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Exercise-based cardiac rehabilitation in heart transplant recipients (Protocol)

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[Intervention Protocol]

Exercise-based cardiac rehabilitation in heart transplant recipients

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effectiveness and safety of exercise-based rehabilitation on the mortality, hospital admissions, morbidity, exercise capacity, health-related quality of life, and return to work of people after heart transplantation.

BACKGROUND

Description of the condition

Despite modern advances in medical treatment, heart transplantation is considered to be the gold standard treatment modality for selected people with end-stage heart failure (Yancy 2013). In general, people with advanced heart failure should be considered for heart transplantation if optimal medical therapy as recommended by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and cardiac resynchronisation therapy have failed to improve symptoms or halt progression of the underlying pathology (Shah 2012; Yancy 2013). About 3800 heart transplants are currently performed annually worldwide (ISHLT 2015). The vast majority of these are performed in the United States (2000 to 2300 annually). In 2013 in the United States over 50% of heart transplants were performed in people with cardiomyopathy, about a third in people with coronary heart disease, and 10% in people with congenital heart disease (Colvin-Adams 2015).

Since the first heart transplantation over 45 years ago, there has been significant progress in the field. Survival and quality of life are now generally considered to be excellent, with many heart transplant recipients now being able to return to work (Hollenberg 2004; Lund 2013). Since the 1970s, the one-year post-transplantation survival rates have improved from 30% to almost 90% (Colvin-Adams 2015; Stehlik 2012), while three- and five-year survival are now approximately 80% and 75%, respectively (Colvin-Adams 2015).

While advances in transplant candidate selection, surgical techniques, immunosuppressive modalities, and postoperative care have led to improved long-term outcomes after transplantation (Butler 2004; Lietz 2007), long-term survival remains limited, and exercise capacity and health-related quality of life of heart transplant recipients remain inferior to that of age-matched healthy individuals. Preoperatively, most heart transplant candidates have chronic debilitating cardiac illness, with concomitant poor exercise capacity and cardiac cachexia. Post-transplantation, exercise capacity remains diminished due to decreased chronotropic competence associated with cardiac allograft denervation (Bengel 2001; Kao 1994; Kao 1995), diastolic dysfunction (Kao 1994; Kao 1995; Paulus 1992), impaired peripheral vascular function (Haykowsky 2005; Jendzjowsky 2007), as well as changes in skeletal muscle strength and biochemistry due to post-transplant deconditioning or treatment with high-dose immunosuppressive therapy (Braith 2000; Lampert 1996). Although maximum exercise capacity increases on average from 40% to 50% of normal values immediately after transplant, to 60% at two years' post-transplant (Douard 1997; Kobashigawa 1999b; Mandak 1995), maximum exercise capacity decreases thereafter at a mean rate of approximately 5% per year (Douard 1997; Mandak 1995), compared with a rate of only 1.5% each year in healthy individuals (Jackson 1996).

Recent data from the United States show that 36% of heart recipients are hospitalised during the first year post-transplantation, and 61% are hospitalised within four years (Colvin-Adams 2014; Colvin-Adams 2015). The most common reasons for hospitalisation are transplant complications and infections. Acute rejection, which used to be one of the main causes of mortality in transplant recipients, now has relatively low incidence due to modern drug therapies, although post-transplant acute rejection still occurs in 24% of heart recipients in the first year post-transplantation and 45% of heart recipients within five years. The most common causes of early mortality during the first three months after transplant are infection, cardiovascular and cerebrovascular events, and graft failure (Colvin-Adams 2015). In the long term, mortality is most often the result of cardiovascular and cerebrovascular events, with coronary allograft vasculopathy being the main cause of death in heart transplant recipients after five years (Taylor 2007; Tjang 2008).

