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[Intervention Protocol]

Physical activity interventions for people with congenital heart disease

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ABSTRACT

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

To assess the effectiveness and safety of physical activity promotion and exercise training interventions in individuals with congenital heart disease.

BACKGROUND

Due to improved medical interventions children with complex congenital heart disease (ConHD) are now living into adulthood, presenting new challenges for health care professionals as this population is now at risk of acquiring non-communicable 'lifestyle' diseases (NCDs) (Giannakoulas 2009; Khairy 2010). It has been reported that people with ConHD fail to meet the minimum requirements for physical activity (Reybrouck 2005; McCrindle 2007); and that the prevalence of obesity is increasing (Andonian 2019). This significantly increases the chance of developing NCDs such as coronary heart disease, type II diabetes mellitus, and breast and colon cancers (Lee 2012). Patients with ConHD also have reduced cardiorespiratory fitness (CRF) (Amedro 2017); this has been significantly linked with mortality and surgical outcomes in this population (Inuzuka 2012; d'Udekem 2017). It is crucial, therefore, that people with ConHD increase their physical activity in line with the current guidelines of 60 minutes of moderate

to vigorous physical activity (MVPA) daily for young people and 150 minutes of MVPA weekly in adults (Department of Health 2011). However, there is currently no consensus on how best to improve physical activity and physical fitness for all ages and disease severities in people with ConHD. The aim of this review is to collate and summarise the randomised controlled trial evidence for physical activity promotion and exercise training interventions in people with ConHD.

Description of the condition

ConHD is a developmental abnormality of the heart or intrathoracic vessels (or both) and can include both structural and electrical abnormalities of the heart (Mitchell 1971). The pathophysiology is complex, from shunting lesions to single ventricles - for a three-part review see Rhodes 2008, Sommer 2008a and Sommer 2008b. The birth prevalence of ConHD has been stable for over

a decade, plateauing around 9.1 in every 1000 live births (95% confidence interval (CI) 9.00 to 9.20). As a result, each year 1.35 million children are born with ConHD globally (van der Linde 2011). Medical innovation has cut infant mortality significantly: in 1987/88 over 30% of ConHD mortality was in children aged less than four years old; in 2004/05 this had fallen to less than 10%, with the highest proportion of deaths occurring in geriatrics (Khairy 2010). This has led to a significant shift in the prevalence of ConHD in adulthood: in 2010 it was estimated that adults accounted for two-thirds of the ConHD population (Marelli 2014). Pregnant women with ConHD are six times more likely to die during labour (OR 6.7, 95% CI 2.9 to 15.4); and their children are at an increased risk of inheriting ConHD (Blue 2012; Opotowsky 2012).

People with ConHD suffer reduced life expectancy, which can be primarily attributed to cardiac sequelae such as progressive heart failure and sudden cardiac death (Zomer 2012; Diller 2015). Health-related quality of life for those with ConHD has been reported as lower compared to healthy controls, specifically in the domains of physical functioning and general health (Gratz 2009; Dulfer 2013). Furthermore, CRF is impaired in children and adults with ConHD, with large heterogeneity both within a condition and between different conditions of ConHD (Kempny 2011; Diller 2015). CRF also declines more steeply throughout childhood and adolescence compared with age-matched controls, which may have implications for adults as lower fitness levels have been linked to a poorer prognosis (Amedro 2017; d'Udekem 2017). Fortunately, regular physical activity, such as a 10-week walking programme, has been shown to improve CRF, physical activity and quality of life in this population (Dua 2010).

Description of the intervention

Physical activity consists of any bodily movement involving skeletal muscles that results in an increased energy expenditure, whereas exercise training is a planned and structured period of physical activity with the intention to maintain or improve physical fitness components (Caspersen 1985). Although MVPA guidelines exist for healthy adults, children and adolescents (Department of Health 2011), there are no national or international MVPA guidelines for people with ConHD. However, a recommendation by the American Heart Association supports an active lifestyle and use of recreational sports and exercise training to enhance the lives of children and adult ConHD patients (Longmuir 2013). Importantly the risks of exercise in an adult ConHD population have been well documented but not at a paediatric level. In a study of 25,790 adults with ConHD, a total of 1189 deaths were reported with only 17 (0.01%) patients dying of sudden cardiac death of arrhythmic origin during physical activity (Koyak 2012). This highlights the relative safety of physical activity in this population.

