbidity and health-related quality of life in patients with heart failure.	1. To determine the independent effects of psychological interventions in patients with CHD	1. Assess effects of patient education on mortality, morbidity, HRQL and healthcare costs in patients with CHD.	To determine the effectiveness of home-based CR programmes compared with supervised centre-based CR on mortality and morbidity, HRQL and modifiable cardiac risk factors in patients with CHD.	To determine the effects, both harms and benefits, of interventions to increase patient uptake of, and adherence to, CR.
Search time frame	Nov 2000 to Dec 2009	2008 to March 2013	2001 to Jan 2009	1990 to Aug 2010	2008 to Nov 2012	2008 to Jan 2013
Study design	RCTs (follow up ≥ 6 months)	RCTs (follow up ≥ 6 months)	RCTs (no minimum follow up)	RCTs (follow up ≥ 6 months)	RCTs (no minimum follow up)	RCTs (no minimum follow up)
Population	*Inclusion* Post-MI Post revascularisation CHD defined by angiography *Exclusion* Heart valve surgery Heart failure Heart transplantation CRT ICD implant	*Inclusion* Heart failure	*Inclusion* Post-MI Post revascularisation Angina CHD defined by angiography *Exclusion* None	*Inclusion* Post-MI Post revascularisation Angina CHD defined by angiography *Exclusion* Heart valve surgery Heart failure Heart transplantation CRT ICD implant.	*Inclusion* Post-MI Post revascularisation Angina Heart failure *Exclusion* Heart valve surgery Heart failure Heart transplantation CRT ICD implant	*Inclusion* Post-MI Post revascularisation Angina Heart failure CHD *Exclusion* Heart valve surgery Heart failure Heart transplantation CRT ICD implant
Intervention	Exercise training with or without the addition of psychosocial and/or educational interventions.	Exercise training with or without the addition psychosocial and/or educational interventions.	Psychological interventions delivered by health care workers with specific training in psychological techniques	Patient education interventions involving direct contact with a health professional and including structured knowledge transfer about CHD.	CR programmes delivered in a home-based setting	CR, plus any intervention with the specific aim of increasing patient uptake of, or adherence to, CR or any of its component parts.
Comparator	No exercise training control that can include psychological and/or educational interventions or	No exercise training control that can include psychological and/or educational interventions or	No psychological intervention control that can include exercise interventions or standard medical care	No education intervention control that can include exercise interventions or standard medical care	CR programmes delivered in a centre-based setting	CR programmes without the intervention

	standard medical care.	standard medical care				

Outcomes	• Mortality (total, CV, non CV)
	• MI (total, fatal, non-fatal)
	• Revascularisations (total, CABG, PTCA, restenting)
	• Hospitalisations (total, CV, other)
	• HRQL
	• Economic: (costs and cost-effectiveness)
		• Mortality (total, HF and sudden death)
		• Hospitalisation (total, HF-related)
		• HRQL
		• Economic: (costs and cost-effectiveness)
			• Mortality (total and CV)
			• Morbidity (Non-fatal MI)
			• Revascularisation (CABG and PTCA)
			• Psychological well-being Anxiety, Depression, stress and Type A
			• Behaviour/hostility
			• HRQL
				• Mortality (total, CV and non CV)
				• Total CV events
				  • MI (fatal and/or non-fatal)
				  • Other fatal and/or non-fatal CV events
				• Revascularisations (CABG, PTCA with or without stenting)
				• Hospitalisations (cardiac-related)
				• HRQL
				• Withdrawals/drop-outs
				• Economic (Healthcare costs and cost-effectiveness)
					• Mortality (total and CV)
					• Morbidity (reinfarction, revascularisation, cardiac associated hospitalisation)
					• Exercise capacity
					• Risk factors (smoking behaviour, blood lipid levels, blood pressure)
					• HRQL
					• Adverse events (withdrawal from the exercise programme),
					• Adherence to rehabilitation
					• Economic (health service use, costs and cost-effectiveness)
						Uptake of, or adherence to, CR (primary)
						• Mortality (total)
						• Morbidity
						• Risk factors (smoking Behaviour, blood lipid levels, blood pressure)
						• HRQL,
						• Economic (Healthcare costs and cost-effectiveness)
						• Any beneficial or adverse events

CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty; CAD: coronary artery disease; CV: cardiovascular; HRQL: health-related quality of life

Table 2. Summary of characteristics of included RCTs

Short title Review Reference	Exercise for CHD Heran 2011 [10]	Exercise for HF Taylor 2014a [8]	Psychological for CHD Whalley 2011 [11]	Education for CHD Brown 2011 [12]	Home vs centre Taylor 2014b [9]	Uptake & adherence Karmali 2014 [13]
Number of RCTs (patients)	47 RCTs (10,794 patients)	33 RCTs (4,740 patients)	24 RCTs (9,296 patients)	13 RCTs (68,556 patients)	17 RCTs (2,172 patients)	18 RCTs (2,505 patients)
Nature of Intervention						Interventions aimed at increasing patient uptake of CR: (10 RCTs)
Exercise only	17	21	0	0	6	
Psychological only	0	0	14	0	0	
Education only	0	0	0	13	0	
>1 intervention	[a]29	12	10 (psych and education)	0	11	Interventions designed to increase adherence to exercise (7 RCTs) or supervised CR: (1 RCT)
Sample size median (range)	142 (28 to 2304)	54 (19 to 2331)	133 (44 to 2481)	288 (87 to 46,606)	104 (20 to 525)	110 (16 to 597)
Intervention duration [months] Median (range) months	3 (1 to 30)	6 (1 to120)	NR	6 (1 to 30)	3 (1.5 to 6)	Not reported
[b]**Publication year**						
1970-9	2	0	2	0	0	0
1980-9	11	0	4	0	1	2
1990-9	20	5	8	4	2	3
2000-9	14	20	10	9	11	8
2010+	0	8	0	0	3	5
Percent male Median (range)	88 (0 to 100)	80 (36 to 100)	84 (0 to 100)	60 (0 to 100)	80 (60 to 100)	84 (0 to 100)
Percent white Median (range)	NR	N = 8 85 (60 to 100)	NR	N=6 86 (55 to 97)	N=1 80	N = 6 79 (43 to 95)
Median Mean Age (range)	55 (49 to 70)	60 (51 to 81)	57 (51 to 62)	62 (51 to 73)	60 (52 to 69)	62 (51 to 77)
[b]**Indication**						
MI only	28	0	10	2	4	4
Angina only	1	0	1	1	0	0
Revasc only	1	0	4	2	4	0
MI and/or revasc	4	0	4	1	5	3
MI or angina	4	0	2	0	0	3
Mixed CHD	9	0	2	4	0	7
HF	0	33	0	3 CHD or HF	3	1
[d]Mean LVEF (%) (range)		29 (21-41)				
Includes NYHA IV		6 (18)0				
[N(%)]Arrhythmia	0		1	0	1	0

[b]**Study location**						
Europe	20 (43)	20 (64)	11 (46)	7 (54)	10 (58)	6(33)
North America	3 (6)	11 (30)	11 (46)	6 (46)	5 (29)	11 (61)
Asia/Australia	7 (15)	1 (3)	2 (8)	0	1 (6)	1(6)
Other	-	1 (3)	0	0	1 (6)	0
Not Reported	17 (36)	0	0	0	0	0
[b]**Single centre**	23 (49)	30 (91)	8 (33)	4 (31)	15 (88)	[c]10/16 (63)
Follow up duration [months] Median (range) months	24 (6 to 120)	6 (6 to 120)	NR	18 (6 to 60)	6 (2 to 72)	3 (1.5 to 12)

[a] 1 RCT randomly assigned to exercise-only or comprehensive intervention
[b]N RCTs (percent);
[c]Two studies were unavailable to us as they were unpublished degree dissertations.
[d]Source, Sagar et al, 2014 [47]

