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Sibilitz KL, Berg SK, Tang LH, Risom SS, Gluud C, Lindschou J, Kober L, Hassager C, Taylor RS, Zwisler AD

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[Intervention Review]

# Exercise-based cardiac rehabilitation for adults after heart valve surgery

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## ABSTRACT

### Background

Exercise-based cardiac rehabilitation may benefit heart valve surgery patients. We conducted a systematic review to assess the evidence for the use of exercise-based intervention programmes following heart valve surgery.

### Objectives

To assess the benefits and harms of exercise-based cardiac rehabilitation compared with no exercise training intervention, or treatment as usual, in adults following heart valve surgery. We considered programmes including exercise training with or without another intervention (such as a psycho-educational component).

### Search methods

We searched: the Cochrane Central Register of Controlled Trials (CENTRAL); the Database of Abstracts of Reviews of Effects (DARE); MEDLINE (Ovid); EMBASE (Ovid); CINAHL (EBSCO); PsycINFO (Ovid); LILACS (Bireme); and Conference Proceedings Citation Index-S (CPCI-S) on Web of Science (Thomson Reuters) on 23 March 2015. We handsearched Web of Science, bibliographies of systematic reviews and trial registers (ClinicalTrials.gov, Controlled-trials.com, and The World Health Organization International Clinical Trials Registry Platform).

### Selection criteria

We included randomised clinical trials that investigated exercise-based interventions compared with no exercise intervention control. The trial participants comprised adults aged 18 years or older who had undergone heart valve surgery for heart valve disease (from any cause) and received either heart valve replacement, or heart valve repair.

## Data collection and analysis

Two authors independently extracted data. We assessed the risk of systematic errors ('bias') by evaluation of bias risk domains. Clinical and statistical heterogeneity were assessed. Meta-analyses were undertaken using both fixed-effect and random-effects models. We used the GRADE approach to assess the quality of evidence. We sought to assess the risk of random errors with trial sequential analysis.

## Main results

We included two trials from 1987 and 2004 with a total 148 participants who have had heart valve surgery. Both trials had a high risk of bias.

There was insufficient evidence at 3 to 6 months follow-up to judge the effect of exercise-based cardiac rehabilitation compared to no exercise on mortality (RR 4.46 (95% confidence interval (CI) 0.22 to 90.78); participants = 104; studies = 1; quality of evidence: very low) and on serious adverse events (RR 1.15 (95% CI 0.37 to 3.62); participants = 148; studies = 2; quality of evidence: very low). Included trials did not report on health-related quality of life (HRQoL), and the secondary outcomes of New York Heart Association class, left ventricular ejection fraction and cost. We did find that, compared with control (no exercise), exercise-based rehabilitation may increase exercise capacity (SMD -0.47, 95% CI -0.81 to -0.13; participants = 140; studies = 2, quality of evidence: moderate). There was insufficient evidence at 12 months follow-up for the return to work outcome (RR 0.55 (95% CI 0.19 to 1.56); participants = 44; studies = 1; quality of evidence: low). Due to limited information, trial sequential analysis could not be performed as planned.

## Authors' conclusions

Our findings suggest that exercise-based rehabilitation for adults after heart valve surgery, compared with no exercise, may improve exercise capacity. Due to a lack of evidence, we cannot evaluate the impact on other outcomes. Further high-quality randomised clinical trials are needed in order to assess the impact of exercise-based rehabilitation on patient-relevant outcomes, including mortality and quality of life.

## PLAIN LANGUAGE SUMMARY

### Exercise-based cardiac rehabilitation for adults after heart valve surgery

#### Background

Cardiac rehabilitation has been recommended as a treatment after heart valve surgery, but we have been unable to identify a previous systematic review of the evidence. This systematic review assesses the benefits and harms of exercise-based cardiac rehabilitation in adults who have undergone heart valve surgery.

#### Study characteristics

We searched for randomised clinical trials (experiments in which participants are randomly allocated to an experimental compared with a control intervention) examining the effect of exercise-based cardiac rehabilitation compared with no exercise after heart valve surgery for heart valve disease (from any cause) in adults (18 years or older). Our literature searches were undertaken up to March 2015.

#### Key results

We found two randomised clinical trials published in 1987 and 2004 that included a total of 148 participants. Due to the limited amount of data, we were not able to determine the effect of exercise-based rehabilitation on mortality, serious adverse events, health-related quality of life, ability to return to work, New York Heart Association class, left ventricular ejection fraction, or cost. However, exercise-based rehabilitation did appear to increase exercise capacity at up to 12 months follow-up, although this should be interpreted with caution as the included trials had a high risk of systematic error (bias). Further randomised clinical trials are needed to definitely understand the effect of physical exercise in adults after heart valve surgery.

#### Quality of the evidence

Given that the included studies are relatively old, and included narrowly-selected trial populations, the evidence is likely to be of limited applicability to clinical practice. Both trials had a high risk of bias (systematic errors) and the quality of the evidence was low. Due to the scarcity of the evidence there is also a high risk that the results may be subject to random errors (play of chance). Therefore, further high-quality randomised clinical trials are needed to assess the effects of exercise-based interventions.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise compared with no exercise for patients after heart valve surgery						
<b>Patient or population:</b> patients after heart valve surgery <b>Settings:</b> in hospital and home-based <b>Intervention:</b> exercise <b>Comparison:</b> no exercise						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No exercise group	Exercise group				
<b>Mortality</b> range 3 to 6 months	0/49 (0.0%)	2/55 (3.6%)	<b>RR 4.46</b> (0.22 to 90.78)	104 (1 RCT)	⊕○○○ <b>very low</b>	1,2,3
<b>Serious adverse events</b> range 3 to 6 months	5/72 (6.9%)	6/76 (7.9%)	<b>RR 1.15</b> (0.37 to 3.62)	148 (2 RCTs)	⊕○○○ <b>very low</b>	1,2,3
<b>Exercise capacity at the end of intervention</b> follow-up 3 to 6 months	The mean range in the control groups was -6.86 to -84	The mean range in the intervention groups was -8.67 to -111.6	SMD 0.47 lower (0.81 to 0.13 lower) i.e. SMD -0.47 (-0.81 to -0.13)	140 (2 RCTs)	<b>moderate</b> ⊕⊕⊕○	3
<b>Return to work</b> Follow-up 12 months	8/23 (34.7%) <sup>4</sup>	4/21 (19%) <sup>4</sup>	<b>RR 0.55</b> (0.19 to 1.56)	44 (1 RCT)	⊕⊕○○ <b>low</b>	1,3

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk Ratio; **SMD:** Standardised Mean Difference.

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.

- 
- 1: Downgraded due to no or few events. One of the trials did not report of any deaths. In total across the trials, in the exercise group there were 2 deaths and in the control group 0 deaths.
  - 2: Downgraded due to none of the trials planned to formally collect data regarding mortality or serious adverse events as an outcome. Therefore, potential information regarding the reporting could be missed.
  - 3: Downgraded due to high risk of bias. Both studies failed to give sufficient detail to assess their potential risk of bias. Based on the information available, both trials were classified as overall high risk of bias.
  - 4: Events here represents participants not returning to work.

## BACKGROUND

### Description of the condition

Heart valve diseases account for one-third of all heart disease and are increasing in prevalence due to an ageing population and advances in treatment methods. At present, heart valve diseases are mostly degenerative in nature (Nkomo 2006), and yet highly prevalent in developing countries due to rheumatic heart disease. The overall prevalence of heart valve diseases is widely discussed, as exact estimates do not exist, both because studies have largely focused on hospitalised patients (Jung 2003), and due to the diagnostic inaccuracy of echocardiography (Nkomo 2006). The prevalence in the United States is 2.5% and it is likely to be similar in Europe, although divergent counts exist worldwide (Supino 2006).

Heart valve disease is either left-sided (aortic and mitral valve disease), right-sided (tricuspid and pulmonary valves), or a combination. Initially, heart valve disease is often asymptomatic; when symptomatic, the clinical presentation includes dyspnoea (difficulty breathing), fatigue, fluid retention, and decreased physical capacity. Symptomatic heart valve disease is associated with significant mortality and morbidity, and severely impacts health-related quality of life and physical capacity (Ben-Dor 2010). Treatment includes medical stabilisation with clinical and echocardiographic follow-up (Vahanian 2012). The treatment of choice when serious symptoms and/or haemodynamic changes occur is valve surgery with valve repair or replacement (Nishimura 2014; Vahanian 2012).

The changing disease pattern and expected increase in healthcare burden of people after heart valve surgery require a well-established after-care programme to support the patient's post-surgical problems. These include both physical and psychological issues and the challenge of returning to work.

Before valve surgery, inactivity due to dyspnoea and physical incapacity is common. After surgery, people are often immobilised due to hospitalisation, possible post-surgery complications, and restrictions designed to assist healing of the sternum. Consequently, their physical capacity is at risk of additional decline. As open heart surgery can be an extraordinary and stressful life event (Karlsson 2010), quality of life may be affected (Hansen 2009), with mental problems such as depressive symptoms and anxiety (Fredericks 2012). A Cochrane review (Whalley 2011) showed that people who had undergone surgery for a coronary artery bypass graft might benefit from psychological interventions; however, the bias risk of the trials was considered to be high (Whalley 2011). Little is known about the effects of psychological interventions in people after heart valve surgery.

In summary, after heart valve surgery not only is there a risk of mortality and morbidity, including hospital readmissions and resultant healthcare costs, but importantly patients also experience

physical, mental or social recovery problems that might negatively impact on their health-related quality of life.

### Description of the intervention

Exercise training is a recognised treatment for patients with heart disease. Cardiac rehabilitation is a comprehensive complex intervention including components of exercise training, education, psychosocial management and a behaviour-modification programme designed to improve the physical and emotional conditions of people with heart disease (Piepoli 2010). Whilst rehabilitation programmes can include exercise training alone, comprehensive exercise-based rehabilitation programmes usually consist of exercise training in combination with other interventions, particularly psycho-educational components (Piepoli 2010).

While there are many definitions of cardiac rehabilitation, the following contains their combined key elements: "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" (BACPR 2012).

European guidelines for people after heart valve surgery recommend rehabilitation that includes exercise training, anticoagulant therapy, and medical and echocardiographic follow-up, but do not mention that psycho-educational interventions should be part of the rehabilitation programmes (Butchart 2005). In contrast, American guidelines do not currently include any recommendations or information about cardiac rehabilitation after heart valve surgery, either exercise-based or including psycho-education (Balady 2007; Nishimura 2014).

No specific information exists about how exercise training should be delivered for people after heart valve surgery. The European Society of Cardiology recommends that physical exercise for people with cardiovascular disease should consist of 150 minutes per week, while others recommend three to four hours per week (Piepoli 2010). Further, the recommendations state that low-risk patients should perform 30 minutes of aerobic exercise daily in order to achieve a weekly expenditure of 1000 kcal, whereas high-risk patients should have the amount of physical activity individually prescribed (Gianuzzi 2003). Preferably, exercise should consist of submaximal endurance training (that is, starting at an intensity of 50% of maximum load), the intensity of which is increased over time, and the programme expanded to also include weight/resistance training. Interventions including psychological and educational interventions should offer individual and/or small group education and counselling on adjustment to heart disease, stress management, and health-related lifestyle change (Gianuzzi 2003). We have not been able to identify any international guidelines or consensus statements providing detailed recommendations for the provision of exercise-based cardiac rehabilitation following heart

valve surgery. Moreover, we could not find any systematic reviews or meta-analyses on the topic.

## How the intervention might work

At present, the effect of exercise-based cardiac rehabilitation on total mortality, serious adverse events, and health-related quality of life after heart valve surgery remains uncertain. Existing evidence from both randomised clinical trials and observational studies indicates that exercise-based interventions following heart valve surgery positively affect physical recovery, blood pressure (decrease), New York Heart Association class (decrease), and left ventricular ejection fraction (increase) (Gohlke-Bärwolf 1992; Landry 1984; Newell 1980; Pardaens 2014; Sire 1987). Further, exercise training for cardiac patients may have direct benefits for the heart and coronary vasculature, including on myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collateral vessels (Clausen 1976; Hambrecht 2000). A trial that included heart valve surgery patients as well as other cardiac patients found that exercise training positively affects exercise duration time, the intensity of exercise performed measured by heart rate, and increased oxygen uptake ( $VO_2$ ) (Vanhees 2004).