How the intervention might work

Physical functioning is a domain of health-related quality of life and can be defined as limitations in mobility activities, such as walking specified distances. Physical functioning has been reported to be lower in people with ConHD compared to healthy controls (Gratz 2009). By increasing a patient's cardiorespiratory or muscular fitness, or both, an intervention may improve self-reported physical functioning as patients will be able to undertake daily activities more efficiently (Gratz 2009). The use of cardiopulmonary exercise testing (CPET), using different exercise modalities (running, cycling) and measuring oxygen uptake and muscular strength testing, are both practical and accurate assessments of physical functioning. We may include less objective measures, such as the 6-minute walk test and multistage fitness test, within the review if there is a lack of 'gold standard' testing, but we will analyse the data separately. Self-reported physical functioning can be assessed using validated questionnaires, examples of which are provided later in this protocol. We will consider both objectively measured and self-reported physical functioning in our review. Physical activity and exercise training have been shown to have direct benefits at the molecular level on skeletal muscle, the endothelium and the myocardium. Muscle fibre adaptations, mitochondrial activity, stem cell proliferation and an increase in nitric oxide bioavailability are just some positive molecular adaptations seen after exercise training (Adams 2017). These underlying mechanisms are proposed to contribute to increased health-related quality of life, exercise capacity and a decrease in morbidity and mortality (Adams 2017).

Why it is important to do this review

Physical fitness is known to be lower in people with ConHD and deteriorates with age faster compared to healthy people (Kempny 2011; Amedro 2017). This has significant implications as CRF is predictive of medium-term mortality rates (Inuzuka 2012), and is considered the most important factor in determining a positive outcome post surgical intervention (Fontan procedure) (d'Udekem 2017).

Currently there is a dearth of evidence to adequately inform what should be the optimal physical activity and exercise interventions for people with ConHD (Gomes-Neto 2016). Consequently, exercise is not adequately discussed in paediatric cardiac clinics; this is primarily attributed to a lack of training and knowledge of the current exercise recommendations for people with ConHD (Williams 2017). We hope by conducting this review to inform health care policy and highlight future avenues for research for those afflicted by a heart condition.

OBJECTIVES

To assess the effectiveness and safety of physical activity promotion and exercise training interventions in individuals with congenital heart disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (with individual patient allocation, cluster allocation, or cross-over design) that compare physical activity promotion or exercise training intervention to a 'no physical activity/no exercise' comparator. We will include trials irrespective of their duration of follow-up and we will include studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

All individuals, irrespective of age and sex, with or without surgical or catheter procedures, with a diagnosis of ConHD, who are deemed by the trial investigators as suitable for participation in physical activity or an exercise training intervention. In a situation where a trial contains a mixed population (i.e. individuals with ConHD and other heart disease diagnoses) we will (1) assess if the subgroup results in ConHD are reported, and if not we will contact the authors; and if results are not available then (2) we will include all the trial data so long as the population with ConHD makes up 50% or more of the total population.

Types of interventions

All interventions - structured or unstructured, supervised or unsupervised - that include physical activity promotion or exercise training, delivered in any setting (community, hospital/outpatient centre and at home). So long as they are considered suitable for physical activity all individuals with ConHD, regardless of age, previous catheter or surgical intervention, are eligible for the intervention. Cardiac rehabilitation (CR) would be considered exercise-based only if it includes some form of exercise training or physical activity promotion intervention. We will consider all exercise-based CR interventions either given alone or as part of a more comprehensive CR programme that has education and psychological components. The intervention can be based in any setting(s), for example at home, in the community, in primary, secondary and tertiary care. Furthermore, interventions can be supervised or unsupervised and single or multi-component. Interventions will need to be adjusted for age, maturity and disease status for those patients participating. The intervention will be compared to no physical activity control or physical activity as usual.