Table 3. R-AMSTAR assessment of included systematic reviews

Short title Review Reference	Exercise for CHD Heran 2011 [10]	Exercise for HF Taylor 2014a [8]	Psychological for CHD Whalley 2011 [11]	Education for CHD Brown 2011 [12]	Home vs centre Taylor 2014b [9]	Uptake & adherence Karmali 2014 [13]
1. Was an 'a priori' design provided?						
(A) 'a priori' design	Yes	Yes	Yes	Yes	Yes	Yes
(B) statement of inclusion criteria	Yes	Yes	Yes	Yes	Yes	Yes
(C) PICO/PIPO research question (population, intervention, comparison, prediction, outcome)	Yes	Yes	Yes	Yes	Yes	Yes
	4	4	4	4	4	4
2. Was there duplicate study selection and data extraction?						
(A) There should be at least two independent data extractors as stated or implied.	Yes	[a]Yes	[a]Yes	[a]Yes	[a]Yes	Yes
(B) Statement of recognition or awareness of consensus procedure for disagreements.	Yes	Yes	Yes	Yes	Yes	Yes
(C) Disagreements among extractors resolved properly as stated or implied	Yes	Yes	Yes	Yes	Yes	Yes
	4	4	4	4	4	4
3. Was a comprehensive literature search performed?						
(A) At least two electronic sources should be searched.	Yes	Yes	Yes	Yes	Yes	Yes
(B) The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE).	Yes	Yes	Yes	Yes	Yes	Yes
(C) Key words and/or MESH terms must be stated **AND** where feasible the search strategy outline should be provided such that one can trace the filtering process of the included articles.	Yes	Yes	Yes	Yes	Yes	Yes
(D) In addition to the electronic databases (PubMed, EMBASE, Medline), all searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	No	Yes	Yes	Yes	Yes	No
(E) Journals were "hand-searched" or "manual searched" (i.e. identifying highly relevant journals and conducting a manual, page-by-page search of their entire contents looking for potentially eligible studies)	No	No	No	No	No	No
	3	4	4	4	4	3
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?						
(A) The authors should state that they searched for reports regardless of their publication type.	[b]No	[b]No	No	[b]No	Yes	[b]No
(B) The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	Yes	Yes	Yes	Yes	Yes	Yes
(C) "Non-English papers were translated" or readers sufficiently trained in foreign language	Yes	No	Yes	Yes	No	No
(D) No language restriction or recognition of non-English articles	Yes	Yes	Yes	Yes	Yes	Yes
	4	3	4	4	4	3
5. Was a list of studies (included and excluded) provided?						
(A) Table/list/or figure of **included** studies, a reference list does not suffice.	Yes	Yes	Yes	Yes	Yes	Yes
(B) Table/list/figure of **excluded** studies, either in the article or in a supplemental source (i.e. online).	Yes	Yes	Yes	Yes	Yes	Yes
(Excluded studies refers to those studies seriously considered on the basis of title and/or abstract, but rejected after reading the body of the text)	Yes	Yes	Yes	Yes	Yes	Yes
(C) Author satisfactorily/sufficiently stated the **reason for exclusion** of the seriously considered studies.	Yes	Yes	Yes	Yes	Yes	Yes
(D) Reader is able to **retrace** the included **and** the excluded studies anywhere in the article bibliography, reference, or supplemental source	4	4	4	4	4	4