We might anticipate the same or similar types of effects of exercise-based cardiac rehabilitation after heart valve surgery as those seen in other cardiac populations that typically receive cardiac rehabilitation, i.e., those with myocardial infarction, post-percutaneous intervention, and heart failure. Further, heart function changes due to valve dysfunction such as changed cardiac output, decreased stroke volume and left ventricular ejection fraction, may respond to exercise. Two Cochrane reviews have shown that exercise-based cardiac rehabilitation has a number of positive effects in these latter populations (Taylor 2014; Heran 2011), that include reductions in hospitalisation and improvements in health-related quality of life. It might also be anticipated that exercise-based cardiac rehabilitation following heart valve surgery reduces the symptom burden, improves symptom and disease management, and decreases rates of anxiety and depression as shown for atrial fibrillation patients (Hegbom 2007).

Possible harmful effects of exercise-based cardiac rehabilitation after heart valve surgery could include increased risk of surgery-related adverse events (e.g. arrhythmias, arterial embolism, death), as well as adverse events associated with valve disease per se (e.g. any arrhythmias, heart failure, death). A prospective trial of rehabilitation after cardiac surgery reported a cardiac event rate (defined as chest pain with typical electrocardiographic modifications, severe ventricular arrhythmias, syncope, cardiopulmonary arrest, or a clinical condition necessitating cardiopulmonary resuscitation, immediate transfer to a coronary care unit or cardiac surgery, and/or use of intravenous drugs) of 1/49,565 patient-hours of training, which the authors considered to be low (Pavy 2006).

## Why it is important to do this review

Whilst a review based on non-randomised trial evidence has summarised the efficacy and safety of exercise-based intervention after valve surgery (Kiel 2011), we have been unable to identify systematic reviews or meta-analyses of the evidence in this field. Without a systematic review, the impact of exercise-based cardiac rehabilitation programmes for adults after heart valve surgery remains unclear.

## OBJECTIVES

To assess the benefits and harms of exercise-based cardiac rehabilitation compared with no exercise training intervention, or treatment as usual, in adults following heart valve surgery. We considered programmes including exercise training with or without another intervention (such as a psycho-educational component).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised clinical trials irrespective of the language of publication, publication year, publication type, and publication status were eligible for inclusion in the review. Observational studies that we identified in our searches for randomised clinical trials have been included for assessment of adverse events.

#### Types of participants

We included adults aged 18 years or older of both sexes and of any ethnicity, who have undergone heart valve surgery for any cause of heart valve disease (i.e. aortic valve disease; mitral valve disease; tricuspid or pulmonary valve disease, or a combination), and received either heart valve replacement or heart valve repair (surgery to the valve and the related anatomical areas without valve replacement, e.g. mitral clips, mitral ring, chordae rupture treatment).

#### Types of interventions

##### Experimental interventions: exercise-based interventions with or without psycho-educational intervention

'Exercise-based' interventions are defined as a supervised or unsupervised programme, conducted in an inpatient, outpatient, community, or home-based setting, that includes any kind of exercise



training. The intervention must have included an exercise training component focusing on increasing exercise capacity, and it may also have included a psycho-educational intervention that focuses on improving mental health and the patient's self-management skills. Patients could engage in the exercise intervention before or after discharge from hospital for heart valve surgery (Kiel 2011). For inclusion in this review, the intervention must have included a post-surgical element and may have included a pre-surgical element in advance of surgery. There was no restriction in the length, intensity, or content of the exercise training intervention.

### Control interventions

We sought control interventions including:

- treatment as usual (e.g. standard medical care, such as drug and anticoagulant therapy and medical follow-up with echocardiography);
- no intervention;
- any other type of cardiac rehabilitation programme, as long as it does not include a physical exercise element.

### Co-interventions

We included trials with co-interventions other than rehabilitation of any kind, as long as these were delivered equally in the experimental and the control groups. Co-interventions could include drug, surgical (percutaneous versus transthoracic surgery), or dietary interventions.

### Types of outcome measures

We planned to assess all outcomes at two time points:

- At the end of the intervention (as defined by the trialists);
- At the longest available follow-up.

There was no minimum length of follow-up for the studies that were eligible for inclusion in the review.

### Primary outcomes

We sought the following primary outcomes:

1. Mortality: all-cause mortality and cardiovascular mortality.
2. Serious adverse events: defined as any untoward medical occurrence that is life threatening, results in death, or is persistent or leads to significant disability; or any medical event that has jeopardised the patient or required intervention to prevent it, or any hospital admission or prolongation of existing hospital admission (ICH-GCP 1997).
3. Health-related quality of life using generic or disease-specific validated instruments, e.g. Short Form-36, EQ-5D, HeartQoL.

### Secondary outcomes

We sought the following secondary outcomes:

1. Symptoms that meet New York Heart Association classification of III or IV.
2. Left ventricular ejection fraction.
3. Exercise capacity: any measure of exercise capacity including direct measurement of oxygen uptake ( $VO_2$  peak/ $VO_2$  max) or indirect measures such as exercise time, walking distance etc.
4. Return to work.
5. Costs and cost-effectiveness.

### Search methods for identification of studies

#### Electronic searches

We searched the following electronic databases from their inception to 23 March 2015 (unless otherwise stated):

- Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2 of 12, 2015 on *The Cochrane Library*;
- Database of Abstracts of Reviews of Effectiveness (DARE) Issue 1 of 4, 2015 on *The Cochrane Library*;
- MEDLINE (Ovid) 1946 to March week 3 2015;
- EMBASE Classic + EMBASE (Ovid) 1947 to 2015 March 20;
- CINAHL plus with Full Text (EBSCO);
- PsycINFO (Ovid) 1806 to March week 3 2015;
- LILACS (Bireme) in English;
- Conference Proceedings Citation Index-S (CPCI-S) on Web of Science (Thomson Reuters) 1990 to 19 March 2015.

The preliminary search strategy for MEDLINE (Ovid) was translated for use in the other databases (Appendix 1). The Cochrane sensitivity-maximising RCT filter was applied to MEDLINE (Lefebvre 2011), and adaptations of it to the other databases where applicable.

#### Searching other resources

We applied no language restrictions. Studies written in languages that the author group did not understand were translated professionally. We handsearched for ongoing trials on:

- ClinicalTrial.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov));
- Controlled-trials.com
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search platform (<http://apps.who.int/trialsearch/>).

The reference list of relevant publications was checked for any unidentified randomised trials. Further, we searched for unpublished studies in the field by handsearching conference programmes and attending relevant conferences in the field such as

EuroPrevent. Several of the co-authors are experts in the field with knowledge of current unpublished trials.

## Data collection and analysis

### Selection of studies

Two authors (KLS and LT) independently read the titles and abstracts of potentially relevant papers retrieved by the searching activities described above. If in doubt about whether a title was relevant, we read the full article. We retrieved full publications of all potentially-relevant studies and they were stored electronically and translated where required. Two authors (KLS and LT) determined trial eligibility independently using a standardised inclusion form, excluding studies that did not meet the inclusion criteria. We resolved any disagreements by discussion between the two authors (KLS and LT), and where necessary, a third author (ADZ) was asked to mediate. Excluded studies and reasons for their exclusion are detailed in the [Characteristics of excluded studies](#) table.

### Data extraction and management

Two authors (KLS and LT) independently extracted data from the identified papers using standardised data extraction forms. Where data were presented numerically (in tables or text) and graphically (in figures), we used numeric data, because of the possibility of making measurement errors when estimating from graphs. A third author (ADZ) confirmed all numeric calculations and extractions from graphs or figures. We resolved any discrepancies by consensus. One of the included studies was only available in Chinese. The data extraction for this paper was undertaken by one of the authors (KLS) in the presence of a translator (native Chinese speaker). The data for the Chinese article were double checked with the English abstract (KLS and LT).

We extracted the following data.

- General information: publication status, title, authors' names, source, country, contact address, language of publication, year of publication, duplicate publication, financial conditions.
- Trial characteristics: design and duration.
- Intervention: type of exercise training, type of rehabilitation programme (comprehensive cardiac rehabilitation or only exercise training), setting (e.g., inpatient, outpatient, community, home setting, or a combination), time after hospitalisation, and nature of control group.
- Participants: sampling method (e.g., convenience, random, etc.), inclusion and exclusion criteria, number of participants in intervention and control groups, participant demographics such as sex and age, baseline characteristics including type of valve affected and classification of heart valve disease, and number of participants lost to follow-up.
- Outcomes: data were sought for primary and secondary outcomes as defined earlier. Following publication of the

protocol, we decided to seek all data on the outcomes of employment and costs.

- Risk of bias: see [Assessment of risk of bias in included studies](#) below.

We sought to compare data from each intervention group for parallel group trials and for cross-over trials, using data from the first phase of the trial (i.e. before the cross-over).

### Data analysis

#### Obtaining standard deviations from standard errors

For assessment of the outcome of exercise capacity, one of the included studies ([Lin 2004](#)) reported mean  $\pm$  standard error of the mean (SEM). We wished to use the standard deviation (SD) in the meta analysis and therefore obtained the SD from the SEM by multiplying the square root of the sample size with the SEM ([Higgins 2011a](#); chapter 7.3.3.2).

#### Assessment of risk of bias in included studies

Two authors (KLS and LT) independently assessed the risk of bias in the included studies as described in the protocol ([Sibilitz 2013b](#)) using The Cochrane Collaboration's recommended tool for assessing risk of bias ([Higgins 2011b](#)).

Factors considered included the quality of the random sequence generation and allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, performance bias, for-profit bias, overall risk of bias, groups balanced at baseline, intention-to-treat analysis and groups received the same intervention ([Higgins 2011a](#)). As it is impossible to blind participants and trial staff for this intervention, when we interpreted results from the domain 'Blinding of participants and personnel' we took the risks of bias due to lack of blinding of participants and of personnel into consideration, and had it in mind when we assessed intervention effects ([Savovic 2012](#); [Wood 2008](#)). We provided assessments of risk of bias in the [Risk of bias in included studies](#) for each trial.

#### Small trial (publication) bias

We planned to construct funnel plots for each outcome, to establish the potential influence of small trial effects and potential publication bias. We planned not to use funnel plots for outcomes for which there were ten or fewer trials, or where all trials were of similar sizes ([Sterne 2011](#)). However, due to the limited number of included studies (2 studies) we could not construct a funnel plot.

### 'Summary of findings' tables

We used GRADE ([tech.cochrane.org/revman/other-resources/gradepro](http://tech.cochrane.org/revman/other-resources/gradepro)) to construct a 'Summary of findings' table for the review outcomes where possible. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias.

### Measures of treatment effect

Dichotomous data are expressed as risk ratios (RR) with 95% confidence intervals (CI). For continuous variables net changes were compared (that is exercise group minus control group to give differences). For each trial we sought the mean change (and standard deviation (SD)) in outcome between baseline and follow-up for both exercise and control groups, and when not available we used the absolute mean (and SD) outcome at follow-up for both groups. Results are expressed as a mean difference (MD) except where studies used different scales or measurements, when we used the standardised mean difference (SMD) (Thompson 2002).

### Unit of analysis issues

If any cluster-randomised clinical trials were included, we planned to contact the trial authors to obtain an estimate of the intra-cluster correlation where appropriate adjustments for the correlation between participants within clusters had not been made, or otherwise impute it using estimates from the other included trials, or from similar external trials. However, we did not identify or include any cluster-randomised clinical trials.

### Dealing with missing data

As we did not obtain missing data by contacting the authors of the trials, we sought to undertake sensitivity analysis to explore the effect of this missingness. For dichotomous outcomes, analyses have been made according to the intention-to-treat method (Higgins 2011c), which includes all participants according to their original random group allocation irrespective of compliance or follow-up. For the primary analyses, we assumed that participants lost to follow-up were alive, and had no serious adverse events. For continuous outcomes we have performed available patient analysis and included data only on those for whom results are known (Higgins 2011c). It was possible to obtain SDs either directly from the articles or by calculation (Furukawa 2006). Where studies reported outcomes with a standard error, the SD was calculated by multiplying the standard error by the square root of the sample size with the SEM (Higgins 2011a; chapter 7.3.3.2). We sought to undertake two sensitivity analyses for binary primary outcomes to examine the impact of losses to follow-up.

### Assessment of heterogeneity

Clinical heterogeneity was explored by comparing the population, intervention and control groups across included trials. Statistical heterogeneity was observed in the trials both by visual inspection of forest plots, by using a standard  $\text{Chi}^2$  value with a significance cut off level of  $P = 0.10$ , and by the  $I^2$  statistic. An  $I^2$  estimate greater than or equal to 50% with a significant value for  $\text{Chi}^2$ , was interpreted as evidence of statistical heterogeneity (Higgins 2011a).

### Assessment of reporting biases

Although we planned to create funnel plots to give a visual assessment of whether intervention effects are associated with the size of the trial, due to the small number of included trials this was not possible.