Both the intervention and control group participants will receive usual medical care as reported by the study. Usual care typically comprises regular check-ups, drug treatment as required and dependent on congenital heart disease status, and general advice for a healthy and active lifestyle. We anticipate most studies will provide usual care; however, where a study does not provide standard care we will not exclude it from the review as this may be because of a trial being conducted in a less economically developed region, where there is no provision for usual care. Physical activity restrictions may be required, dependent on the type of congenital heart disease.

Types of outcome measures

For us to include them, studies should have intended to assess any of the outcomes in both the intervention and the control groups. We will extract outcomes at all time points and we will categorise as up to 6 months; 6 to 12 months; and longer than 12 months at follow-up. As long-term follow-up (> 12 months) is our period of most interest, due to its usefulness in influencing policy decisions, we will include this follow-up period in the 'Summary of findings' table. We will seek the following primary and secondary outcomes, but they will not form the basis of inclusion/exclusion criteria for the review.

Primary outcomes

1. Health-related quality of life determined by a validated questionnaire
2. Maximal cardiorespiratory fitness (CRF)
3. Device-worn 'objective' measures of physical activity

Secondary outcomes

1. Validated questionnaire-based 'subjective' measures of physical activity
2. Return to work or full-time education
3. Hospital admissions
4. Sub-maximal CRF
5. Muscular strength determined by:
 - o grip strength
 - o isokinetic testing
 - o muscular endurance capacity
6. Adverse events

We anticipate there will be a substantial variability in the reported outcome measures; we will approach this as follows.

Health-related quality of life (HRQoL)

There is large variability in the HRQoL scales used in studies focusing on people with ConHD and these include but are not limited to: the Child Health Questionnaire, Pediatric Quality of Life Inventory, Congenital Heart Disease-TNO/AZL Adult Quality

of Life, Child Quality of Life Questionnaire, EQ-5D and the 36-Item Short Form Health Survey (Dulfer 2017). If the questionnaire reported is validated, we will pool all studies' HRQoL data and analyse accordingly.

Maximal cardiorespiratory fitness (CRF)

Recent research has reported that a supramaximal bout after an incremental cardiopulmonary exercise test verifies maximal oxygen consumption (VO_2 max) in nearly 90% of cases in both children and adolescents (Sansum 2019). We will therefore pool both peak VO_2 and VO_2 max assessed by cardiopulmonary exercise testing on a treadmill or cycle ergometer, as we expect a dearth of objectively measured CPET data to be reported. We will report other validated cardiorespiratory fitness tests, such as the multi-stage fitness test, but we will not pool these into the main analysis but will analyse and report them separately.

Device-worn measures of physical activity

We will pool for one analysis all 'movement' data collected from either accelerometers (Actigraph, GENEACTIV) and smart watch devices (Polar, Garmin). We will analyse heart rate data separately from movement data, but again we will pool all data from heart rate devices - portable electrocardiography to smart watches - into the same analyses.

Questionnaire-based measures of physical activity

We will include and analyse in one analysis all validated questionnaires that have physical activity components, such as the General Practice Physical Activity Questionnaire (GPPAQ) and the Global Physical Activity Questionnaire (GPAQ).

Hospital admissions

We will assess hospital admission based on the number of people with at least one admission during a study's follow-up. The purpose of this is to reduce the impact of outpatient appointments or unrelated admissions (or both) skewing the data.

Sub-maximal CRF

We note that it has been suggested that 'anaerobic threshold' (if calculated according to ventilation parameters) should be superseded by the term 'gas exchange threshold' (Jones 2005), and we will not count anaerobic threshold (AT) and the gas exchange threshold (GET) as two separate outcomes. The task of determining abnormal and normal is very difficult because of the paucity of the reference or normative database. The issue here is confidence in the maximal test to determine cardiorespiratory fitness. The criteria will not be different for children compared to adults.

Muscular strength

Grip strength, isokinetic testing and muscular endurance capacity are our key suboutcomes of muscular fitness. We will analyse and report all within the report separately but only include grip strength within the 'Summary of findings' table.

