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Physical activity interventions for people with congenital heart disease (Review)

Williams CA, Wadey C, Pieles G, Stuart G, Taylor RS, Long L

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[Intervention Review]

Physical activity interventions for people with congenital heart disease

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ABSTRACT

Background

Congenital heart disease (ConHD) affects approximately 1% of all live births. People with ConHD are living longer due to improved medical intervention and are at risk of developing non-communicable diseases. Cardiorespiratory fitness (CRF) is reduced in people with ConHD, who deteriorate faster compared to healthy people. CRF is known to be prognostic of future mortality and morbidity: it is therefore important to assess the evidence base on physical activity interventions in this population to inform decision making.

Objectives

To assess the effectiveness and safety of all types of physical activity interventions versus standard care in individuals with congenital heart disease.

Search methods

We undertook a systematic search on 23 September 2019 of the following databases: CENTRAL, MEDLINE, Embase, CINAHL, AMED, BIOSIS Citation Index, Web of Science Core Collection, LILACS and DARE. We also searched ClinicalTrials.gov and we reviewed the reference lists of relevant systematic reviews.

Selection criteria

We included randomised controlled trials (RCT) that compared any type of physical activity intervention against a 'no physical activity' (usual care) control. We included all individuals with a diagnosis of congenital heart disease, regardless of age or previous medical interventions.

Data collection and analysis

Two review authors (CAW and CW) independently screened all the identified references for inclusion. We retrieved and read all full papers; and we contacted study authors if we needed any further information. The same two independent reviewers who extracted the data then processed the included papers, assessed their risk of bias using RoB 2 and assessed the certainty of the evidence using the GRADE approach. The primary outcomes were: maximal cardiorespiratory fitness (CRF) assessed by peak oxygen consumption; health-related quality of life (HRQoL) determined by a validated questionnaire; and device-worn 'objective' measures of physical activity.

Main results

We included 15 RCTs with 924 participants in the review. The median intervention length/follow-up length was 12 weeks (12 to 26 interquartile range (IQR)). There were five RCTs of children and adolescents (n = 500) and 10 adult RCTs (n = 424). We identified three types of intervention: physical activity promotion; exercise training; and inspiratory muscle training. We assessed the risk of bias of results for

CRF as either being of some concern (n = 12) or at a high risk of bias (n = 2), due to a failure to blind intervention staff. One study did not report this outcome. Using the GRADE method, we assessed the certainty of evidence as moderate to very low across measured outcomes.

When we pooled all types of interventions (physical activity promotion, exercise training and inspiratory muscle training), compared to a 'no exercise' control CRF may slightly increase, with a mean difference (MD) of 1.89 mL.kg^{-1}.min^{-1} (95% CI −0.22 to 3.99; n = 732; moderate-certainty evidence). The evidence is very uncertain about the effect of physical activity and exercise interventions on HRQoL. There was a standardised mean difference (SMD) of 0.76 (95% CI −0.13 to 1.65; n = 163; very low certainty evidence) in HRQoL. However, we could pool only three studies in a meta-analysis, due to different ways of reporting. Only one study out of eight showed a positive effect on HRQoL. There may be a small improvement in mean daily physical activity (PA) (SMD 0.38, 95% CI −0.15 to 0.92; n = 328; low-certainty evidence), which equates to approximately an additional 10 minutes of physical activity daily (95% CI −2.50 to 22.20).

Physical activity and exercise interventions likely result in an increase in submaximal cardiorespiratory fitness (assessed with VO_2 mL.kg^{-1}.min^{-1} at the gas exchange threshold; MD 2.05, 95% CI 0.05 to 4.05; n = 179; moderate-certainty evidence). Physical activity and exercise interventions likely increase muscular strength (measured by maximal voluntary contraction of knee extensions; MD 17.13, 95% CI 3.45 to 30.81; n = 18; moderate-certainty evidence). Eleven studies (n = 501) reported on the outcome of adverse events (73% of total studies). Of the 11 studies, six studies reported zero adverse events. Five studies reported a total of 11 adverse events; 36% of adverse events were cardiac related (n = 4); there were, however, no serious adverse events related to the interventions or reported fatalities (moderate-certainty evidence). No studies reported hospital admissions.