### Data synthesis

Data synthesis was performed according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), using Review Manager 5.3 (RevMan 2014). Meta-analyses were undertaken using a random-effects and a fixed-effect model (Deeks 2011; DeMets 1987; DerSimonian 1986). The SMD was used because the studies all assessed the same outcome but measured it in different ways. As we did not find any differences in inference across outcomes between the two models, only the result for the random-effects model is reported, as stated in the protocol. We used the random-effects model as we assume that the true effect size varies from one study to the next, and that the studies in our analysis represent a random sample of effect sizes that could have been observed.

### Trial sequential analysis

We performed trial sequential analysis for the dichotomous outcomes mortality and serious adverse events (Thorlund 2011; TSA 2011; Wetterslev 2008), but due to the limited number of included studies we did not reach the adjusted boundaries. For the continuous outcomes we could not perform trial sequential analysis as the outcomes in the trials do not use the same unit.

### Subgroup analysis and investigation of heterogeneity

We planned to analyse the primary outcomes, using stratified meta-analysis, according to the following subgroups:

- trials at overall low risk of bias compared to trials at overall high risk of bias; for trials categorised as being at overall low risk of bias, we would perform subgroup analysis on trials at overall lower risk of bias compared to trials at overall higher risk of bias;
- trials including women only versus trials including men only;
- trials including younger patients only versus trials including older patients only;

- trials with an exercise intervention only, compared to trials with an exercise intervention plus any other co-intervention, such as a psycho-educational intervention.

However, due to the small number of included trials and limited amount of data, it was not possible to perform these subgroup analyses.

### **Sensitivity analysis**

For the primary outcomes, we planned to perform the following sensitivity analyses:

#### **Binary outcomes**

*Best/worst-case scenario:* for this analysis we would assume that all participants lost to follow-up in the intervention group have survived, and have had no serious adverse events; and all those with missing outcomes in the control group have not survived, and have had serious adverse events.

*Worst/best-case scenario:* for this analysis we would assume that all participants lost to follow-up in the intervention group have not

survived, and have had serious adverse events; and all those with missing outcomes in the control group have survived, and have had no serious adverse events.

#### **Continuous data**

We had planned to perform the following sensitivity analyses:

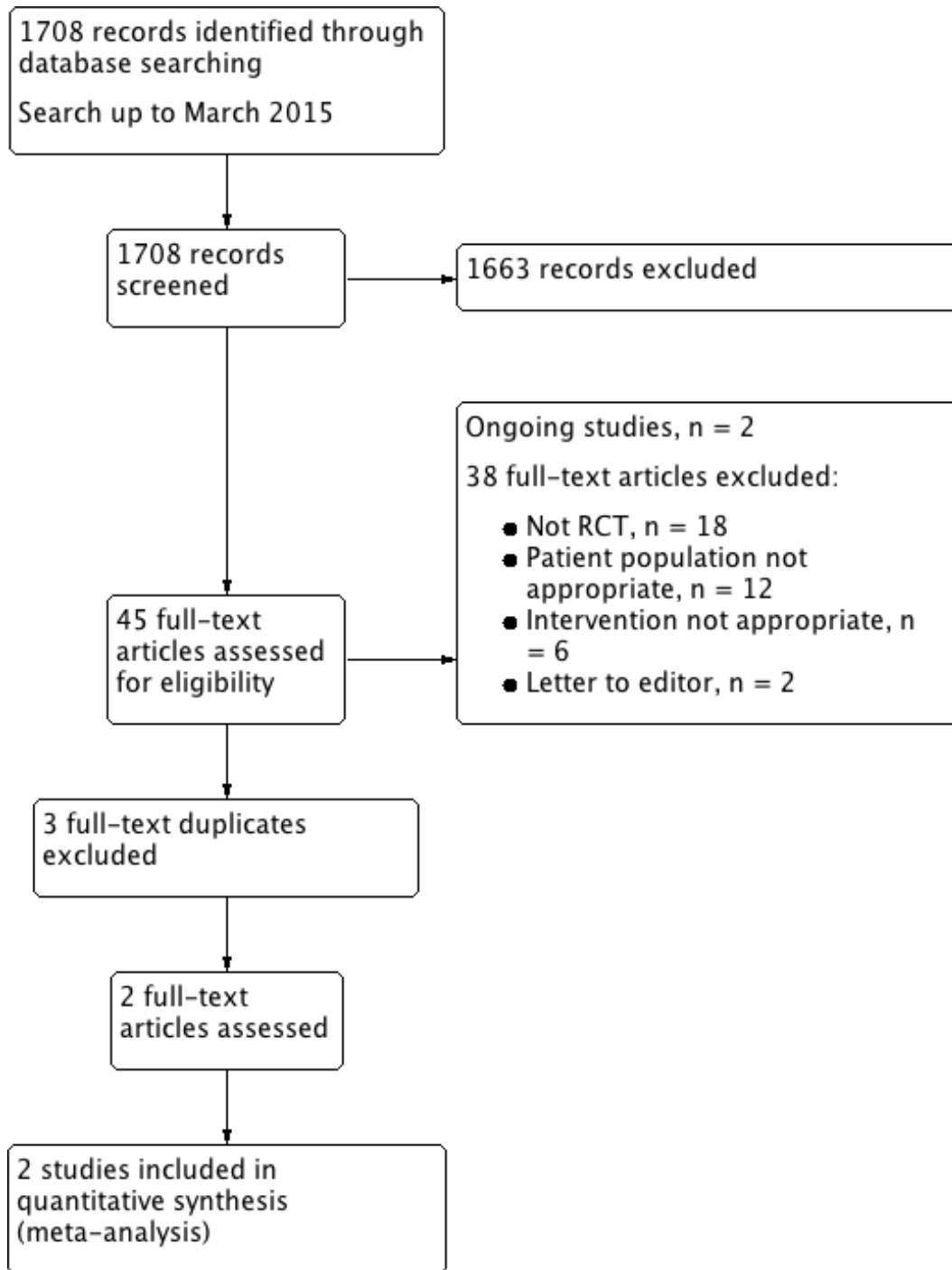
*Assumptions for lost data:* where assumptions had been made for lost data ([Dealing with missing data](#)), we compared the findings from our assumptions with data only from those participants who completed the trials.

## **RESULTS**

### **Description of studies**

The trial selection process is shown in the PRISMA flowchart shown in [Figure 1](#).

Figure 1. Study flow diagram



## Results of the search

Our searches retrieved a total of 1708 titles, of which 1663 did not fulfil the inclusion criteria and were excluded. At full paper review stage we excluded 40 records (38 completed studies and 2 ongoing studies): 18 were non-randomised studies, 6 had an inappropriate intervention, 12 included non-valve surgery patients, 2 were published letters, and 3 were duplicate publications with no additional data. Two were ongoing trials ([CopenHeartVR 2014; Rehabilitation in Aortic Stenosis Patients \(RASP\)](#)) and will be assessed during future updates of this review. For description, please see [Characteristics of ongoing studies](#). Two studies (two publications) met the inclusion criteria.

## Included studies

See: [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

The two included trials randomised a total of 148 participants with either aortic valve replacement ([Sire 1987](#)) or mitral valve replacement ([Lin 2004](#)). Both trials included participants with several valve procedures at a time (e.g. two valve procedures) and excluded patients with ischaemic heart disease. Whilst both studies had published abstracts in English, one was published in full in Chinese. Both were single-centre trials and neither seemed to be industry-sponsored.

Patients were predominantly male (57% [[Lin 2004](#)] and 72% [[Sire 1987](#)]) and the trials had a mean participant age of 31.3 years ([Lin 2004](#)) and 45.5 years ([Sire 1987](#)). Ethnicity was not reported. However, as one trial was undertaken in Norway and the other in

China, ethnicity was likely to be Caucasian and Chinese, respectively. The longest trial follow-up time reported was 12 months ([Sire 1987](#)) and 3 months ([Lin 2004](#)).

Both trials had one exercise arm that consisted of combined aerobic and resistance training, that began either one day ([Lin 2004](#)) or eight weeks post-surgery ([Sire 1987](#)). One of the trials ([Lin 2004](#)) also included a psychological intervention and an exercise training element that were both undertaken before surgery. In both trials the intervention was in a combined hospital- and home-based setting. The dose and intensity of the prescribed exercise training varied from 20 to 30 minutes per session for two to three times weekly over a three month period ([Lin 2004](#)) to four hours daily for four weeks ([Sire 1987](#)). Further details of the studies included in the review are shown in the [Characteristics of included studies](#).

## Excluded studies

Thirty eight studies were excluded and the reasons for exclusion are presented in the [Characteristics of excluded studies](#). The most common reason was that the study was not a randomised clinical trial.

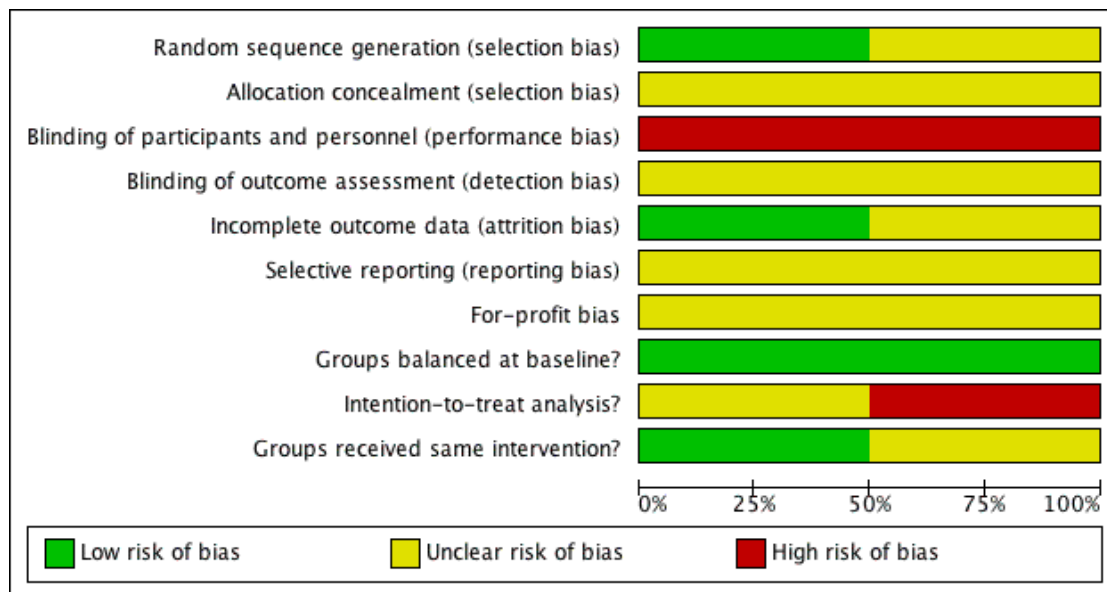
## Risk of bias in included studies

Risk of bias assessments are summarised in [Risk of bias in included studies](#) and [Figure 2](#) and [Figure 3](#). Both studies failed to give sufficient detail to enable a clear assessment of their potential risk of bias. Based on the information available, both trials were classified as having an overall high risk of bias.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	For-profit bias	Groups balanced at baseline?	Intention-to-treat analysis?	Groups received same intervention?
Lin 2004	+	?	-	?	?	?	?	+	-	+
Sire 1987	?	?	-	?	+	?	?	+	?	?

**Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**



### Allocation

Whilst one of the trials (Lin 2004) reported the use of a table of random numbers to generate the allocation sequence, neither trial provided details on allocation concealment. However, neither trial appeared to have imbalance in baseline characteristics between intervention and control groups.

### Blinding

Given the nature of an exercise intervention, it was not possible to blind participants and personnel. Information about blinding of outcome assessment was not reported in either trial.

### Incomplete outcome data

The number and reasons for dropouts and withdrawals was fully described in both trials, but imputation is not described and therefore probably not is used. One trial (Lin 2004) used available case analysis. Whilst neither of the studies formally stated the use of intention-to-treat analysis, both appeared to analyse groups according to the original random allocation. However, one trial (Lin 2004) reported that only patients who did not drop out and were

not lost to follow-up were included in analysis, and therefore the results of this trial are subject to bias.

### Selective reporting

All intended outcomes for the two trials were reported as stated in the objectives of the trials, but we did not identify any published protocols for the trials to confirm this. However, neither trial was specifically designed to capture the primary outcomes of this review (i.e. mortality, serious adverse events, and health-related quality of life).

### Other potential sources of bias

#### Co-interventions (performance bias)

One trial might be prone to performance bias because a part of the exercise-based intervention programme included breathing and coughing exercises (Lin 2004), which could be a potential confounder. Both trials included a co-intervention in the intervention group but not in the control group (psychological co-intervention (Lin 2004) and vocational assistance (Sire 1987)).



### For-profit bias

It is unclear whether the trials were industry sponsored, and they therefore may or may not be free of for-profit bias.