Adverse events

We conducted a preliminary scoping search: no adverse events or serious adverse events were reported in 20 physical activity or exercise training studies in people with ConHD. Adverse events are classified as any untoward occurrence, which may not necessarily be directly caused by the intervention (European Commission 2011). Expected adverse events are minor arrhythmia; illnesses; muscle, ligament and tendon damage. We will also report serious adverse events: these are classified as any occurrence that can result in life-threatening situations, disability or death, or requires hospitalisation of any duration (European Commission 2011). Expected serious adverse events are malignant cardiac arrhythmias and myocardial infarctions. Due to the dearth of available data, we will present all reported events (regardless of whether they were considered to be 'adverse' or 'serious adverse' events) in the review (by individual adverse event type) and in the 'Summary of findings' table (> 12 months post intervention). This is because it is the most relevant outcome encompassing patient-centred outcomes and physical activity guideline development.

Search methods for identification of studies

Electronic searches

We will search the following databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; MEDLINE (Ovid); Embase (Ovid); BIOSIS Citation Index (Thomson Reuters); Database of Abstracts of Reviews of Effects (DARE via www.crd.york.ac.uk/CRDWeb/HomePage.asp); Cumulative Index to Nursing and Allied Health Literature (CINAHL via EBSCOhost); Latin American and Caribbean Health Sciences Literature (LILACS via BIREME); Physiotherapy evidence database (PEDro via www.pedro.fhs.usyd.edu.au/index.html); Allied and Complementary Medicine Database (AMED via Ovid); and Web of Science (Thomson Reuters).

We will draw up a systematic search strategy to identify relevant randomised controlled studies without language or date restrictions. The preliminary search strategy for MEDLINE (Appendix 1) will be adapted across all other databases. We will apply the Cochrane sensitivity-maximising RCT filter (Lefebvre 2011) to MEDLINE (Ovid), and adaptations of it to the other databases, except CENTRAL.

We will search for any ongoing trials in the following clinical trial registers.

1. www.ClinicalTrials.gov;
2. The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

Searching other resources

We will search by hand the reference list of relevant reviews, randomised and non-randomised studies, and editorials for additional studies. We will contact the main authors of studies and experts in the field to ask for any missed, unreported or ongoing trials. We will also search for any retraction statements and errata for included studies.

Data collection and analysis

Selection of studies

Two review authors (CAW and CW) will independently screen titles and abstracts for inclusion from all the potential trials we identify from the search. We will then source full texts and both review authors (CAW and CW) will independently read them to confirm eligibility; or they will record their reasons for exclusion. If there are any disagreements that cannot be rectified through discussion, CAW and CW will ask LL and RST to arbitrate. Once complete, CAW and CW will extract the data using a piloted data collection sheet, if necessary linking multiple reports from the same trial. CAW and CW will resolve any disagreement through discussion or, if required, will consult both LL and RST. We will record the selection process with a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Initially, two authors (CAW and CW) will independently pilot a data collection form for study characteristics and outcome data for one of the included studies. The two review authors (CAW and CW) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving LL and RST. One review author will transfer data into the Review Manager 5 file (Review Manager 2014); and a second author will check that the data is entered correctly.

We will extract the following study characteristics.

1. Participants: N randomised, N lost to follow up, N analysed, mean age (\pm range), gender, severity of condition*, diagnostic criteria, inclusion criteria, and exclusion criteria.
2. Methods: study design, total duration of study, study setting, date of study, withdrawals, number of study centres and location.
3. Interventions: intervention (including the dose (frequency, intensity and time) and the nature of the intervention), comparison, and co-interventions.

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.

*As ConHD is an incredibly varied and complex disease the severity of the condition will be classified using the Hoffman 2002 criteria as 'mild', 'moderate' or 'severe' (see Appendix 2 for further information). We have chosen the Hoffman classification as it is very inclusive and does not bias against individual intra-diagnosis differences; it has since been adopted in the most recent guidelines from the US Task Force for adult congenital heart disease (Warnes 2008). We will adopt diagnostic criteria most important for outcomes related to activity and exercise participation (Budts 2013); the five criteria are as follows.

1. Ventricular function and hypertrophy
2. Pulmonary artery pressure
3. Aortic dilation
4. Arrhythmia
5. Blood oxygen saturation at rest and exercise

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the recently revised 'Risk of bias in randomised trials (RoB 2.0)' tool (Higgins 2019). We will resolve any disagreements by discussion or by involving another author.