6. Were the characteristics of the included studies provided?												
(A) In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions **AND** outcomes.	Yes		Yes		Yes		Yes		Yes		Yes	
(B) Provide the ranges of **relevant** characteristics in the studies analysed (e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.)	Yes		Yes		Yes		Yes		Yes		Yes	
(C) The information provided appears to be complete and accurate (i.e. there is a tolerable range of subjectivity here. Is the reader left wondering? If so, state the needed information and the reasoning).	Yes		Yes		Yes		Yes		Yes		Yes	
		4		4		4		4		4		4
7. Was the scientific quality of the included studies assessed and documented?												
(A) 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	Yes		Yes		Yes		Yes		Yes		Yes	
(B) The scientific quality of the included studies appears to be meaningful.	Yes		Yes		Yes		Yes		Yes		Yes	
(C) Discussion/recognition/awareness of level of evidence	Yes		Yes		Yes		Yes		Yes		Yes	
(D) Quality of evidence should be rated/ranked based on characterized instruments. (Characterized instrument is a created instrument that ranks the level of evidence, e.g. GRADE [Grading of Recommendations Assessment, Development and Evaluation.])	No		No		No		No		No		No	
		3		3		3		3		3		3
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?												
(A) The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review	Yes		Yes		Yes		Yes		Yes		Yes	
(B) The results of the methodological rigor and scientific quality are **explicitly stated** in formulating recommendations.	No		No		No		No		No		Yes	
(C) To have conclusions integrated/drives towards a clinical consensus statement	Yes		Yes		Yes		Yes		Yes		Yes	
(D) This clinical consensus statement drives toward revision or confirmation of clinical practice guidelines	No		No		No		Yes		No		No	
		2		2		2		3		2		3
9. Were the methods used to combine the findings of studies appropriate?												
(A) Statement of criteria that were used to decide that the studies analysed were similar enough to be pooled?	Yes Yes		Yes Yes		No Yes		Yes Yes		Yes Yes		Yes NA	
(B) For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2).	Yes		Yes		Yes		Yes		Yes		Yes	
(C) Is there a recognition of heterogeneity or lack of thereof	Yes		Yes		Yes		Yes		Yes		NA	
(D) If heterogeneity exists a "random effects model" should be used and/or the rationale (i.e. clinical appropriateness) of combining should be taken into consideration (i.e. is it sensible to combine?), or stated explicitly	Yes		Yes		NA		NA		Yes		NA	
(E) If homogeneity exists, author should state a rationale or a statistical test		4		4		3		4		4		2
10. Was the likelihood of publication bias (a.k.a. "file drawer" effect) assessed?												
(A) Recognition of publication bias or file-drawer effect	Yes		Yes		Yes		Yes		Yes		Yes	
(B) An assessment of publication bias should include graphical aids (e.g., funnel plot, other available tests)	Yes		Yes		Yes		Yes		Yes		No	
(C) Statistical tests (e.g., Egger regression test).	Yes		Yes		Yes		Yes		Yes		No	

		4		4		4		4		4		2
11. Was the conflict of interest stated?												
(A) Statement of sources of support	Yes		Yes		Yes		Yes		Yes		Yes	
(B) No conflict of interest. This is subjective and may require some deduction or searching.	Yes		Yes		Yes		Yes		Yes		Yes	
(C) An awareness/statement of support or conflict of interest in the **primary** inclusion studies	No		No		No		No		No		No	
		3		3		3		3		3		3
Total score (n/44)		39		39		39		41		40		35

[a] Studies were screened independently by two review authors. Data was extracted by one review author and checked by a second

[b] While the authors didn't explicitly state that they searched for reports regardless of publication type, it was clear from the included studies and/or text that a search of grey literature was conducted.

Table 4. Risk of bias of included RCTs

Short title Review Reference	Exercise for CHD Heran 2011 [10]	Exercise for HF Taylor 2014a [8]	Psychological for CHD Whalley 2011 [11]	Education for CHD Brown 2011 [12]	Home vs centre Taylor 2014b [9]	Uptake & adherence Karmali 2014 [13]	Total
[a]Random sequence generation	8 (17)	10 (30)	7 (29)	9 (69)	4 (24)	9 (50)	47 (31)
[a]Allocation concealment	7 (15)	6 (18)	7 (29)	7(54)	7 (41)	8 (44)	41 (27)
[a]Groups balanced at baseline	[b]27 (57)	32 (97)	[b]10 (42)	12(92)	14 (82)	[bc]9(56)	103 (68)
[a]Outcome blinding	4 (9)	11 (33)	5 (21)	4(31)	7 (41)	5 (28)	36 (24)
[a]Selective reporting	0 (0)	31 (94)	16 (67)	12(92)	16 (94)	15 (83)	90 (59)
[a]Loss to follow < 20%	33 (70)	29 (88)	13 (54)	10(77)	11 (65)	4 (22)	99 (65)
[a]Intention to treat analysis	[b]19 (40)	29 (88)	22(92)	11(85)	14 (82)	[bc]7 (44)	101 (66)
[a]Groups received same treatment apart from intervention*	[b]21 (45)	21 (64)	[b]16 (67)	11(85)	15 (88)	[bc]15 (94)	100 (66)

[a]N RCTs with low risk of bias (percent)
[b]Risk of bias was not reported within the review, but was assessed by the authors of this overview
[c]denominator = 16 as two studies were unavailable to us as they were unpublished degree dissertations.