### Small trial bias

There were insufficient trials to assess small trial bias.

### Groups balanced at baseline

According to baseline characteristics there seemed to be no baseline imbalances.

### Intention-to-treat analysis

In both trials the numbers of drop outs and participants lost to follow-up is clearly reported, however, the data analysis seems to apply available case analysis.

### Groups received same intervention

For both trials, the intervention is clearly described for both groups.

### Effects of interventions

See: [Summary of findings for the main comparison](#)

### Primary outcomes

#### Mortality (all-cause and cardiovascular mortality)

Neither of the trials stated that they sought to formally collect mortality as an outcome. Only two deaths were reported across the two trials. In [Lin 2004](#), two participants died in the exercise group and none in the control group (2/55 (3.6%) versus 0/49 (0%)). One was due to sudden death and one due to brain stem death. The trial of Sire and colleagues reported no deaths in either the exercise or control arm (0/21 (0%) versus 0/23 (0%)) ([Sire 1987](#)) (RR 4.46, 95% confidence interval (CI) 0.22 to 90.78, quality of evidence: very low).

Sensitivity analyses for mortality showed in a best/worst-case scenario that exercise is superior to control (RR 0.59, 95% CI 0.10 to 3.41, quality of evidence: very low), and in a worst/best-case scenario that control is superior to exercise in reducing mortality (RR 9.82, 95% CI 0.56 to 173.19, quality of evidence: very low), although none of the findings were statistically significant.

### Serious adverse events

Neither of the trials stated that they sought formally to collect serious adverse events as an outcome. A total of 11 serious adverse events was seen across the two trials (RR 1.15, 95% CI 0.37 to 3.62; [Table 1](#)). No significant difference was found between groups in the number of participants with a serious adverse event (6/76 (7.9%) versus 5/72 (6.9%)).

Analysing the data in the best/worst-case scenario regarding missing data reveals an insignificant effect estimate favouring cardiac rehabilitation (RR 0.64, 95% CI 0.24 to 1.70, quality of the evidence: very low). Analysing the data in the worst/best-case scenario regarding missing data reveals an insignificant effect favouring the control group (RR 2.33, 95% CI 0.87 to 6.27).

Trial sequential analysis could not be performed due to too little information. Presently, only 1.57% of the Diversity Adjusted Required Information Size (DARIS) of 9456 participants has been obtained.

### Adverse events in observational studies

Observational studies and other relevant literature that we identified during the literature search were screened for adverse events. We identified thirteen observational studies ([Gohlke-Bärwolf 1992](#); [Habel-Verge 1987](#); [Jairath 1995](#); [Kappagoda 1979](#); [Kassirskii 1983](#); [Kassirskii 1991](#); [Landry 1984](#); [Meurin 2005](#); [Newell 1980](#); [Niemelä 1983](#); [Roseler 1997](#); [Toyomasu 1990](#); [Vanhees 2004](#)). Of these, nine stated that they did not observe adverse events, and the remaining four observational studies reported the following specifically-described adverse events.

A study by Habel-Verge ([Habel-Verge 1987](#)) in patients after mitral valve surgery reported a non-significant slight increase in haemolysis without clinical relevance for some patients in the training group. [Meurin \(Meurin 2005\)](#) found that among 251 patients, 66 patients had at least one atrial fibrillation episode during exercise lasting more than 24 hours. Further, the adverse events observed were small or moderate pericardial effusion (12% of patients), pleural effusion requiring no pleural drainage (7%), urinary tract infection (5%), and transient ischaemic attack (3.9%). The study by [Newell \(Newell 1980\)](#) tested a physical exercise programme: The Royal Canadian Air Force exercise programme comprising daily exercise for 11 to 12 minutes, including muscle strengthening exercises (callisthenics) and a stationary run. It is described that out of 24 patients, 3 patients in the exercise training group developed postoperative complications necessitating clinical intervention (subacute bacterial endocarditis and cardiac failure), but no complications attributable to training arose in the patients who undertook the complete training procedure.

[Vanhees \(Vanhees 2004\)](#) described in an observational study that included all cardiovascular patients (patients with artificial valve surgery comprised only 3.61% of the total population) that the incidence of complications requiring resuscitation during exercise over 20 years of cardiac rehabilitation was 21 out of 1909 patients

(1 patient resuscitated in 29,214 training hours), with the following complications: acute myocardial infarction during training (n = 4), ventricular tachycardia with temporary loss of consciousness but with spontaneous recovery (n = 7), sustained atrial tachycardia (n = 1), and the remaining undescribed.

#### Health-related quality of life

None of the trials reported on health-related quality of life.

#### Secondary outcomes

##### New York Heart Association (NYHA) class III-IV

None of the trials reported NYHA class at follow-up.

##### Ejection fraction

None of the trials reported left ventricular ejection fraction at follow-up.

##### Exercise capacity

Both trials reported exercise capacity assessed using strenuous exercises (not specified) and standardised bicycle exercise, respectively (not specified whether maximal or submaximal): one trial at 2, 6 and 12 months follow-up (Sire 1987), and the other trial (Lin 2004) at baseline (immediately before discharge) and at 3 months follow-up. The trials assessed physical capacity using either metabolic equivalents (METs) or kilo joules (kJ) which are both measures of energy expenditure at a given activity. Both trials reported a positive effect of exercise training on exercise capacity that achieved statistical significance ( $P < 0.05$ ).

Due to the differences in follow-up we have reported exercise capacity pooled across studies at two time points, as stated in the protocol (Sibilitz 2013b):

1. At the end of intervention (short-term follow-up): 3 months (Lin 2004) and 6 months (Sire 1987);
2. At longest follow-up: 3 months (Lin 2004) and 12 months (Sire 1987).

When pooled across both studies, exercise-based rehabilitation increased exercise capacity between groups both at follow-up at the end of intervention (SMD -0.47 kJ, 95% CI -0.81 to -0.13, random effects) and at longest follow-up (12 months) (SMD -0.50, 95% CI -0.85 to -0.14, quality of the evidence: moderate). Thus, the effect has not diminished with longer follow-up. There was no evidence of statistical heterogeneity ( $I^2$  statistic: 0% and 6%). We were not able to perform trial sequential analysis, as the two trials assessed physical capacity using two different scales. Therefore, the results are reported as SMD.

#### Other outcomes (added following protocol publication)

##### Return to work

Only one trial assessed resumption of employment. The Sire trial reported a non-significant difference in the proportion of patients in the exercise group compared to control on return to work at 12 months follow-up (RR 0.55, 95% CI 0.19 to 1.56, quality of evidence: low) (Sire 1987). The trial found that after surgery 17/21 (81%) patients in the cardiac rehabilitation group compared with 15/23 in the control group (65%) had returned to work (4/21 (19%) versus 8/23 (35%) not returning to work).

##### Costs and cost-effectiveness

Neither trial reported costs or cost-effectiveness at follow-up.

##### Subgroup analyses

There were insufficient trials to undertake stratified meta-analysis and neither trial reported a subgroup analysis.

## DISCUSSION

### Summary of main results

This systematic review identified two randomised clinical trials with a high risk bias, in a total of 148 participants after valve surgery comparing exercise-based cardiac rehabilitation with no exercise control. The exercise-based programmes in these trials consisted of both aerobic exercise and resistance training/joint movements, and comply with European Society of Cardiology recommendation for physical activity for secondary prevention (Corra 2010). There are inadequate data to assess the effects of exercise-based cardiac rehabilitation on the primary outcomes: mortality, serious adverse events, and health-related quality of life. Both of the included randomised clinical trials did show exercise training to be beneficial in terms of short-term improvements in exercise capacity. When outcomes were pooled across both trials, we found a significant improvement in exercise capacity at the end of intervention and at longest follow-up of an average of 0.47 and 0.50 standard deviation units, respectively. However, this result might be due to random or systematic errors. Due to the lack of data we cannot assess the impact of exercise-based cardiac rehabilitation on other secondary outcomes of this review: left ventricular ejection fraction, New York Heart Association class, return to work, costs and cost-effectiveness.

From observational data we found that exercise-based cardiac rehabilitation might have an impact on adverse events. The intervention appears to be safe for selected individuals, but might for some people induce adverse events, such as atrial fibrillation and heart failure. Therefore one of the main findings in this review is that exercise-based cardiac rehabilitation does increase exercise capacity, but not without risk of complications. It is therefore recommended at present, that exercise should not be prescribed for all patients after heart valve surgery, but tailored for low-risk individuals and those without any postsurgical complications in order to avoid adverse events.

### Overall completeness and applicability of evidence

The generalisability of the findings of this review is limited by the small amount of data identified. Both of the included trials recruited highly-selected trial populations consisting of young patients with low to moderate risk, and few women. Moreover, the trials are relatively old (undertaken in 1987 and 2004) and may not reflect contemporary clinical practice. Therefore, several issues need to be addressed when interpreting the implications of the findings of this review for daily clinical practice. For example, throughout the last decade, novel repair techniques have evolved including less invasive techniques, and treatment after heart valve surgery (such as an anticoagulation strategy) has been updated since the publication of the studies included in this review. Further, none of the trials have addressed post-surgical complications, such as readmission, atrial fibrillation, pericardial exudate, and poor self-reported health. These issues need to be included when planning post-surgery management, and considered for inclusion in a rehabilitation programme after valve surgery. In summary, the applicability of the evidence in this review to current practice might be limited, and results should be interpreted with caution, because the trials in the review to some extent are outdated and do not reflect the heart valve populations of today.

### Quality of the evidence

The lack of reporting of methods of the two included trials, especially in terms of the description of the randomisation process and blinding of outcome assessment, made it difficult to assess their risk of bias. However, the risks of bias and of random errors are considered to be high, the quality of evidence ranged from moderate to very low, and both the trial sequential analysis and the sensitivity analyses emphasise that further randomised trials are warranted.

### Potential biases in the review process

To our knowledge this is the first systematic review of randomised trials assessing the impact of exercise-based cardiac rehabilitation for adults after heart valve surgery. We conducted the review according to the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We followed our peer-reviewed published protocol (Sibiltz 2013b) with predefined participants, interventions, comparisons, and outcomes, to avoid biases during review preparation. We performed a comprehensive literature search to identify published and unpublished studies, followed our prespecified inclusion and exclusion criteria, and conducted the meta-analysis using available data or based it on intention-to-treat when possible. We were unable to locate full copies of one paper that may have included important data (Ha 2011). We excluded this trial based on the information provided in the abstract only. However, the bias of this omission is difficult to assess.

The included trials were relatively small and had short-term follow-up; thus the number of reported events (mortality and serious adverse events) was small. Neither of the trials sought formally to collect mortality or serious adverse events as outcomes, and we were only able to capture these outcomes based on the descriptions of losses to follow-up and drop-outs. Another potential limitation in the review process includes translation bias when translating the Chinese article.

### Agreements and disagreements with other studies or reviews

We found that exercise-based cardiac rehabilitation increased physical capacity at short-term follow-up although the result may be due to random or systematic errors. However, this finding concurs with a previous review (Kiel 2011) and observational studies (Jairath 1995; Kassirskii 1991; Landry 1984; Newell 1980). Kiel and colleagues (Kiel 2011) state that cardiac rehabilitation improves quality of life and facilitates return to work. Further, their clinical review was non-systematic, restricted to English literature, included both randomised clinical trials and observational studies, and did not undertake a meta-analysis. Nevertheless, the review concludes that exercise-based cardiac rehabilitation should be part of after-care following heart valve surgery (Kiel 2011). Because Kiel's conclusions are based on data without assessment of the included trials' risk of bias, they must be considered with caution. Cochrane reviews of the effects of exercise-based cardiac rehabilitation have been undertaken for other heart diseases including people with heart failure and Ischaemic heart disease (Heran 2011; Taylor 2014). These reviews demonstrate that cardiac rehabilitation decreases rates of hospitalisation and increases health-related quality of life. Similar outcomes remain to be confirmed for patients after heart valve surgery in future systematic reviews when more data are available.

As the studies in the present review only reported mortality and serious adverse events in the short term, we cannot assess the pos-

sible long-term harms of exercise-based cardiac rehabilitation after valve surgery. Future research therefore needs to address the long-term benefits of exercise training after valve surgery. In this review, both of the participants who died had dropped out of the trial before the end of follow-up, and no information about comorbidities is available.

The populations of exercise-based rehabilitation trials were typically highly selected. Based on the observational studies identified in this review, the intervention appears to be safe for some selected individuals but also for some with a risk of adverse events. Criteria and predictors to identify the patients who benefit the most from rehabilitation are still lacking. Until further evidence emerges for the general heart valve population, exercise-based rehabilitation should therefore be tailored and adjusted throughout if necessary. One of the included trials (Sire 1987) found a positive effect of a cardiac rehabilitation programme including return to work, which is in accordance with former findings (Kittel 2008). However, at present it is unclear whether cardiac factors or psychosocial factors are the reason for unemployment after surgery.