Risk of bias will be assessed using the following Cochrane RoB 2.0 criteria (Higgins 2019).

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

We will assess risk of bias in each domain. An algorithm (or decision tree) using a series of signalling questions with the answers (yes, probably yes, no information, probably no, no) will determine the risk of bias (low risk, some concerns and high risk). We will include a text box alongside the questions and judgements to provide supporting information for decisions.

Our analysis of bias due to deviations from intended interventions will assess the effect of assignment to the intervention at baseline, sometimes known as the 'intention-to-treat effect'. We will minimise selective reporting, which could overestimate the effects of an intervention, by contacting authors for unpublished data. We will grade each potential source of bias as a 'low', 'high' or 'some concerns' 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 an author, we will note this in the 'Risk of bias' table. When analysing treatment effects, we will consider the risk of bias for the studies that con-

tribute to that outcome.

Measures of treatment effect

We will analyse dichotomous data as risk ratios with 95% confidence intervals and continuous data as mean difference with 95% confidence intervals. For any outcomes which are measured by studies in a variety of ways, we will either analyse these outcomes separately or we will use the standardised mean difference (SMD) with 95% confidence intervals as a summary statistic. We will enter data presented as a scale with a consistent direction of effect. We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

In accordance with Section 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (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. We will use multiple time points from individual trials, and to define completely separate pooled analysis of outcomes (e.g. HRQoL less than 6 months; HRQoL between 6 and 12 months etc.). This will avoid the situation where the same data appears more than once in the same analysis. We will adjust cluster RCTs' sample sizes or standard errors using the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial, from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this result and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we have identified both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and if we consider the interaction between the effect of intervention and the choice of randomisation unit to be unlikely. We will also acknowledge heterogeneity in the randomisation unit, and perform a subgroup analysis to investigate the effects of the randomisation unit if necessary

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). We will also use the Review Manager 5 calculator to calculate any missing standard deviation data if there is sufficient data reported (standard error or 95% CI) to allow us to calculate this (Review Manager 2014).

Assessment of heterogeneity

We will explore heterogeneity amongst included studies qualitatively (by comparing the characteristics of included studies) and quantitatively (using the Chi² test of heterogeneity and I² statistic). We will use a threshold of I² greater than 50% (considered to represent substantial heterogeneity (Deeks 2017) for both dichotomous and continuous outcomes to determine the statistical model to be used for meta-analysis. We will employ a random-effects model where there was formal evidence of statistical heterogeneity (i.e. Chi² test P value < 0.10 and I² statistic > 50%). We will also explore any substantial heterogeneity by subgroup analysis; and we will use visual inspection of the forest plots to assess heterogeneity.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot and employ the Egger test to explore possible small-study biases for the primary outcomes (Egger 1997).

Data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will express dichotomous outcomes for each comparison as risk ratios with 95% CI. We will express continuous data as mean difference with 95% CI; or, where an outcome is measured and reported in more than one way, as SMD with 95% CI. We will enter data presented as a scale with a consistent direction of effect. If meta-analysis indicates that there is evidence of an outcome difference, we will aim to calculate the associated number needed to treat (and 95% CI) for an additional beneficial or harmful outcome. 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 HRQoL using SMD. We will calculate numbers needed to treat for all outcomes together with their 95% CI. For outcomes where the meta-analysis indicates an effect of the intervention we will use the random-effects model; and we will also report the fixed-effect pooled estimate and 95% CI because of the tendency of smaller trials, which are more susceptible to publication bias, to be over-weighted with a random-effects analysis (Heran 2008a; Heran 2008b).

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 software (Review Manager 2014). We will conduct meta-regression analysis using the "metareg" command in Stata version 14.2 (Stata 2015 [Computer program]).

'Summary of findings' table

Two reviewers will independently undertake GRADE analysis using GRADEpro to grade the certainty of the available evidence and therefore help inform decisions based on this evidence (Schünemann 2017). 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 pre-specified outcomes. GRADEpro GDT will be used to import data from Review Manager 5 to create a 'Summary of findings' table (Table 1). We will aim to create a 'Summary of findings' table using the following outcomes: health-related quality of life, maximal cardiorespiratory fitness, device-worn 'objective' measures of physical activity, hospital admissions, sub-maximal CRF, muscular strength (grip strength), and adverse events. 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 downgrade the quality of studies using footnotes and will include comments to aid readers' understanding of the review where necessary.