Authors' conclusions

This review summarises the latest evidence on CRF, HRQoL and PA. Although there were only small improvements in CRF and PA, and small to no improvements in HRQoL, there were no reported serious adverse events related to the interventions. Although these data are promising, there is currently insufficient evidence to definitively determine the impact of physical activity interventions in ConHD. Further high-quality randomised controlled trials are therefore needed, utilising a longer duration of follow-up.

PLAIN LANGUAGE SUMMARY

Physical activity interventions for people with congenital heart disease

Review question

This review aimed to gather evidence for the use of any physical activity intervention for people with congenital heart disease. We aimed to compare interventions including exercise training, physical activity promotion or lung training with no intervention (usual care).

Background

Congenital heart disease is the term used for a range of birth defects that affect how the heart works. People with congenital heart disease have reduced life expectancy, physical fitness and quality of life. However, due to better prenatal diagnoses, surgical procedures (often performed in the early years of life) and earlier interventions, the survival rate for those born with this disease has improved dramatically, such that most people will now live into adulthood. Exercise training and physical activity interventions are known to improve fitness, physical activity, survival and quality of life in healthy people, but it is not clear how effective these programmes are for people with long-term medical conditions.

Study characteristics

We searched for studies in September 2019 and identified 15 studies involving 924 participants. The studies used three main types of interventions, including programmes designed to increase physical activity, aerobic fitness and health-related quality of life and compared physical activity intervention and control interventions in people with congenital heart disease.

Key results

We included 15 trials with 924 participants. Half of the participants were female. Of the 15 trials, 5 used a total of 500 young people (less than 18 years of age) and 10 trials used a total of 424 adult participants. We found that physical fitness and physical activity may slightly increase but we are very uncertain about quality of life. There is currently no data to say if this small increase in fitness will result in fewer visits to the hospital. But there were no recorded deaths or serious events that were related to participation in physical activity.

Quality of evidence

Using a validated scientific approach (GRADE), the certainty in the evidence base was moderate for fitness, low for physical activity and very low for quality of life. Most outcomes were limited due to small study participant numbers and poor reporting of study details.

Summary of findings 1. Summary of findings for the main comparison. Physical activity and exercise interventions compared to usual care for people with congenital heart disease.

Patient or population: people with congenital heart disease.
Setting: hospital-based and home-based settings.
Intervention: physical activity promotion, inspiratory muscle training and exercise training interventions.
Comparison: usual care.

Outcomes Length of intervention in weeks (Median, (IQR))	Anticipated absolute effects* (95% CI)		No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with all interventions			
Maximal cardiorespiratory fitness (CRF) Assessed with: treadmill or cycle ergometry (12 (12, 26))	Mean 22 to 46	**MD 1.89 higher** (0.22 lower to 3.99 higher)	732 (14 RCTs (15 training arms))	⊕⊕⊕⊖[ab] MODERATE	Physical activity and exercise interventions may increase cardiorespiratory fitness slightly. Sensitivity analyses did not change the inference to a clinically important MD.
Health-related quality of life (HRQoL) Assessed with: Questionnaires (12 (12, 12))	-	**SMD 0.76 higher** (0.13 lower to 1.65 higher)	163 (3 RCTs)	⊕⊖⊖⊖[cde] VERY LOW	The evidence is very uncertain about the effect of physical activity and exercise interventions on health-related quality of life.
Physical activity (PA) Assessed with: Accelerometer (19 (12, 46))	Mean 11 to 41	**SMD 0.38** (0.15 lower to 0.92 higher)	328 (4 RCTs)	⊕⊕⊖⊖[ce] LOW	Physical activity and exercise interventions may increase physical activity slightly.
Submaximal cardiorespiratory fitness Assessed with: treadmill or cycle ergometry (VO_2 mL.kg^{-1}.min^{-1} at the gas exchange threshold). (12 (12, 15))	Mean 18 to 22	**MD 2.05** (0.05 higher to 4.05 higher)	179 (5 RCTs (6 training arms))	⊕⊕⊕⊖[e] MODERATE	Physical activity and exercise interventions likely results in an increase in submaximal cardiorespiratory fitness.