Table 5. Summary of outcome results across Cochrane systematic reviews

Short title Review Reference	Exercise for CHD Heran 2011 [10]	Exercise for HF Taylor 2014a [8]	Psychological for CHD Whalley 2011 [11]	Education for CHD Brown 2011 [12]	Home vs centre Taylor 2014b [9]	Uptake & adherence Karmali 2014 [13]
Total mortality	**Follow up < 12 months** N=19 RCTs (6000 patients), RR = 0.82 [0.67 to 1.01] I^2 = 0% **Follow up > 12 months** N=16 RCTs (5790 patients) RR = 0.87 (0.75 to 0.99) I^2= 0%	**Follow up < 12 months** N =25 RCTs (1871 patients) RR = 0.93 [0.697 to1.27] I^2= 0% **Follow up > 12 months** N=6 RCTs (2845 patients) RR=0.88 [0.75 to 1.02] I^2 = 34%	N=17 RCTs (6852 patients) RR = 0.89 [0.75 to 1.05] I^2=2%	N = 6 RCTs (2330 patients) RR=0.79 [0.55 to 1.13] I^2 = 16%	**Follow up < 12 months** N =7 RCTs (1166 patients) RR = 0.79 [0.43 to 1.47] I^2 = 0% **Follow up > 12 months** N = 1 (525 patients) RR = 1.99 [0.50 to 7.88]	N = 3 RCTs (211 patients) 0/3 RCTs reported a significant difference between intervention and control groups (no pooling of data)
Cardiovascular mortality	**Follow up < 12 months** N= 9 RCTs (4130 patients) RR = 0.93 [0.71 to 1.21] I^2= 0.0% **Follow-up > 12 Months** N = 12 RCTs (4757) RR = 0.74 [0.63 to 0.87] I^2 = 0.0%	*"Studies did not consistently report deaths due to heart failure or sudden death"*	N = 5 RCTs (3893 patients) RR = 0.80 [0.6 to 1.00] I^2 = 0.0%	NR	NR	NR
Hospitalisation	**Follow up < 12 months** N = 4 RCTs (463 patients) RR = 0.69 [0.51 to 0.93] I^2 = 12% **Follow up >12 months** N = 7 RCTs (2009 patients) RR = 0.98 [0.87 to 1.11] I^2 = 56%	**Follow up < 12 months** N = 15 RCTs (1328 patients) RR = 0.75, [0.62 to 0.92] I^2 = 0.0% **Follow up > 12 months** N = 5 RCTs (2722) RR 0.92 [0.66 to 1.29] I^2 = 63%	NR	**At end of follow up period** N = 4 RCTs (12905 patients) RR = 0.83 [0.65 to 1.07] I^2 = 32%	N = 1 RCT No difference between home and centre based CR	N = 3 RCTs (numbers not provided) No significant difference between intervention and control groups (no pooling of data)
Heart failure-specific admissions	NR	**Follow up > 12 months** N =12 RCTs (1036 patients) RR = 0.61 [0.46 to 0.80] I^2 = 34%	NR	N = 1 RCT Patients in the intervention group had 41% fewer heart-related admissions (p = 0.05) and 61% fewer Heart-related inpatient days (p=0.02) than in the control group.)	NR	NR
Events **MI**	**Fatal and/or nonfatal MI** Follow up < 12 months	NR	**Non-fatal MI** N = 12 RCTs (7534 patients)	**MI at the end of the follow up period** N =2 RCTs (209	N = 2 RCTs No difference	**CHD Event rates** N = 3 RCTs