Long-term follow-up (> 12 months) is our follow-up period of most interest because it is useful in influencing policy decisions. Therefore, long-term follow-up will be included in the 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We anticipate length of follow-up to be a driver of intervention effect, with the size of effect for some outcomes being related to the length of the follow-up. We will therefore aim to stratify meta-analysis of each outcome according to the length of trial duration: i.e. 'short-term' follow-up (< 6 months); 'medium-term' follow-up (6 to 12 months); and 'long-term' follow-up (more than 12 months). We will also aim to undertake univariate meta-regression to explore heterogeneity and examine potential treatment effect modifiers. We will aim to test the following hypotheses regarding differences in the effect of exercise-based CR on health-related

quality of life, physical activity and exercise capacity across particular subgroups (Anderson 2016; Anderson 2017).

1. Type of intervention (physical activity or exercise only versus multi-component intervention (categorical variable)).
2. 'Dose' of exercise intervention (dose = number of weeks of exercise training × average number of sessions/week × average duration of session in minutes) (dose 1000 units versus dose < 1000 units) (continuous variable).
3. Follow-up period (continuous variable).
4. Sample size (continuous variable).
5. Setting (home- or centre-based CR) (categorical variable).
6. Study location (continent) (categorical variable).
7. Mean age of participants (paediatrics and adults will be analysed separately) (continuous variable).
8. Percentage of male participants (continuous variable).

Given the anticipated small ratio of trials to co-variables, we will limit meta-regression to univariate analysis (Higgins 2011). Given the anticipated small number of included studies, however, we recognise that it would be unlikely that meta-regression or a stratified meta-analysis will be possible. We will aim to extract results of subgroup analyses, including participant-level subgroup analyses, if reported by individual included studies; for example, if a trial reports whether there was a difference in the effectiveness of CR between males and females.

Sensitivity analysis

We will compare meta-analysis results of including all studies versus only including those studies we judge to have overall low risk of bias (low risk in all domains).

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. 'Summary of findings' table

Physical activity and exercise interventions vs. control for the treatment of congenital heart disease at follow-up of more than 12 months								
Patient or population: people with congenital heart disease								
Setting: any setting (community, hospital/outpatient centre and at home)								
Intervention: physical activity promotion or exercise training								
Comparison: usual care								
Outcomes	Anticipated	absolute	effects*	Relative effect	No	of	Certainty of the	Comments
	(95% CI)							
	Risk with con-	Risk with treat-			studies)		(GRADE)	
	trol	ment						

Table 1. 'Summary of findings' table (Continued)

Health-related quality of life (follow-up mean and range)						
Maximal cardiorespiratory fitness (CRF) (follow-up mean and range)						
Device-worn 'objective' measures of physical activity (follow-up mean and range)						
Hospital admissions (number of people with at least 1 admission; follow-up mean and range)						
Sub-maximal CRF (follow-up mean and range)						
Muscular strength determined by grip strength (follow-up mean and range)						
Adverse events (follow-up mean and range)						

***The risk in the intervention group** (and its 95% 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; **OR:** Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the

Table 1. 'Summary of findings' table (Continued)

effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix I. Preliminary MEDLINE (Ovid) search strategy