## AUTHORS' CONCLUSIONS

### Implications for practice

Current guidelines from the European Society of Cardiology recommend exercise-based cardiac rehabilitation for patients after heart valve surgery, based on reviews of observational studies, and clinical expertise. Our systematic review of randomised trials shows that there is insufficient evidence to decide whether exercise-based cardiac rehabilitation should be provided for patients after heart valve surgery. In particular, the impact of exercise-based cardiac rehabilitation after heart valve surgery on mortality, serious adverse events, and health-related quality of life remains unclear. Additionally, the impact on adverse events needs to be further investigated, and used to tailor the exercise prescription to relevant individuals. Nevertheless, our review indicates that exercise-based cardiac rehabilitation may improve short-term physical capacity after heart valve surgery and may positively affect return to work.

Both trials included in this review have investigated interventions that were largely based on exercise training. It is widely accepted that contemporary cardiac rehabilitation is a complex intervention and should consist of other elements including risk-factor education and counselling, and psychosocial interventions (Anderson 2014). Additional interventions may also include breathing and coughing exercises and vocational evaluation advice. The rehabilitation programmes in the trials included in this review concur with daily clinical practice for cardiac rehabilitation, in which it is emphasized that other elements than exercise should be included. Moreover, due to the risk of complications and of readmissions, a rehabilitation programme for heart valve surgery patients also

needs to address medical issues and medical stabilisation, along with anticoagulation treatment and thorough information about endocarditis prophylaxis. A relevant practical question is whether patients could benefit from having several options for their intervention, such as centre-based or home-based cardiac rehabilitation or a combination, but again this would need more trials focusing on the association between the risk of mortality and serious adverse events with regards to exercise programmes. Further evidence is needed to justify addition of exercise training in the after care for patients with heart valve surgery.

### Implications for research

This systematic review shows that adequately powered randomised trials are needed to assess the impact of exercise-based cardiac rehabilitation on the outcomes that matter most to patients, clinicians and policy makers. These outcomes include mortality and serious adverse events, health-related quality of life, return to work, and costs and cost-effectiveness. These trials need to be well conducted and reported in accordance with CONSORT guidelines for non-pharmacological interventions (Boutron 2008).

Future clinical trials of exercise-based cardiac rehabilitation in heart valve surgery patients should address the following considerations:

- generalisability of trial populations (i.e. inclusion of women, people with different valve lesions and types of valve surgery (both replacement and repair), and older people who typically remain under-represented in trial populations);
- interventions to minimise the risk of re-hospitalisation, days in bed during, after and up to 12 months after surgery, post-surgery complications;
- interventions to enhance long-term mortality, costs and cost-effectiveness, and adherence, compliance and referral to rehabilitation programmes.

Regarding future Cochrane reviews, it would be reasonable to establish a minimum limit for the number of patients or studies when the review is to be updated, in order to make the review as relevant as possible.

Cardiac rehabilitation is a multifaceted intervention, including different components. A comparison of different kinds of programmes should be tested, in order to better define exercise training, e.g., in terms of 1) type of exercise (cardiovascular training, stretching exercise, strength exercises), 2) workloads (high versus low intensity training), 3) frequency of sessions, 4) programme duration and 5) location of training (home-based or hospital-based).

This review identified two ongoing trials: *CopenHeartVR 2014* and *Rehabilitation in Aortic Stenosis Patients (RASP)*. The *CopenHeart<sub>VR</sub> Trial* (Sibilitz 2013a) will be the first randomised

trial to assess the impact of exercise-based cardiac rehabilitation on mortality, serious adverse events, adverse events, and health-related quality of life in an unselected population after heart valve surgery. The primary and secondary outcomes of the CopenHeart<sub>VR</sub> trial are expected to be published in 2016. The [Rehabilitation in Aortic Stenosis Patients \(RASP\)](#) is still recruiting and the expected publication status is at present unclear (information from [clinicaltrials.gov](http://clinicaltrials.gov) and personal email communication with the investigators).

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

Lin 2004

Methods	Parallel group randomised clinical trial
Participants	<p><b>Country and setting:</b> China, single-centre trial</p> <p><b>N randomised:</b> N total = 104 (intervention 55; control 49)</p> <p><b>Number of participants lost to follow-up:</b> 7</p> <p><i>Number of drop-outs:</i> 3 (2 due to irregular heart rhythm, 1 delayed pericardial tamponade)</p> <p><i>Number with complications:</i> 4 (rehabilitation group: 1 sudden death, 1 with brain stem disease; control group: 1 with paravalvular leakage, 1 endocarditis)</p> <p><b>Diagnosis:</b></p> <p><i>Aetiology:</i></p> <p>The kind of valve disease is not specified; we assume that all kinds of valve diseases are included</p> <p><b>Kind of surgery:</b> mechanical valve replacement of any kind</p> <p><b>Sex:</b></p> <p><i>Total:</i> Men: 59; Women: 45</p> <p><i>Intervention:</i> Men: 31; Women: 24</p> <p><i>Control:</i> Men: 28; Women: 21</p> <p><b>Age (years, mean):</b></p> <p><i>Intervention:</i> 32.8 ± 12.1</p> <p><i>Control:</i> 29.8 ± 9.4</p> <p><b>Inclusion/exclusion criteria</b></p> <p><i>Inclusion criteria:</i> patients of 20 to 45 years, who have undergone a single or double heart valve replacement</p> <p><i>Exclusion criteria:</i> co-morbidities including pathological changes associated with coronary arteries, re-operations of valve replacement surgeries (patients who have undergone valve replacement before), severe pathological changes associated with other organs</p>
Interventions	<p><i>Type of rehabilitation programme:</i> combined physical exercise, breathing exercises and psychological intervention</p> <p><i>Setting:</i> hospital-based and at home. At hospital and at home before and after surgery</p> <p><i>Time after hospitalisation:</i> the day after surgery, and continuing until 3 months after surgery</p> <p><i>Total duration:</i> starting the week before surgery with breathing exercises and psychological intervention, and the day after surgery with physical exercise</p> <p><b>1) Psychological intervention:</b></p> <p>Conducted before surgery. To prevent anxiety and mental pressure before surgery. Introduction to the surgery in detail, and information about safety of the surgery</p> <p><b>2) Breathing and coughing exercises:</b></p> <p>Conducted before and after surgery.</p> <p><i>Frequency and duration:</i> two times a day one week before surgery and after surgery</p> <p><i>Before surgery:</i></p> <p><i>Breathing exercises:</i> lie down or sit up, pillow under knees, relax muscles in stomach, breathe in through the nose so stomach puffs up, breathe out through the nose. 10 to 12 times per minute. The patients monitor themselves</p>

	<p><i>Coughing exercises:</i> after deep breath, chest and stomach power to cough as much as possible, 2 times daily, 20 times each session, the week before surgery. Breathing machine (Sherwood Voldyne) controls the frequency. The patient can overview the results during the exercises. The exercises are to be performed both sitting up, and half laying down</p> <p>After surgery:</p> <p>Day one: stomach breathe exercise, cough exercise to get rid of mucus, half lying down, relaxing whole body</p> <p>Day two: both breathing and coughing exercises</p> <p><b>3) Physical exercise:</b></p> <p>Conducted after surgery. Includes limb stretch/joint exercises and aerobic exercises</p> <p><i>Frequency:</i> limb stretch/joint exercises: patients were advised to do so whenever they felt like it at home; aerobic exercise 2 to 3 times per week</p> <p><i>Duration:</i> 3 to 5 minutes limb stretch/joint exercises and 20 to 30 minutes aerobic exercise/session</p> <p><i>Purpose:</i> The purpose of the training is to increase endurance, and increase pulmonary and cardiac capacity</p> <p>At hospital (after surgery):</p> <p>Day two: joint exercises with passive arms and switch exercises</p> <p>Day three: joint exercises including both arms and legs exercises</p> <p>Day four: go out of the hospital, sitting, standing, get out of bed and walking exercises. Aerobic exercises</p> <p>At home (after discharge):</p> <p><i>Resistance training:</i> stretch arms and legs 3 to 5 minutes equivalent to 5 to 7 metabolic equivalents (METs) each session. The patients were encouraged to do the exercises whenever possible. The purpose of the exercises was to increase joint mobility, to warm up the body and relieve chest pressure</p> <p><i>Aerobic exercise:</i> consisted of either walking slowly uphill, using treadmill or exercise bike at home. Goal of 5 to 7 METs per session</p> <p><i>Intensity:</i> not reported</p> <p><i>Modality:</i> not relevant</p> <p><b>Both groups:</b> follow regular principles and normal procedure for surgery. During surgery the same equipment is used for all patients. After surgery all patients have the same amount of analgesics, antibiotics, and anticoagulants</p> <p><b>Type of control intervention:</b> usual care by the hospital's heart doctor</p>
<p>Outcomes</p>	<p><b>Outcomes:</b></p> <ol style="list-style-type: none"> <li>1. Postoperative incidence of pulmonary complications after surgery: measured once in all patients in % of the control group and rehabilitation group, respectively, during the 3-month period</li> <li>2. The duration of hospitalisation for surgery: days of hospitalisation calculated once after all patients have been discharged after surgery. The number of days between groups was compared</li> <li>3. The body activity energy level; measured at baseline and after 3 months in METs spent using low strenuous physical exercises to test pulmonary and cardiac capacity</li> </ol> <p>Besides outcome measurement the purpose of the test was to assess for which patients the exercise could include a potential risk and thus tailor the exercise plan in the most appropriate way</p>

Notes	First author involved in selecting patients, not in randomisation. The authors emphasise that cardiac rehabilitation including physical exercise should be tailored and concrete, based on different patients' needs and adjusted if necessary	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk	Table of randomised numbers.
Allocation concealment (selection bias)	Unclear risk	Insufficient information about concealment of allocation to assess whether the method used could bias the estimate of the effect
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of exercise-based intervention, blinding is impossible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information is provided on the blinding of the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information about all patients is available, and the number and reasons for dropouts and withdrawals are properly described. However, only patients who did not drop out and were not lost to follow-up were included in the analysis, and therefore the results of this trial are subject to bias
Selective reporting (reporting bias)	Unclear risk	All intended outcomes have been reported, however, a protocol was not published so it remains unclear
For-profit bias	Unclear risk	The trial appears to be without industry sponsorship or other kind of for-profit support, but sources of funding are not stated
Groups balanced at baseline?	Low risk	There seemed to be no imbalance between the two study groups according to baseline characteristics
Intention-to-treat analysis?	High risk	All dropouts and participants lost to follow-up are clearly reported. However, the data analysis only included data on participants whose results were known (available case analysis)

Groups received same intervention?	Low risk	Yes, both groups received usual medical care and the only difference between the groups was the comprehensive rehabilitation programme consisting of physical exercise, psychological intervention and breathing and coughing exercises
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**Sire 1987**