New challenges to heart transplantation have recently arisen. In the last decade, antibody-mediated rejection has been recognised as a particularly challenging form of rejection in heart transplant recipients, which is a major cause of allograft failure and is associated with a greater risk of coronary allograft vasculopathy and death (Colvin 2015; Nair 2011). The demographics of heart transplant recipients are also changing, with a greater number of more complicated, older recipients in their 60s and 70s, who tend to have higher risks of infection, coronary allograft vasculopathy, and malignancy, which compromise their long-term survival (Kobashigawa 2012). In the United States, the proportion of candidates for heart transplantation aged 65 years or older increased from 13% in 2002 to 20% in 2012 (Colvin-Adams 2014). Advances in heart surgery have also led to a greater proportion of younger people with congenital heart disease who are surviving past childhood and later develop heart failure. These patients can have complex cardiopulmonary anatomy and have commonly received multiple median sternotomies, which increase the risk of postoperative bleeding and mortality (Tonsho 2014). The candidacy for heart transplant has also been altered in recent years by the increase in the management of candidates with mechanical ventricular assist devices prior to transplantation, with almost 40% of all adult heart transplant recipients now bridged to transplant with a durable device (Stehlik 2014).

Description of the intervention

Based on current evidence, national and international guidelines on the management of coronary heart disease and heart failure including those by the ACC/AHA, European Society of Cardiology, and National Institute for Health and Care Excellence in the United Kingdom, consistently recommend cardiac rehabilitation (CR) as an effective and safe intervention (McMurray 2012; NICE 2013; Yancy 2013). Many definitions of CR have been proposed, but the following definition encompasses the key concepts of CR: “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). Cardiac rehabilitation is a complex intervention that may involve a variety of therapies, including exercise, risk factor management and lifestyle education, behaviour change, psychological support, and strategies that are aimed at targeting traditional risk factors for cardiovascular disease, that is ‘comprehensive CR’ (Corra 2005). The patient groups routinely recommended for CR include people with post-myocardial infarction, postrevascularisation and/or valvular procedure and heart failure heart surgery (that is bypass surgery or valvular surgery, or both). CR programmes have traditionally been offered in a supervised, centre-based setting. However, many people do not receive rehabilitation (Bethell 2008), and with uptake of CR for both coronary heart disease and heart failure currently at suboptimal levels (Dalal 2012; NICE 2013; Tierney 2011), home-based CR programmes are increasingly being introduced to widen access and participation.

How the intervention might work

Recent Cochrane reviews of exercise-based CR in coronary heart disease and heart failure populations have shown CR to be a safe and effective intervention in reducing the risk of hospital admissions and conferring important improvements in health-related quality of life in these patient groups (Anderson 2016; Taylor 2014).

For decades, exercise restrictions were applied to heart transplant recipients, as it was believed that the transplanted heart remained denervated, with a higher resting heart rate and a reduced heart rate response (chronotropic incompetence). However, there is now ample evidence that both endurance and resistance training are well tolerated in heart transplant recipients, and it is widely believed that reinnervation and autonomic nervous control can be improved by physical training (Bernardi 2007), although it is unclear whether time alone may result in the normalisation of chronotropic responses, or whether this occurs in combination with exercise and/or other factors (Nytroen 2013).

There is evidence from small, non-randomised studies that aerobic exercise training is an effective intervention to reverse the pathophysiological consequences associated with cardiac denervation and prevent immunosuppression-induced adverse effects (Braith 2005; Braith 2008; Haykowsky 2005; Keteyian 1991; Kobashigawa 1999a; Marconi 2003). In an assessment of the time course of physical reconditioning and skeletal muscle adaptation by exercise training in people five years' post-transplantation, a persistent improvement in exercise capacity was reported, indicating that exercise training could counteract the negative side effects of immunosuppressive treatment on skeletal muscles (Tegtbur 2005). In a more recent randomised controlled trial (RCT), supervised exercise training was reported to improve peak oxygen uptake in clinically stable heart recipients. This improvement was thought to be as a function of favourable skeletal muscle adaptations that result in increased oxygen utilisation by the active muscles (Haykowsky 2009). Furthermore, results from several randomised trials suggest that high-intensity interval training is safe in heart transplant recipients (Haykowsky 2009; Hermann 2011; Nytroen 2012), and leads to superior improvements in peak oxygen uptake compared with moderate exercise (Dall 2014).