- 1 exp Exercise/ (175393)
- 2 Physical Fitness/ (26125)
- 3 exp Sports/ (169572)
- 4 Rehabilitation/ (17785)
- 5 Dance Therapy/ (319)
- 6 exp Exercise Therapy/ (45320)
- 7 Recreation Therapy/ (109)
- 8 Physical Exertion/ (55694)
- 9 exp "Physical Education and Training"/ (13196)
- 10 Dancing/ (2650)
- 11 exercis*.tw. (269291)
- 12 aerobic\$.tw. (80096)
- 13 sport\$.tw. (66217)
- 14 walk\$.tw. (105374)
- 15 bicycle\$.tw. (12292)
- 16 ((lifestyle or life-style) adj5 activ\$.tw. (5360)
- 17 ((lifestyle or life-style) adj5 physical\$.tw. (4512)
- 18 (physical\$ adj5 (fit\$ or train\$ or activ\$ or endur\$ or exert\$ or perform* or inact*)).tw. (145418)
- 19 anaerobic.tw. (69805)
- 20 rehabilitat\$.tw. (149916)
- 21 heart rate recovery.tw. (957)
- 22 danc*.tw. (6455)
- 23 (run* or jog*).tw. (175912)
- 24 or/1-23 (1011713)
- 25 exp Heart Defects, Congenital/ (143874)
- 26 exp Heart Diseases/cn [Congenital] (6434)
- 27 (heart adj2 (defect* or abnormal* or malform*)).tw. (14919)
- 28 (congenital adj2 (heart or cardiac or cardio*)).tw. (39864)
- 29 or/25-28 (164769)
- 30 24 and 29 (6071)
- 31 randomized controlled trial.pt. (477274)
- 32 controlled clinical trial.pt. (92948)
- 33 randomized.ab. (436415)
- 34 placebo.ab. (195896)
- 35 drug therapy.fs. (2088505)
- 36 randomly.ab. (306719)
- 37 trial.ab. (455958)

38 groups.ab. (1887768)
39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (4390511)
40 exp animals/ not humans.sh. (4554611)
41 39 not 40 (3796835)
42 30 and 41 (1081)

Appendix 2. Severity classification in congenital heart disease

Severity of congenital heart disease is most often classified by lesion-specific data. While this approach is appropriate in most cases, it must be stressed that severity is highly individual and should be judged by a physician using validated criteria (Budts 2013).

Mild ConHD

Mild ConHD is the least severe classification in our planned review. Patients with mild ConHD may be asymptomatic and have no significant murmur. Some example lesions of mild ConHD are as follows.

- Bicuspid aortic valve (BAV)
- Small atrial septal defects (ASD)
- Small ventricular septal defects (VSD)
- Small patent ductus arteriosus

(PDA)

Moderate ConHD

Patients with moderate ConHD are likely to be symptomatic and the lesions will likely be identified in a clinical study. For example:

- mild or moderate aortic stenosis (AS) or aortic incompetence;
- moderate pulmonary stenosis (PS) or incompetence

;

- non-critical coarctation of the aorta;
- large atrial septal defect;
- complex forms of ventricular septal defect

.

Severe ConHD

This category includes complex conditions that usually require immediate medical intervention. Some example lesions are:

- dextro-transposition of the great arteries;
- tetralogy of fallot, including pulmonary atresia and absent pulmonary valve;
- hypoplastic right heart;
- tricuspid atresia

;

- pulmonary atresia with an intact ventricular septum;
- Ebstein anomaly;
- hypoplastic left heart;
 - aortic atresia
 - mitral atresia
- hypoplastic left heart;
 - aortic atresia
 - mitral atresia
- double outlet right ventricle

;

- truncus arteriosus

;

- total anomalous pulmonary venous connection;
- large atrioventricular septal defect; large VSD; large PDA;
- severe AS and/or severe PS;
- critical coarctation of the aorta.

This framework has been adopted from the work of Hoffman 2002 and Warnes 2008.

CONTRIBUTIONS OF AUTHORS

CAW was responsible for coordinating all authors and co-writing this protocol.

CW co-wrote the protocol, added the protocol to Review Manager 5 and redrafted the protocol after peer review.

GEP gave special insight into the literature and population with congenital heart disease.

GS gave special insight into the literature and population with congenital heart disease.

LL advised on Cochrane-specific procedures and oversaw the research group.

RST advised on Cochrane-specific procedures and oversaw the research group.

All authors contributed to the drafting of the protocol.

DECLARATIONS OF INTEREST

CAW has received funding to complete research into the heart health of young people. The author had full control of the design of the study, methods used, outcome parameters, analysis of the data and production of any manuscripts.

CW has no known conflicts of interest.

GEP is lead researcher in a contractual research partnership between the University of Bristol and Canon Medical Systems UK Ltd. investigating cardiac function during exercise in children.

GS is Medical Director of Sports Cardiology UK.

LL has no known conflicts of interest.

RST has no known conflicts of interest.

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