Methods	Parallel group RCT
Participants	<p><b>Country and setting:</b> Norway, single-centre trial</p> <p><b>N randomised:</b> N total = 50 (allocation at randomisation not specified; after drop outs: intervention 21; control 23)</p> <p><b>Number of participants lost to follow-up:</b> 8</p> <p><i>Number of drop outs:</i> 6</p> <p><i>Number with complications:</i> 2 (1 early (with paravalvular leakage), 1 late after 6 months (symptoms of angina pectoris))</p> <p><b>Diagnosis:</b></p> <p><i>Aetiology:</i></p> <p>Aortic valve insufficiency (32%)</p> <p>Aortic stenosis (27%)</p> <p>Combined aortic valve insufficiency and aortic stenosis (41%)</p> <p><b>Kind of surgery:</b> isolated aortic valve replacement</p> <p><b>Sex:</b></p> <p><i>Total:</i> Men: 36; Women: 8</p> <p><i>Intervention:</i> Men: 18; Women: 3</p> <p><i>Control:</i> Men: 18; Women: 5</p> <p><b>Age (years, mean):</b></p> <p><i>Intervention:</i> 45.5±11.7</p> <p><i>Control:</i> 45.5±12.2</p> <p><b>Inclusion/exclusion criteria</b></p> <p><i>Inclusion criteria:</i> patients who have undergone an uncomplicated aortic valve operation</p> <p><i>Exclusion criteria:</i> patients who could not tolerate and perform a physical training programme, patients with signs and symptoms of other heart disease, over 60 years of age, disease in the locomotor system and obvious mental ailments or social disturbances. Male patients with heart volumes exceeding 750 ml/m BSA and females with hearts larger than 650 ml/m BSA</p>
Interventions	<p><i>Type of rehabilitation programme:</i> combined physical exercise and vocational follow-up</p> <p><i>Setting:</i> hospital-based exercise supplemented with home-based exercises</p> <p><i>Time after hospitalisation:</i> 8th to the 12th week after operation</p> <p><b>Exercise:</b></p> <p><i>Total duration:</i> 4 weeks, week 8 to 12 after surgery</p> <p><i>Frequency:</i> daily training</p> <p><i>Duration:</i> 3 to 4 hours/session</p> <p><i>Aerobic/resistance/mix:</i> mix of aerobic and resistance training (including bicycling; dynamic and isometric exercises; callisthenics of alternating heavy and light exercises; vol-</p>

	leyball). The patients also had a home-based programme with few simple exercises <i>Intensity:</i> 85% to 90% of maximal heart rate <i>Modality:</i> not relevant <i>Type of control intervention:</i> none	
Outcomes	<b>Outcomes:</b> 1) Physical work capacity (expressed as cumulated work): measured 2, 6 and 12 months after surgery using a standardised bicycle exercise test; 2) Rate of re-employment: measured after 3 months	
Notes	Follow-up at 2, 6 and 12 months	
<b><i>Risk of bias</i></b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Patients were allocated at random to training or control group, but details about allocation sequence generation are missing
Allocation concealment (selection bias)	Unclear risk	Insufficient information about concealment of allocation to assess whether the method used could bias the estimate of the effect
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of exercise-based intervention, blinding is impossible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information is provided on the blinding of the outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information about all patients is available, and the number and reasons for dropouts and withdrawals are properly described
Selective reporting (reporting bias)	Unclear risk	All intended outcomes have been reported, however, a protocol was not published so it remains unclear
For-profit bias	Unclear risk	The trial appears without industry sponsorship or other kind of for-profit support, but sources of funding are not stated
Groups balanced at baseline?	Low risk	There seemed to be no imbalance between the two study groups according to baseline characteristics
Intention-to-treat analysis?	Unclear risk	All dropouts and participants lost to follow-up are clearly reported except for one participant (unclear which group the patient belonged to), but it is not reported whether the two groups both received usual care

Groups received same intervention?	Unclear risk	Not enough information to judge whether all participants received the same usual care
------------------------------------	--------------	---

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Amat Santos 2012	Patient population not appropriate. Conference paper
Batra 2012	Not randomised trial
Brosseau 1995	Patient population not appropriate
Chambers 2005	Letter to the Editor, not randomised trial
Chan 2012	Not randomised trial (systematic review of effectiveness of qigong in cardiac rehabilitation)
de Charmoy 2000	Intervention not appropriate (chest physiotherapy)
Dull 1983	Patient population not appropriate
Fang 2002	Inappropriate intervention (rehabilitation guidance at 24 hours after surgery and QoL measure) and unclear patient population (both including patients with rheumatic heart disease and patients after valve replacement)
Ferreira 2009	Intervention not appropriate (inspiratory breathing exercises)
Gaita 1999	Patient population not appropriate (randomisation method and study population unclear)
Ghalamghash 2008	Not randomised trial
Gortner 1988	Intervention not appropriate (nursing intervention, no physical exercise)
Green 2013	Not randomised trial
Grunewald 1971	Not randomised trial
Ha 2011	Not randomised trial. Not possible to obtain full paper
Hokanson 2011	Letter to the Editor, not randomised trial
Hui 2006	Patient population not appropriate
Jairath 1995	Not randomised trial (non-randomised cluster trial)



(Continued)

Johnson 1996	Intervention not appropriate (physical intervention in control group)
Kardis 2007	Not randomised trial (randomised case control study)
Kassirskii 1983	Not randomised trial (observational study)
Kassirskii 1991	Not randomised trial
Kodric 2013	Patient population not appropriate (patients after all kind of major cardiac surgery)
Kübler 1984	Patient population not appropriate
Liao 2004	Intervention not eligible (no physical intervention, only psychological and behavioural intervention)
Lim 1998	Patient population not appropriate
Martsinkivichus 1980	Not randomised trial
Nagashio 2003	Patient population not appropriate
Nehyba 2009	Not randomised trial (non-randomised cluster trial) and patient population including patients with coronary artery bypass surgery
Newell 1980	Not randomised trial (non-randomised cluster trial)
Petrulina 1980	Not randomised trial
Rizwan 2012	Not randomised trial
Roseler 1997	Not a randomised trial and inappropriate patient population
Rosenfeldt 2011	Patient population not appropriate (both patients with valve surgery and coronary artery bypass graft surgery)
Sumide 2009	Not randomised trial
Therrien 2003	Patient population not appropriate (repaired tetralogy of Fallot)
Ueshima 2004	Not randomised trial
Widimsky 2009	Patient population not appropriate (patients with acute myocardial infarction)

## Characteristics of ongoing studies [ordered by study ID]

### CopenHeartVR 2014

Trial name or title	CopenHeartVR (VR = Valve replacement or repair)
Methods	Parallel group RCT
Participants	Adults after any kind of heart valve surgery or replacement
Interventions	12 weeks of combined exercise training 3 times per week to either home-based, centre-based or community-based training and psycho-educational intervention comprising 5 nurse consultations within the first 6 months of surgery
Outcomes	<i>Primary:</i> Change in physical capacity measured by VO <sub>2</sub> peak before and at 4 months after surgery <i>Secondary:</i> Change in self-assessed mental health measured by Short Form-36 Mental Component Score at 6 months after surgery
Starting date	Feb. 2012
Contact information	laerum@gmail.com
Notes	Estimated enrolment: 210. Enrolment finished May 2014 Location: Rigshospitalet, Copenhagen University Hospital, Denmark

### Rehabilitation in Aortic Stenosis Patients (RASP)

Trial name or title	Rehabilitation in Aortic Stenosis Patients (RASP)
Methods	Parallel group RCT
Participants	Adults with aortic stenosis who have undergone aortic valve replacement
Interventions	12 weeks of supervised exercise training 3 times per week to home-based training based upon public health recommendations of minimum level of physical activity
Outcomes	<i>Primary:</i> Change in peak oxygen uptake. Time frame: Before (within one week before intervention), 1 week after and 12 months after intervention. Physical capacity is measured with cardiopulmonary exercise testing (CPET) on bicycle ergometer <i>Secondary:</i> Change in Health-related Quality of Life. Time frame: Before (within one week before intervention), 1 week after and 12 months after intervention. Short-form 36, version 2
Starting date	Estimated enrolment: 40. Enrolment scheduled to finish December 2013 but email correspondence with authors confirm that enrolment is yet ongoing (2014)

**Rehabilitation in Aortic Stenosis Patients (RASP)** *(Continued)*

Contact information	Contact: Kristofer Hedman, BSc, kristofer.hedman@liu.se and Sabina Borg, BSc, sabina.borg@lio.se
Notes	Study director: Eva Nylander, PhD Location: Linköping University, Sweden

## DATA AND ANALYSES

### Comparison 1. Exercise versus no exercise

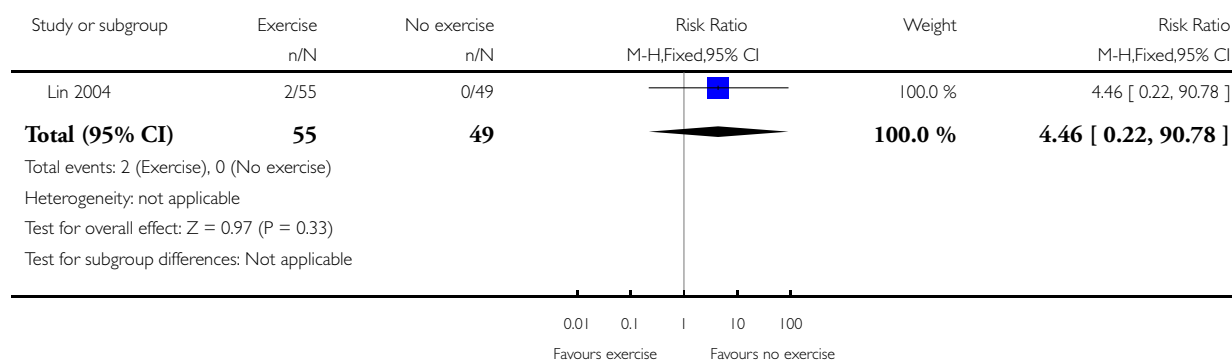
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	104	Risk Ratio (M-H, Fixed, 95% CI)	4.46 [0.22, 90.78]
2 Mortality: best/worst-case scenario	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.10, 3.41]
3 Mortality: worst/best-case scenario	1	104	Risk Ratio (M-H, Fixed, 95% CI)	9.82 [0.56, 173.19]
4 Serious adverse events	2	148	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.37, 3.62]
5 Serious adverse events: best/worst-case scenario	2	148	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.24, 1.70]
6 Serious adverse events: worst/best-case scenario	2	148	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.87, 6.27]
7 Exercise capacity at the end of intervention	2	140	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.81, -0.13]
8 Exercise capacity at longest follow-up	2	140	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.85, -0.14]
9 Return to work	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.19, 1.56]

#### Analysis 1.1. Comparison 1 Exercise versus no exercise, Outcome 1 Mortality.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 1 Mortality

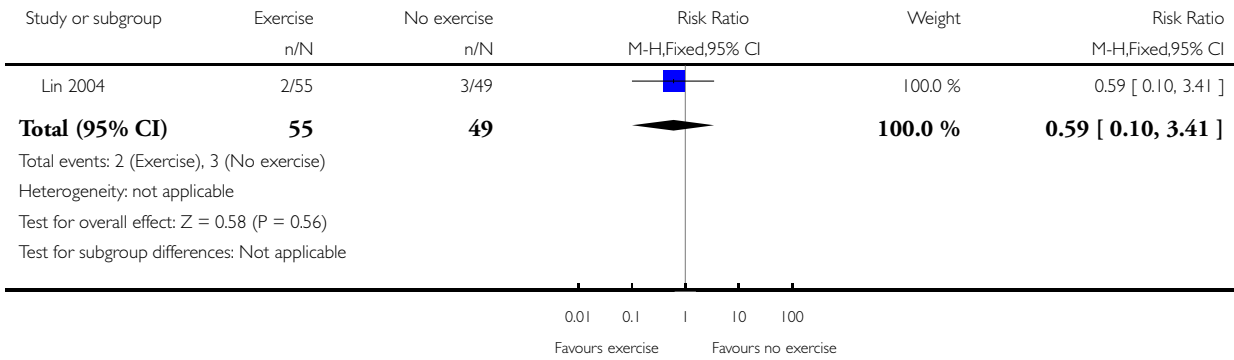


### Analysis 1.2. Comparison 1 Exercise versus no exercise, Outcome 2 Mortality: best/worst-case scenario.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 2 Mortality: best/worst-case scenario

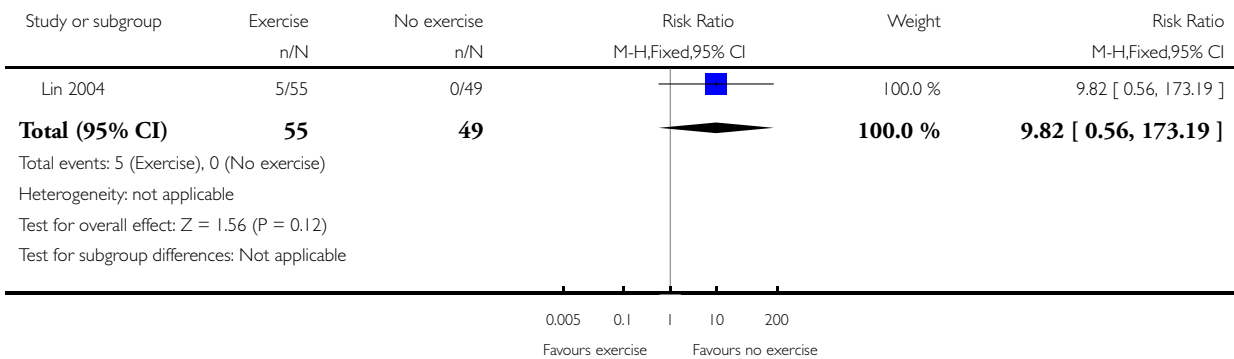


### Analysis 1.3. Comparison 1 Exercise versus no exercise, Outcome 3 Mortality: worst/best-case scenario.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 3 Mortality: worst/best-case scenario