Large epidemiological studies have demonstrated the existence of an inverse and independent association between exercise capacity and mortality in apparently healthy participants (Kokkinos 2008), older men (Kokkinos 2010b), and people with documented cardiovascular disease (Kokkinos 2008; Myers 2002). Indeed, a 1.0 metabolic equivalent (MET; 1 MET = 3.5 ml/kg/min) increase in exercise capacity has been shown to translate into a 12% improvement in survival in individuals with existing cardiovascular disease (Kokkinos 2010a). However, uncertainty remains regarding the precise role that exercise may play in reversing the abnormal cardiovascular and skeletal muscle function that remains after heart transplantation, and whether such an exercise-based intervention has an effect on long-term survival of transplant recipients.

Why it is important to do this review

A 2010 position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation, in reference to post-cardiac transplantation, stated: "Early training programme can be beneficial in the early post-operative period as well as in the long-term. Although exercise training would theoretically delay or prevent CAD progression in the transplanted heart, this still has to be studied" (Piepoli 2010). Nonetheless, despite this apparent lack of evidence, clinical practice guidelines recommend exercise training as standard care for heart transplant recipients. The 2010 guidelines from the International Society of Heart and Lung Transplantation for the care of heart transplant recipients gave a Class 1 recommendation for the routine use of CR with aerobic exercise training and resistance exercise after heart transplantation. This was based on a level B rating of the evidence (that is RCT), although "there is currently no information on potential long-term benefits" (Costanzo 2010).

A recent systematic review and meta-analysis identified 9 RCTs of exercise training in 250 participants, 1 month to 7 years following heart, lung, kidney, or liver transplantation (Didsbury 2013). This review concluded that "exercise training is a promising but unproven intervention for improving cardiovascular outcomes of solid organ transplant recipients". Studies of exercise in cardiac transplant recipients have generally been performed early after transplantation using moderate exercise training (Bernardi 2007; Karapolat 2008; Kobashigawa 1999a). While several of these studies have reported that aerobic exercise leads to improved exercise capacity after heart transplantation, the results are not entirely consistent, and little is known about the type, frequency, or intensity of exercise that provides the greatest health benefits in this population. Moreover, little is known about the impact of exercise-based CR on health-related quality of life or long-term mortality and morbidity (Hsieh 2011).

Our scoping searches have identified additional RCTs that have been published since the June 2012 cutoff of the systematic review by Didsbury and colleagues.

OBJECTIVES

To determine the effectiveness and safety of exercise-based rehabilitation on the mortality, hospital admissions, morbidity, exercise capacity, health-related quality of life, and return to work of people after heart transplantation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include RCTs of either a parallel-group or cross-over design.

Types of participants

We will include adults aged 18 years or older who have received a heart transplant.

Where we identify studies that meet all of our inclusion criteria but include a mixed population of participants, we will make every effort to obtain outcome data for the subset of relevant participants, by contacting the authors. If this approach is not viable, then we will include the data from the study in the meta-analysis if the subset of relevant participants comprises 50% or more of the total included participants, and we will perform a sensitivity analysis with and without data from this study.

If considerable heterogeneity of the severity of participants is detected amongst the included studies, then outcome data will be stratified accordingly.

Types of interventions

Exercise-based interventions either alone or where exercise training is a component of comprehensive CR (defined as programmes including such components as health education and psychological interventions in addition to exercise interventions). For the purposes of this review, exercise includes any structured or taught programmes with the aim of improving functional ability and quality of life.