	N = 12 RCTs (4216 patients) RR = 0.92 [0.70 to 1.22] I^2 = 19% **Follow up >12 months** N =16 RCTs (5682 patients) RR = 0.97 [0.82 to 1.15] I^2 = 25%		RR = 0.87 [0.67 to 1.13] I^2= 31%	patients) RR = 0.63 [0.26 to 1.48] I^2 = 0%	between home- and centre-based CR (no pooling of data performed)	(414 patients) 2/3 RCTs reported no difference between intervention and control groups N = 1 (228 patients) RR=1.66, p < 0.01
CABG	**Follow up < 12 months** N = 14 RCTs (2312 patients) RR = 0.91 [0.67 to 1.24] I^2 = 0% **Follow up > 12 months** N = 9 RCTs (2189 patients) RR = 0.93 [0.68 to 1.27] I^2 = 0%	NR	**Revascularisation (CABG and PTCA combined)** N = 12 RCTs (6670 patients) RR = 0.95 [0.80 to 1.13] I^2 = 13%	**At end of follow-up period** N =2 RCTs (209 patients) RR = 0.58 [0.19 to 1.71] I^2= 0%	Not reported by RCTs	
PTCA	**Follow up < 12 months** N =7 RCTs (1328 patients) RR = 1.02 [0.69 to 1.50] I^2 = 12% **Follow up >12 months** N=6 RCTs (1322 patients) RR= 0.89 [0.66 to 1.19] I^2=20%	NR	See above	Not reported by RCTs	Not reported by RCTs	
HRQL	N = 10 7/10 RCTs reported evidence of a significantly higher level of HRQL with intervention at follow-up.	N = 20 **MLWHF score** **Follow up < 12 months** N = 13 RCTs (1270 patients) WMD = -5.8 [-9.2 to -2.4] I^2 = 70% **Follow up > 12 months** N = 3 RCTs (329 patients) WMD = -9.5[-17.54 to -1.5] I^2 = 73% **All HRQL measures pooled** N = 20 RCTs	N = 7 1/7 RCTs reported evidence of a significantly higher level of HRQL with intervention at follow-up.	Across 11 RCTs, 81 HRQL outcome scores/subscores reported: • 14/81 in favour of intervention compared to control • 67/81 no significant difference between intervention and control 5/11 RCTs reported evidence of a significantly higher level of some HRQL domains with intervention at follow-up.	N = 10 8/10 studies reported improvements in HRQL at follow-up with both home- and centre-based CR compared to baseline. No strong evidence of difference in overall HRQL outcomes or domain score at follow up between home- and centre-based CR.	N = 2 1/2 studies reported improvement in HRQL with intervention (ns) 1/2 studies reported improvement in both groups but no significant difference between intervention and control

		(3240 patients) SMD = -0.5[-0.7 to -0.3] I^2 = 79%		No consistent difference in HRQL total or domain score at follow-up between intervention and control		
Economics Costs Cost-effectiveness	**Costs** 2/3 studies reported total healthcare costs was not statistically significantly different between groups. **Cost-effectiveness** N = 1 Authors concluded that rehabilitation was an efficient use of health-care resources and may be economically justified	N = 3 Two studies undertook a cost effectiveness analysis and one reported costs There was no evidence of significantly different costs or outcomes	NR	N = 5 RCTs reported healthcare utilisation costs. 2/5 RCTs reported an overall average net saving of US$965 per patient at 6 months follow up and US$1420 per patient at 24 months follow up. 1/5 reported an increase in average net costs of US$52 per patient 2/5 reported no difference between groups No RCTs reported cost-effectiveness	3/4 RCTs reported healthcare costs associated with CR were lower for the home-based than centre-based programmes 1/4 reported that home-based CR was more costly than centre-based CR but costs would be the same if patient costs were included. 8 studies reported different aspects of consumption of healthcare resources. No significant between group differences were seen.	NR
All cause withdrawal /drop out at follow-up	NR	NR	NR	**At follow-up** N = 8 RCTs (2862 patients) RR = 1.03 [0.83 to 1.27] I^2 = 34%	**At follow-up** N = 18 (1894 patients) RR = 1.04 [1.00 to 1.08] I^2 = 44%	NR
Uptake	NR	NR	NR	NR	NR	N = 10 (1,338 patients) 8/10 studies reported uptake was significantly higher in intervention group
Adherence	NR	NR	NR	NR	N = 14 [a]3/14 studies reported adherence was significantly higher in home-based CR	N = 8 (1,150 patients) 3/8 studies reported adherence was significantly higher in intervention group

NR = Not reported
ns = not significant

[a]As reported in the Summary of Findings table. Effects of interventions section states 4/1