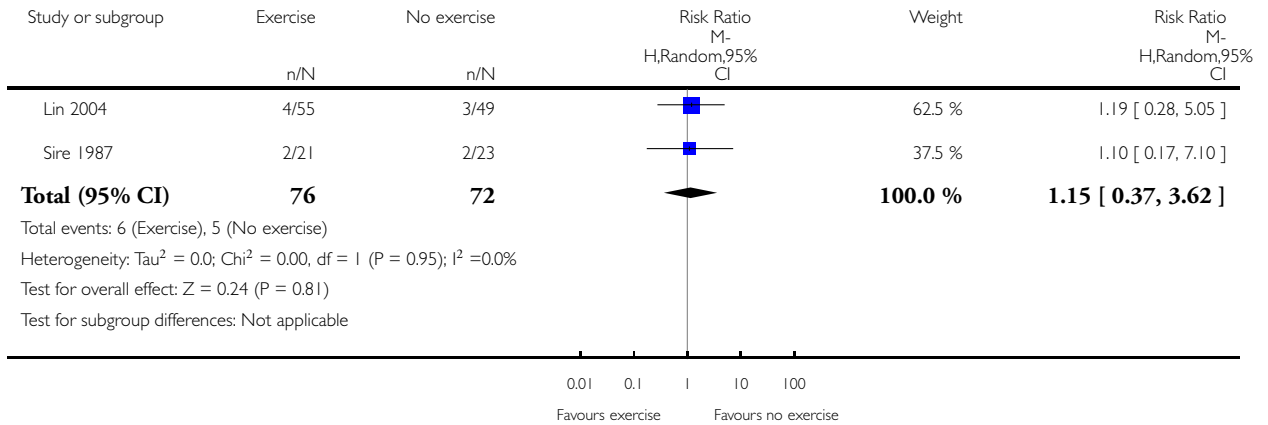


#### Analysis I.4. Comparison I Exercise versus no exercise, Outcome 4 Serious adverse events.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: I Exercise versus no exercise

Outcome: 4 Serious adverse events

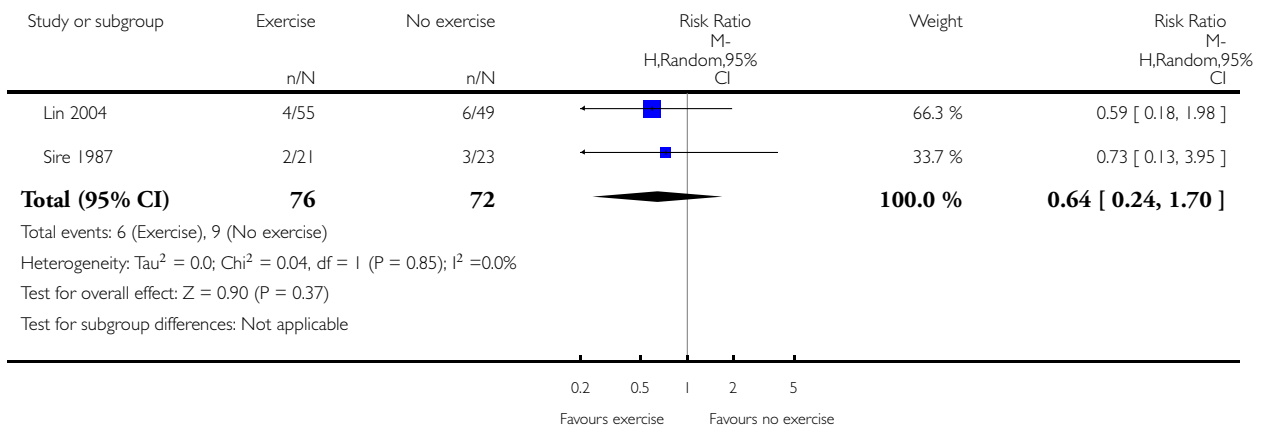


#### Analysis I.5. Comparison I Exercise versus no exercise, Outcome 5 Serious adverse events: best/worst-case scenario.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: I Exercise versus no exercise

Outcome: 5 Serious adverse events: best/worst-case scenario

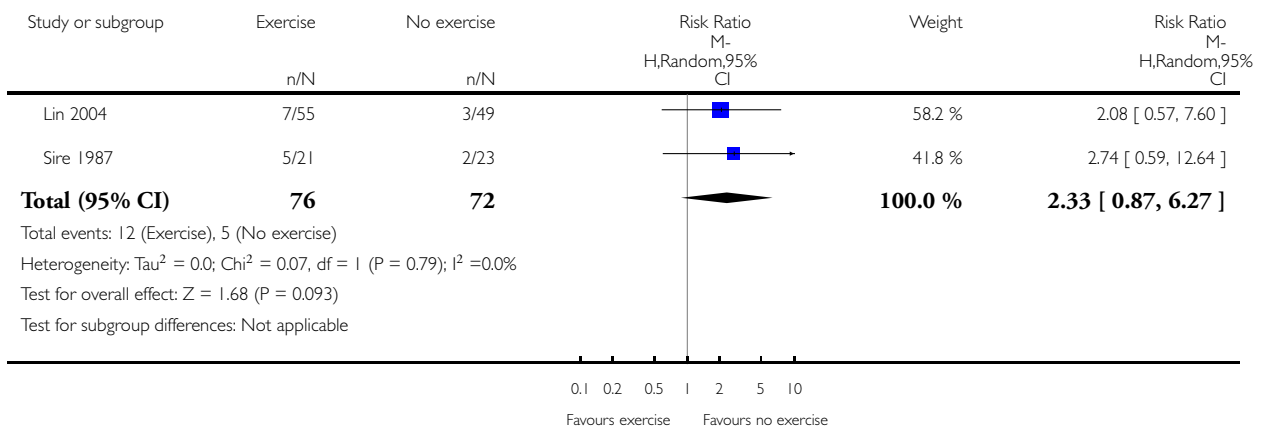


**Analysis 1.6. Comparison 1 Exercise versus no exercise, Outcome 6 Serious adverse events: worst/best-case scenario.**

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 6 Serious adverse events: worst/best-case scenario

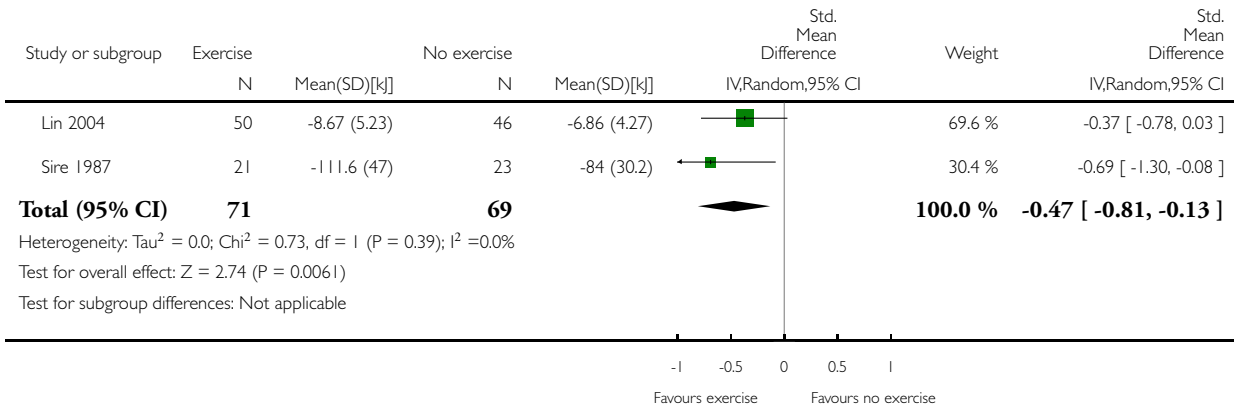


### Analysis 1.7. Comparison 1 Exercise versus no exercise, Outcome 7 Exercise capacity at the end of intervention.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 7 Exercise capacity at the end of intervention

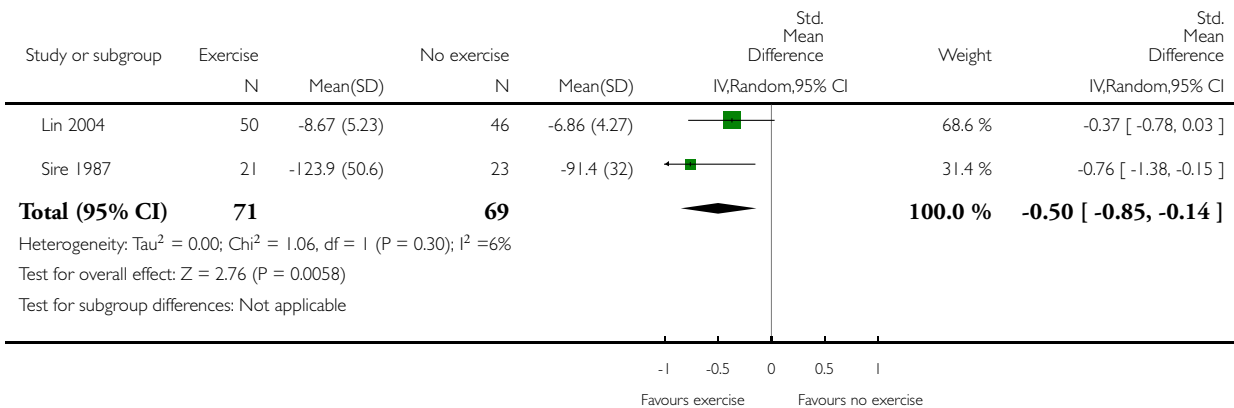


### Analysis 1.8. Comparison 1 Exercise versus no exercise, Outcome 8 Exercise capacity at longest follow-up.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 8 Exercise capacity at longest follow-up



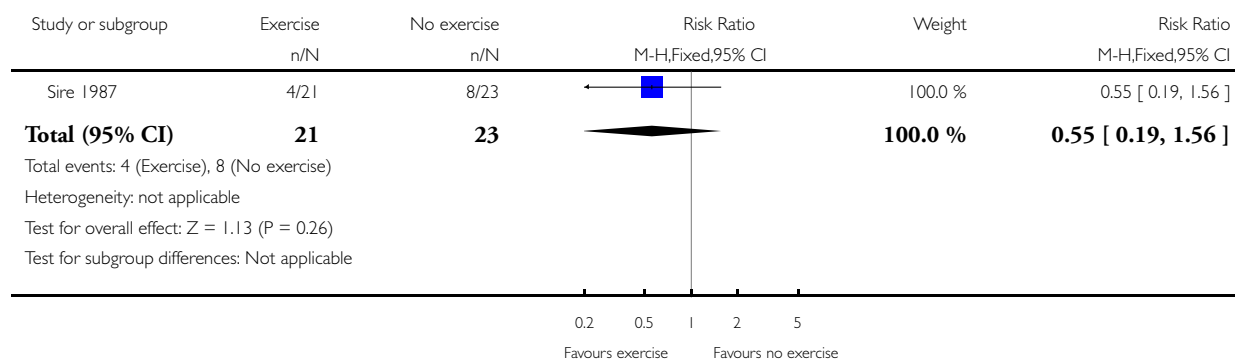


### Analysis 1.9. Comparison 1 Exercise versus no exercise, Outcome 9 Return to work.

Review: Exercise-based cardiac rehabilitation for adults after heart valve surgery

Comparison: 1 Exercise versus no exercise

Outcome: 9 Return to work



## ADDITIONAL TABLES

Table 1. Description of severe adverse events

	Lin 2004	Sire 1987	Total events
<b>No exercise group</b>	<b>3 patients:</b> 1 pericardial effusion 1 paravalvular leakage 1 endocarditis	<b>2 patients:</b> 2 non-fatal thromboembolism	5
<b>Exercise group</b>	<b>4 patients:</b> 2 heart arrhythmias 1 sudden death 1 brain stem death	<b>2 patients:</b> 1 hematoma in abdominal muscle 1 angina pectoris	6

## APPENDICES

### Appendix I. Search strategies

#### Cochrane Library

#1MeSH descriptor: [Exercise] explode all trees  
#2MeSH descriptor: [Exercise Therapy] explode all trees  
#3MeSH descriptor: [Exercise Tolerance] this term only  
#4MeSH descriptor: [Sports] explode all trees  
#5MeSH descriptor: [Physical Exertion] this term only  
#6exercis\*  
#7sport\*  
#8MeSH descriptor: [Physical Fitness] this term only  
#9MeSH descriptor: [Physical Education and Training] explode all trees  
#10(fitness or fitter or fit)  
#11muscle\* near/3 (train\* or activ\*)  
#12train\* near/5 (strength\* or aerobic\* or exercise\*)  
#13(aerobic or resistance) near/3 (train\* or activ\*)  
#14physical\* near/5 (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*)  
#15(exercise\* or fitness) near/3 (treat\* or interven\* or program\* or train\* or physical or activ\*)  
#16MeSH descriptor: [Rehabilitation] this term only  
#17MeSH descriptor: [Rehabilitation Centers] this term only  
#18rehabilitat\*  
#19MeSH descriptor: [Dance Therapy] this term only  
#20kinesiotherap\*  
#21danc\*  
#22("lifestyle" or life-style) near/5 activ\*  
#23("lifestyle" or life-style) near/5 physical\*  
#24walk\*  
#25run\*  
#26jog\*  
#27#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20  
or #21 or #22 or #23 or #24 or #25 or #26  
#28MeSH descriptor: [Heart Valve Diseases] explode all trees  
#29valve near/2 (disease\* or stenosis\* or insufficien\*)  
#30MeSH descriptor: [Heart Valve Prosthesis Implantation] this term only  
#31MeSH descriptor: [Heart Valve Prosthesis] this term only  
#32valve near/2 (surg\* or replace\* or repair\* or prosthe\*)  
#33#28 or #29 or #30 or #31 or #32  
#34#27 and #33