The comparator group could include standard medical care, such as drug therapy, and may have received (i) no exercise training; (ii) a different dose of exercise training (for example low- versus high-intensity exercise training); or (iii) an active intervention (that is education, psychological intervention).

Types of outcome measures

Primary outcomes

- Cardiovascular mortality
- Hospital admissions (all-cause and cardiovascular related)
- Reported adverse events (including those related to (i) exercise and (ii) transplantation treatments or drugs)

Secondary outcomes

- All-cause mortality
- Non-cardiovascular mortality (including chronic allograft vasculopathy, acute rejection, malignancy, and infection)
- Return to work (including return to either full- or part-time employment, to the same or a reduced role, and to either the previous job or any new employment)
- Exercise capacity assessed by validated outcome measure (e.g. VO_2 peak, 6-minute walk test)
- Health-related quality of life assessed using validated instruments (e.g. 36-Item Short Form Health Survey (SF-36), EQ-5D)
- Costs
- Adherence to exercise programme

Reporting of outcomes is not an inclusion or exclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will search:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- Database of Abstracts of Reviews of Effects (DARE);
- Health Technology Assessment (HTA);
- MEDLINE & MEDLINE In-Process (OVID);
- EMBASE (OVID);
- CINAHL Plus (EBSCO);
- Conference Proceedings Citation Index - Science (CPCI-S) on Web of Science Core Collection (Thomson Reuters).

We will design the search strategies with reference to those of the previous related systematic reviews of exercise-based cardiac rehabilitation (Heran 2011). We will search databases using a strategy combining selected MeSH terms and free-text terms relating to exercise-based rehabilitation and heart transplantation, with filters applied to limit to RCTs. We will use the Cochrane sensitivity-maximising RCT filter for MEDLINE, and will apply terms recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* for EMBASE (Lefebvre 2011). We will apply adaptations of this filter to CINAHL and Web of Science. We will translate the MEDLINE search strategy for use with the other databases using the appropriate controlled vocabulary as applicable. We will apply no date limits. We will impose no language or other limitations and will give consideration to variations in terms used and spellings of terms in different countries so that the search strategy will not miss studies because of such variations. See Appendix 1 for details of the search strategies.

Searching other resources

We will handsearch reference lists of retrieved articles and systematic reviews for any studies not identified by the electronic searches. We will also search trial registers (World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://www.who.int/ictrp/en) and ClinicalTrials.gov (https://clinicaltrials.gov)) for ongoing clinical trials and will seek expert advice.

Data collection and analysis

Selection of studies

Two review authors (TN and LA) will independently screen titles and abstracts of all the studies we identify as a result of the search for inclusion and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. In case of disagreement, a third review author will be asked to arbitrate (RST). We will retrieve the full-text study reports/publication, and two review authors (TN and LA) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. Any disagreements will be resolved through discussion or, if required, by consulting a third person (RST). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form that has been piloted on at least one study in the review to extract study characteristics and outcome data. One review author (TN) will extract study characteristics from included studies, and a second review author (LA) will check against the trial report for accuracy. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, time since transplant, inclusion criteria, and exclusion criteria.
3. Interventions: intervention (including mode of exercise, duration, frequency, and intensity), description of usual care, and length of follow-up
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial and notable conflicts of interest of trial authors.

Two review authors (TN and LA) will independently extract outcome data from included studies. Any disagreements will be resolved by consensus or by involving a third person (RST). One review author (TN) will transfer data into the Review Manager file (RevMan 2014). We will double-check that data is entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (LA) will spot-check study characteristics for accuracy against the trial report. If we find multiple reports of the same study, we will assess the duplicate publications for additional data. We will contact study authors where necessary to provide additional information.

Assessment of risk of bias in included studies

Two review authors (TN and LA) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Incomplete outcome data.
5. Selective outcome reporting.
6. Other (specifically sources of funding).