Appendices

Appendix A: Search Strategy

The Cochrane Library

#1 cardiac near/4 rehab*

#2 cardiac near/4 exercise*

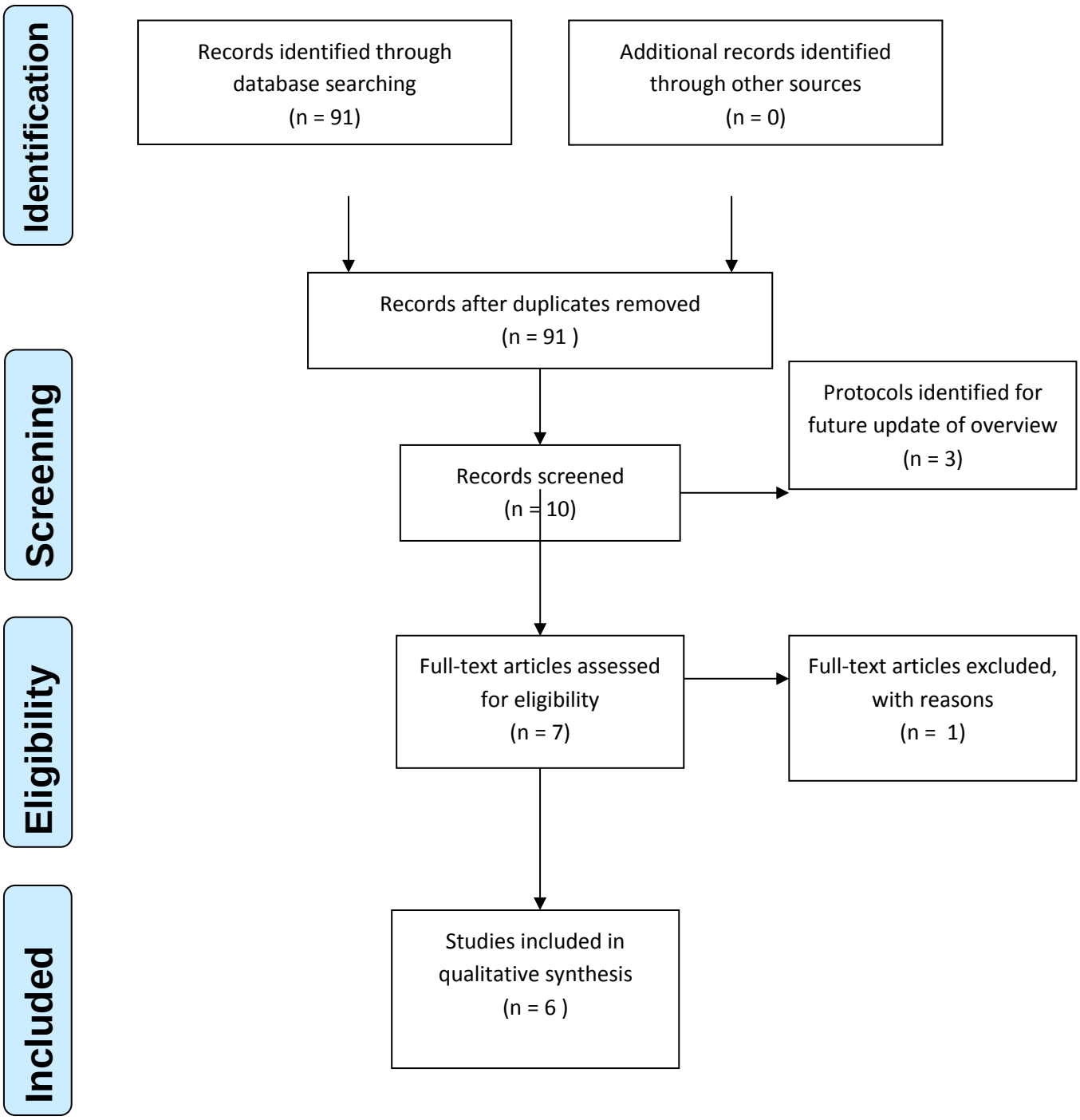
#1 OR #2

Appendix B: Protocols identified

Author	Year	Title
Devi	2011	Internet based interventions for the secondary prevention of coronary heart disease
Euler	2013	Interventions to support return-to-work for patients with coronary heart disease
Sibilitz	2013	Exercise-based cardiac rehabilitation for adults after heart valve surgery
Rissom	2014	Exercise-based cardiac rehabilitation for adultswith atrial fibrillation
*Mechta-Nielsen		Exercise-based cardiac rehabilitation for adult patients with ICD

*We are aware of this proposed title through Personal Communication with the authors

Figure 1 PRISMA Flow Diagram



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