#### MEDLINE

1 exp Exercise/  
2 exp Exercise Therapy/  
3 Exercise Tolerance/  
4 exp Sports/  
5 Physical Exertion/  
6 exercis\*.tw.  
7 sport\*.tw.  
8 Physical Fitness/

9 exp "Physical Education and Training"/  
 10 (fitness or fitter or fit).tw.  
 11 (muscle\* adj3 (train\* or activ\*)).tw.  
 12 (train\* adj5 (strength\* or aerobic\* or exercise\*)).tw.  
 13 ((aerobic or resistance) adj3 (train\* or activ\*)).tw.  
 14 (physical\* adj5 (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*)).tw.  
 15 ((exercise\* or fitness) adj3 (treat\* or interven\* or program\* or train\* or physical or activ\*)).tw.  
 16 Rehabilitation/  
 17 Rehabilitation Centers/  
 18 rehabilitat\*.tw.  
 19 Dance Therapy/  
 20 kinesiotherap\*.tw.  
 21 danc\*.tw.  
 22 (("lifestyle" or life-style) adj5 activ\$).tw.  
 23 (("lifestyle" or life-style) adj5 physical\$).tw.  
 24 walk\*.tw.  
 25 run\*.tw.  
 26 jog\*.tw.  
 27 or/1-26  
 28 exp Heart Valve Diseases/  
 29 (valve adj2 (disease\* or stenosis\* or insufficien\*)).tw.  
 30 Heart Valve Prosthesis Implantation/  
 31 Heart Valve Prosthesis/  
 32 (valve adj2 (surg\* or replace\* or repair\* or prosthesis\*)).tw.  
 33 or/28-32  
 34 27 and 33  
 35 randomized controlled trial.pt.  
 36 controlled clinical trial.pt.  
 37 randomized.ab.  
 38 placebo.ab.  
 39 drug therapy.fs.  
 40 randomly.ab.  
 41 trial.ab.  
 42 groups.ab.  
 43 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42  
 44 exp animals/ not humans.sh.  
 45 43 not 44  
 46 34 and 45

## EMBASE

1. exp exercise/  
 2. exp kinesiotherapy/  
 3. exercise tolerance/  
 4. exp sport/  
 5. exercis\*.tw.  
 6. sport\*.tw.  
 7. fitness/  
 8. fitness/  
 9. physical education/  
 10. (fitness or fitter or fit).tw.  
 11. (muscle\* adj3 (train\* or activ\*)).tw.  
 12. (train\* adj5 (strength\* or aerobic\* or exercise\*)).tw.

13. ((aerobic or resistance) adj3 (train\* or activ\*)).tw.
14. (physical\* adj5 (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*)).tw.
15. ((exercise\* or fitness) adj3 (treat\* or interven\* or program\* or train\* or physical or activ\*)).tw.
16. rehabilitation/
17. rehabilitation center/
18. rehabilitat\*.tw.
19. dance therapy/
20. kinesiotherap\*.tw.
21. danc\*.tw.
22. (("lifestyle" or life-style) adj5 activ\$).tw.
23. (("lifestyle" or life-style) adj5 physical\$).tw.
24. walk\*.tw.
25. run\*.tw.
26. jog\*.tw.
27. or/1-26
28. exp valvular heart disease/
29. (valve adj2 (disease\* or stenosis\* or insufficien\*)).tw.
30. exp heart valve replacement/
31. exp heart valve prosthesis/
32. (valve adj2 (surg\* or replace\* or repair\* or prosthe\*)).tw.
33. or/28-32
34. 27 and 33
35. random\$.tw.
36. factorial\$.tw.
37. crossover\$.tw.
38. cross over\$.tw.
39. cross-over\$.tw.
40. placebo\$.tw.
41. (doubl\$ adj blind\$).tw.
42. (singl\$ adj blind\$).tw.
43. assign\$.tw.
44. allocat\$.tw.
45. volunteer\$.tw.
46. crossover procedure/
47. double blind procedure/
48. randomized controlled trial/
49. single blind procedure/
50. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
51. (animal/ or nonhuman/) not human/
52. 50 not 51
53. 34 and 52
54. limit 53 to embase

## CINAHL

- S47 S28 AND S46  
 S46 S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45  
 S45 TX cross-over\*  
 S44 TX crossover\*  
 S43 TX volunteer\*  
 S42 (MH "Crossover Design")  
 S41 TX allocat\*  
 S40 TX control\*

S39 TX assign\*  
 S38 TX placebo\*  
 S37 (MH "Placebos")  
 S36 TX random\*  
 S35 TX (doubl\* N1 mask\*)  
 S34 TX (singl\* N1 mask\*)  
 S33 TX (doubl\* N1 blind\*)  
 S32 TX (singl\* N1 blind\*)  
 S31 TX (clinic\* N1 trial?)  
 S30 PT clinical trial  
 S29 (MH "Clinical Trials+")  
 S28 S22 AND S27  
 S27 S23 OR S24 OR S25 OR S26  
 S26 valve N2 (surg\* or replace\* or repair\* or prosth\*)  
 S25 (MH "Heart Valve Prosthesis")  
 S24 valve N2 (disease\* or stenosis\* or insufficien\*)  
 S23 (MH "Heart Valve Diseases+")  
 S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21  
 S21 walk\* or run\* or jog\*  
 S20 (("lifestyle" or life-style) N5 physical\*)  
 S19 (("lifestyle" or life-style) N5 activ\*)  
 S18 kinesiotherap\* or danc\*  
 S17 (MH "Dance Therapy")  
 S16 rehabilitat\*  
 S15 (MH "Rehabilitation Centers")  
 S14 (MH "Rehabilitation")  
 S13 (exercise\* or fitness) N3 (treat\* or interven\* or program\* or train\* or physical or activ\*)  
 S12 physical\* N5 (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*)  
 S11 (aerobic or resistance) N3 (train\* or activ\*)  
 S10 train\* N5 (strength\* or aerobic\* or exercise\*)  
 S9 muscle\* N3 (train\* or activ\*)  
 S8 fitness or fitter or fit  
 S7 (MH "Physical Education and Training+")  
 S6 (MH "Physical Fitness")  
 S5 exercis\* or sport\*  
 S4 (MH "Sports+")  
 S3 (MH "Exercise Tolerance+")  
 S2 (MH "Therapeutic Exercise+")  
 S1 (MH "Exercise+")

## PsycINFO

1. exp Exercise/
2. exp Sports/
3. exercis\*.tw.
4. sport\*.tw.
5. physical fitness/
6. physical education/
7. (fitness or fitter or fit).tw.
8. (muscle\* adj3 (train\* or activ\*)).tw.
9. (train\* adj5 (strength\* or aerobic\* or exercise\*)).tw.
10. ((aerobic or resistance) adj3 (train\* or activ\*)).tw.

11. (physical\* adj5 (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*)).tw.
12. ((exercise\* or fitness) adj3 (treat\* or interven\* or program\* or train\* or physical or activ\*)).tw.
13. rehabilitation/
14. rehabilitation centers/
15. rehabilitat\*.tw.
16. dance therapy/
17. kinesiotherap\*.tw.
18. danc\*.tw.
19. (("lifestyle" or life-style) adj5 activ\*).tw.
20. (("lifestyle" or life-style) adj5 physical\*).tw.
21. walk\*.tw.
22. run\*.tw.
23. jog\*.tw.
24. or/1-23
25. (valve adj2 (disease\* or stenosis\* or insufficien\*)).tw.
26. prostheses/
27. (valve adj2 (surg\* or replace\* or repair\* or prosthe\*)).tw.
28. or/25-27
29. 24 and 28
30. random\$.tw.
31. factorial\$.tw.
32. crossover\$.tw.
33. cross-over\$.tw.
34. placebo\$.tw.
35. (doubl\$ adj blind\$).tw.
36. (singl\$ adj blind\$).tw.
37. assign\$.tw.
38. allocat\$.tw.
39. volunteer\$.tw.
40. control\*.tw.
41. "2000".md.
42. or/30-41
43. 29 and 42

## LILACS

(exercis\$ or sport\$ or fit\$ or train\$ or activ\$ or aerobic\$ or rehabilit\$ or walk\$ or jog\$ or run\$) [Words] and ("heart valve\$" or "heart prosthesis\$") [Words]

## CPCI-S

- # 16 #15 AND #14
- # 15 TS=(random\* or blind\* or allocat\* or assign\* or trial\* or placebo\* or crossover\* or cross-over\*)
- # 14 #13 AND #10
- # 13 #12 OR #11
- # 12 TS=(valve and (surg\* or replace\* or repair\* or prosthe\*))
- # 11 TS=(valve and (disease\* or stenosis\* or insufficien\*))
- # 10 #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
- # 9 TS=(("lifestyle" or life-style) and physical\*)
- # 8 TS=(("lifestyle" or life-style) and activ\*)
- # 7 TS=(rehabilitat\* or danc\* or kinesiotherap\* or walk\* or run\* or jog\*)
- # 6 TS=((exercise\* or fitness) and (treat\* or interven\* or program\* or train\* or physical or activ\*))
- # 5 TS=(physical\* and (fit\* or train\* or therap\* or activ\* or strength or endur\* or exert\* or capacit\*))

# 4 TS=((aerobic or resistance) and (train\* or activ\*))  
# 3 TS=(train\* and (strength\* or aerobic\* or exercise\*))  
# 2 TS=(muscle\* and (train\* or active\*))  
# 1 TS=(exercis\* or sport\* or fitness or fitter or fit)

## CONTRIBUTIONS OF AUTHORS

KLS drafted the review. All authors have revised and contributed to the drafting of the review, and all have approved the final version of the review for publication. RST and JL contributed significantly to supervision of the statistical analyses.

## DECLARATIONS OF INTEREST

Christian Hassager has participated in three industry-sponsored trials on other topics than cardiac rehabilitation.

Kirstine L Sibilitz, Selina K Berg, Lars H Tang, Signe S Risom, Christian Gluud, Jane Lindschou, Lars Kober, and Ann-Dorthe Zwisler are involved in conducting three randomised clinical trials, investigating the effect of cardiac rehabilitation for 1) people with atrial fibrillation treated with radiofrequency ablation, 2) people treated for infective endocarditis, and 3) people after heart valve surgery. None of these trials were industry sponsored, but sponsored by private and public funding, mainly The Danish Strategic Research Council, The Research Council of the Heart Centre of Rigshospitalet, and Region Zealand Research Council. None of the founders had any involvement in the analyses, collection of data or interpretation of results of the trials.

Kirstine L Sibilitz, Selina K Berg, Signe S Risom, and Ann-Dorthe Zwisler are currently co-authoring other Cochrane reviews of cardiac rehabilitation.

Rod S Taylor is author on previous Cochrane reviews of cardiac rehabilitation and is the Chief Investigator for a current ongoing UK NIHR funded trial (REACH-HF) assessing the clinical effectiveness and cost-effectiveness of home-based self-directed exercise-based cardiac rehabilitation intervention for people with heart failure and their carers.

## SOURCES OF SUPPORT

### Internal sources

- The Research Foundation at the Heart Centre, Rigshospitalet, Denmark.  
The foundation supported salary to the first author as part of PhD scholarship.

### External sources

- The Strategic Research Council, Denmark.  
The foundation supported salary to the first author as part of PhD scholarship.

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

Due to the limited amount of evidence within the field, several of the analyses proposed in the protocol ([Sibilitz 2013b](#)) could not be performed. The section regarding bias has been modified compared with the protocol, and three domains ('groups balanced at baseline', 'intention-to-treat-analysis', 'groups received same intervention') added. The rationale for adding these three bias domains was to unify the portfolio of Cochrane reviews of cardiac rehabilitation by Rod S Taylor/Lindsey Anderson.

Given their importance to policy makers, we added the following secondary outcomes to the review: 1) return to work; 2) costs; and 3) cost-effectiveness.