We will also assess two further quality criteria: whether the study groups were balanced at baseline, and if the study groups received comparable care (apart from the exercise component of the intervention). These criteria, agreed upon in advance by the review authors, have not been validated but have been used to assess quality in previous CR reviews (Anderson 2016; Brown 2011; Sibilitz 2016; Taylor 2014; Taylor 2015). We will assess these two further quality criteria as follows.

Groups balanced at baseline

- *Low risk of bias*: The characteristics of the participants in the intervention and control groups at baseline are reported to be comparable or can be judged to be comparable (e.g. baseline data reported in Table 1) in terms of likely main prognostic factors.
- *Unclear risk of bias*: Whether the characteristics of the participants in the intervention and control groups are balanced at baseline is not reported, and reported information is inadequate to assess this (e.g. no Table 1).
- *High risk of bias*: There is evidence of substantive imbalance in the baseline characteristics of the intervention and control groups with regard to likely major prognostic factors.

Groups received comparable treatment (except exercise)

- *Low risk of bias*: All co-interventions were delivered equally across intervention and control groups.
- *Unclear risk of bias*: Information to assess whether co-interventions were delivered equally across groups was insufficient.
- *High risk of bias:* The co-interventions were not delivered equally across intervention and control groups.

A second review author (LA) will check all 'Risk of bias' assessments, and any discrepancies will be resolved by consensus. We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Unit of analysis issues

In accordance with Section 16.4 of the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011), we will aim to include data from both periods of any cross-over trials identified, assuming (i) there has been a wash-out period considered long enough to reduce carry-over, (ii) no irreversible events such as mortality have occurred, and (iii) appropriate statistical approaches have been used.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (for example when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies on the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will explore heterogeneity amongst included studies qualitatively (by comparing the characteristics of included studies) and quantitatively (using the Chi^2 test of heterogeneity and I^2 statistic). We will use a threshold of I^2 greater than 50% for both dichotomous and continuous outcomes to determine the statistical model to be used for meta-analysis.

Assessment of reporting biases

If more than 10 trials can be pooled, we will create and examine a funnel plot to explore possible small-study biases for the primary outcomes.

Data synthesis

Dichotomous outcomes for each comparison will be expressed as risk ratios with 95% confidence intervals. Continuous data will be expressed as mean difference with 95% confidence intervals, or, where an outcome is measured and reported in more than one way, as standardised mean difference with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect. If there is a statistically significant absolute risk difference, we will calculate the associated number needed to treat to benefit/harm.

Where appropriate, we will pool data from each study using a fixed-effect model, except where substantial heterogeneity exists. If possible, we will pool the results for health-related quality of life using a standardised mean difference. If there is substantial statistical

heterogeneity (P value less than 0.10, I^2 greater than 50%) associated with an effect estimate, we will apply a random-effects model, which provides a more conservative statistical comparison of the difference between intervention and control because a confidence interval around the effect estimate is wider than a confidence interval around a fixed-effect estimate. If a statistically significant difference is still present using the random-effects model, we will also report the fixed-effect pooled estimate and 95% confidence interval because of the tendency of smaller trials, which are more susceptible to publication bias, to be overweighted with a random-effects analysis (Heran 2008a; Heran 2008b).

We will use the funnel plot and the Egger test to examine small-study bias (Egger 1997). We will process data in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will complete data synthesis and analyses using Review Manager 5.3 software and Stata version 13.0 (RevMan 2014; StataCorp 2013).

Summary of findings table

We will employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to interpret result findings and use GRADEpro GDT 2015 to import data from Review Manager to create 'Summary of findings' tables. We will create a 'Summary of findings' table using the following outcomes: all-cause mortality, cardiovascular mortality, non-cardiovascular mortality (including chronic allograft vasculopathy, acute rejection, malignancy, and infection), hospital admissions, adverse events, exercise capacity, and return to work. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* using GRADEpro software (Higgins 2011). We will justify all decisions to down- or up-grade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

As we anticipate length of follow-up to be a driver of intervention effect, we will seek to stratify meta-analysis of each outcome according to the length of trial duration, that is 'short-term' follow-up (6 to 12 months), 'medium-term' follow-up (13 to 36 months), and 'long-term' follow-up (more than 36 months). We will also aim to undertake univariate meta-regression to explore heterogeneity and examine potential treatment effect modifiers. We will seek to test eight a priori hypotheses that there may be differences in the effect of exercise-based CR on total mortality, cardiovascular mortality, and hospitalisations and exercise capacity across particular subgroups:

1. type of CR (exercise-only CR versus comprehensive CR);
2. 'dose' of exercise intervention [dose = number of weeks of exercise training x average number of sessions/week x average duration of session in minutes] (dose ≥ 1000 units versus dose < 1000 units);
3. follow-up period;
4. year of publication;
5. sample size;
6. setting (home- or centre-based CR);
7. study location (continent).

Given the anticipated small ratio of trials to covariates, meta-regression will be limited to univariate analysis (Higgins 2011). However, given the anticipated small number of included studies, it is unlikely that we will be able to use stratified meta-analysis or meta-regression methods.

We will extract results of subgroup analyses, including participant-level subgroup analyses, if reported by individual included studies, for example if a trial reported whether there was a difference in the effectiveness of CR between males and females.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice, and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

Sensitivity analysis

Where there is any doubt as to whether the findings of the meta-analysis are robust to the inclusion of any data, we will conduct a sensitivity analysis. For example, a sensitivity analysis may be conducted to test the robustness of the anlaysis to the inclusion of studies of high versus low risk of bias, or where there is missing data. We will report results of both analyses in a summary table.

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APPENDICES

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

Preliminary search strategy

Cochrane Library

#1 MeSH descriptor: [Exercise Therapy] explode all trees

#2 MeSH descriptor: [Sports] explode all trees

#3 MeSH descriptor: [Physical Exertion] explode all trees

#4 rehabilitat*

#5 (physical* near (fit* or train* or therap* or activit*))

#6 MeSH descriptor: [Exercise] explode all trees

#7 (train*) near (strength* or aerobic* or exercise*)

#8 ((exercise* or fitness) near/3 (treatment or intervent* or program*))

#9 MeSH descriptor: [Rehabilitation] explode all trees

#10 kinesiotherap*

#11 MeSH descriptor: [Physical Education and Training] explode all trees

#12 (run* or walk* or jog* or danc*)

#13 ((lifestyle or life-style) near/5 (interven* or program* or treatment*))

#14 MeSH descriptor: [Dance Therapy] this term only

#15 MeSH descriptor: [Patient Education as Topic] this term only

#16 (patient* near/5 educat*)

#17 ((lifestyle or life-style) near/5 (interven* or program* or treatment*))

#18 MeSH descriptor: [Self Care] this term only

#19 (self near/5 (manag* or care or motivate*))

#20 MeSH descriptor: [Psychotherapy] explode all trees

#21 psychotherap*

#22 (psycholog* near/5 intervent*)

#23 MeSH descriptor: [Counseling] this term only

#24 (counselling or counseling)

#25 ((behavior* or behaviour*) near/5 (modify or modificat* or therap* or change))

#26 (psycho-educat* or psychoeducat*)

#27 (motivat* near/5 (intervention or interv*))

#28 MeSH descriptor: [Health Education] this term only

#29 (health near/5 educat*)

#30 (psychosocial or psycho-social)

#31 (cognitive near/2 behav*)

#32 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31

#33 MeSH descriptor: [Heart Transplantation] explode all trees

#34 (heart near/2 transplant*)

#35 (cardiac near/2 transplant*)

#36 heart next graft*

#37 #33 or #34 or #35 or #36

#38 #32 and #37

MEDLINE OVID

1. exp Exercise Therapy/

2. Sports/

3. Physical Exertion/

4. rehabilitat*.mp.

5. (physical* adj5 (fit* or train* or therap* or activit*)).mp.

6. exp Exercise/

7. (train* adj5 (strength* or aerobic* or exercise*)).tw.

8. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.

9. exp Rehabilitation/

10. kinesiotherap*.tw.

11. "Physical Education and Training"/

12. (run* or walk* or jog* or danc*).tw.

13. (("lifestyle" or life-style) adj5 (physical* or activ*)).tw.

14. Dance Therapy/

15. Patient Education as Topic/

16. (patient* adj5 educat*).tw.

17. ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.

18. Self Care/

19. (self adj5 (manag* or care or motivate*)).tw.

20. exp Psychotherapy/

21. psychotherap*.tw.

22. (psycholog* adj5 intervent*).tw.

23. Counseling/

24. (counselling or counseling).tw.

25. ((behavior* or behaviour*) adj5 (modify or modificat* or therap* or change)).tw.

26. (psycho-educat* or psychoeducat*).tw.

27. (motivat* adj5 (intervention or interv*)).tw.

28. Health Education/

29. (health adj5 educat*).tw.

30. (psychosocial or psycho-social).tw.

31. (cognitive adj2 behav*).tw.

32. or/1-31

33. exp Heart Transplantation/

34. (heart adj2 transplant*).tw.

35. (cardiac adj2 transplant*).tw.

36. heart graft*.tw.

37. or/33-36

38. 32 and 37

39. randomized controlled trial.pt.

40. controlled clinical trial.pt.

41. randomized.ab.

42. placebo.ab.

43. drug therapy.fs.

44. randomly.ab.

45. trial.ab.

46. groups.ab.

47. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

48. exp animals/ not humans.sh.

49. 47 not 48

50. 38 and 49

EMBASE OVID

1. exp kinesiotherapy/

2. exp sport/

3. exp exercise/

4. rehabilitat*.tw.

5. (physical* adj5 (fit* or train* or therap* or activit*)).tw.

6. (train* adj5 (strength* or aerobic* or exercise*)).tw.

7. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.

8. exp rehabilitation/

9. kinesiotherap*.tw.

10. (run* or walk* or jog* or danc*).tw.

11. (("lifestyle" or life-style) adj5 (physical* or activ*)).tw.

12. dance therapy/

13. patient education/

14. (patient* adj5 educat*).tw.

15. ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.

16. self care/

17. (self adj5 (manag* or care or motivate*)).tw.

18. exp psychotherapy/

19. psychotherap*.tw.

20. (psycholog* adj5 intervent*).tw.

21. counseling/

22. (counselling or counseling).tw.

23. ((behavior* or behaviour*) adj5 (modify or modificat* or therap* or change)).tw.

24. (psycho-educat* or psychoeducat*).tw.

25. (motivat* adj5 (intervention or interv*)).tw.

26. health education/

27. (health adj5 educat*).tw.

28. (psychosocial or psycho-social).tw.

29. (cognitive adj2 behav*).tw.

30. or/1-29

31. exp heart transplantation/

32. (heart adj2 transplant*).tw.

33. (cardiac adj2 transplant*).tw.

34. heart graft*.tw.

35. or/31-34

36. 30 and 35

37. random$.tw.

38. factorial$.tw.

39. crossover$.tw.

40. cross over$.tw.

41. cross-over$.tw.

42. placebo$.tw.

43. (doubl$ adj blind$).tw.

44. (singl$ adj blind$).tw.

45. assign$.tw.

46. allocat$.tw.

47. volunteer$.tw.

48. crossover procedure/

49. double blind procedure/

50. randomized controlled trial/

51. single blind procedure/

52. 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 or 50 or 51

53. (animal/ or nonhuman/) not human/

54. 52 not 53

55. 36 and 54

CINAHL

S55 S36 AND S54

S54 S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53

S53 TX cross-over*

S52 TX crossover*

S51 TX volunteer*

S50 (MH "Crossover Design")

S49 TX allocat*

S48 TX control*

S47 TX assign*

S46 TX placebo*

S45 (MH "Placebos")

S44 TX random*

S43 TX (doubl* N1 mask*)

S42 TX (singl* N1 mask*)

S41 TX (doubl* N1 blind*)

S40 TX (singl* N1 blind*)

S39 TX (clinic* N1 trial?)

S38 PT clinical trial

S37 (MH "Clinical Trials+")

S36 S30 AND S35

S35 S31 OR S32 OR S33 OR S34

S34 "heart graft*"

S33 cardiac N2 transplant*

S32 heart N2 transplant*

S31 (MH "Heart Transplantation+")

S30 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 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

S29 (cognitive N2 behav*)

S28 (psychosocial or psycho-social)

S27 (health N5 educat*)

S26 (MH "Health Education")

S25 (motivat* N5 (intervention or interv*))

S24 psycho-educat* or psychoeducat*

S23 ((behavior* or behaviour*) N5 (modify or modificat* or therap* or change))

S22 counselling or counseling

S21 (MH "Counseling+")

S20 (psycholog* N5 intervent*)

S19 psychotherap*

S18 (MH "Psychotherapy+")

S17 (self N5 (manag* or care or motivate*))

S16 (MH "Self Care+")

S15 ((lifestyle or life-style) N5 (interven* or program* or treatment*))

S14 patient* N5 educat*

S13 (MH "Dance Therapy")

S12 (("lifestyle" or life-style) N5 (physical* or activ*))

S11 (run* or walk* or jog* or danc*)

S10 kinesiotherap*

S9 (MH "Rehabilitation+")

S8 ((exercise* or fitness) N3 (treatment or intervent* or program*))

S7 (train* N5 (strength* or aerobic* or exercise*))

S6 physical* N5 (fit* or train* or therap* or activit*)

S5 rehabilitat*

S4 (MH "Exertion+")

S3 (MH "Physical Activity")

S2 (MH "Sports+")

S1 (MH "Therapeutic Exercise+")

Web of Science

8 #7 AND #6

7 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

6 #5 AND #4

5 TS=("heart transplant*" or "cardiac transplant*" or "heart graft*")

4 #3 OR #2 OR #1

3 TS=(psychotherap* or psycholog* or counselling or counseling or behavior* or behaviour* or psycho-educat* or psychoeducat* or motivat* or psychosocial or psycho-social or cognitive)

2 TS=("self manag*" or "self car*" or "self motivat*")

1 TS=(rehabilitat* or physical* or fit* or train* or exercise* or fitness or kinesiotherap* or run* or walk* or jog* or danc* or "lifestyle" or life-style or sport*)

CONTRIBUTIONS OF AUTHORS

LA led the writing of the protocol and approved the final manuscript.

CD assisted in writing the protocol and approved the final manuscript.

TN approved the final manuscript.

LB approved the final manuscript.

RST assisted in writing the protocol and approved the final manuscript.

DECLARATIONS OF INTEREST

LA is an author on a number of other Cochrane CR reviews.

CD is an author of several publications on exercise in heart transplant recipients.

TN declares she has no conflicts of interest.

LB declares she has no conflicts of interest.

RST is an author on a number of other Cochrane CR reviews and is currently the co-chief investigator on the programme of research with the overarching aims of developing and evaluating a home-based CR intervention for people with heart failure and their carers (PGfAR RP-PG-0611-12004).

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INDEX TERMS

Medical Subject Headings (MeSH)

*Exercise; *Exercise Tolerance; Cardiac Rehabilitation [*methods]; Heart Transplantation [*rehabilitation]; High-Intensity Interval Training; Physical Conditioning, Human [*methods]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male; Middle Aged