Muscular strength (12)	Mean 103	**MD 17.13** (3.45 higher to 30.81 higher)	18 (1 RCT)	⊕⊕⊕⊖[e] MODERATE	Physical activity and exercise interventions likely increases muscular strength.
Adverse events (12 (12, 26))	A total of 11 adverse events were reported in a population of 501 (2.2%), 7 of which were mild (1.4%). Mild adverse events included dizziness, discomfort, musculoskeletal (strains/ sprains) and a minor head injury. The 4 (0.8%) moderate adverse events were cardiac. There were no major adverse events reported.		501 (11 RCTs)	⊕⊕⊕⊖[f] MODERATE	Physical activity promotion and exercise training interventions did not lead to any serious adverse events.
Hospital admissions	No data available				

CI: confidence interval; IQR: 25th and 75th quartiles; MD: mean difference; SMD: standardised mean difference; RCT: randomised controlled trial; CRF: Cardiorespiratory fitness; HRQoL: Health-related quality of life. The mean SMD effect size was interpreted using Cohen effect sizes, i.e. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.

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 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.

[a] Statistical heterogeneity was present in CRF (I^2 = 75%). But it was explained using a sensitivity analysis by excluding high risk of bias studies (I^2 = 18%). Therefore, we chose not to downgrade by 1 level evidence due to inconsistency.
[b]The confidence interval includes both appreciable harm and appreciable benefit (i.e. 95% CI spans 0). Therefore, the certainty of evidence was downgraded by 1 level due to imprecision.
[c]Inconsistent directions of effect and considerable heterogeneity (HRQoL, I^2 = 82%; PA, I^2 = 77%). Therefore, the certainty of evidence was downgraded by 1 level due to inconsistency.
[d]Total high risk of bias in all studies included within the analysis, hence bias highly likely. Therefore, the certainty of evidence was downgraded by 2 levels due to the methodological limitations (risk of bias).
[e]Imprecise due to small numbers of events (< 400) (Ryan 2016). Therefore, the certainty of evidence was downgraded by 1 level due to imprecision.
[f]Over 25% of studies did not report data on adverse events. Therefore, the certainty of evidence was downgraded by 1 level due to publication bias.

BACKGROUND

Description of the condition

Congenital heart disease (ConHD) is a term for a range of developmental abnormalities of the heart or intrathoracic vessels, or both (Mitchell 1971). There are over 18 distinct types of ConHD, ranging in complexity (Rhodes 2008; Sommer 2008a; Sommer 2008b), that can be broadly classified as mild, moderate or severe (Hoffman 2002). During the period 2010 to 2017 the birth prevalence of ConHD is approximately 1% of all live births (9.41 per 1000 births; 95% confidence interval (CI) 8.60 to 10.25), with the mild conditions representing 65% (95% CI 58.7% to 71.7%) of the total ConHD births (Liu 2019).

Long-term survival is reduced in ConHD, but due to improved medical care this has improved dramatically over previous decades. The most recent meta-analysis reported that survival up to the age of 10 years was 81.4% (95% CI 73.80 to 87.90); however, 87.0% of the between-article variance can be accounted for by the year of the study (Best 2016). Consequently, survival up to the age of 10 years of age has increased from 75% to 90% over the past two decades due to improvements in surgical correction, prenatal diagnosis and earlier interventions (Best 2016). ConHD is therefore a changing chronic medical condition with the highest proportion of deaths now occurring in geriatrics (Khairy 2010).

In both healthy and clinical (coronary heart disease) populations, impaired physical activity (PA) and cardiorespiratory fitness (CRF) are associated with the development of non-communicable disease, morbidity and mortality (Franklin 2013; Lee 2012; Letnes 2019). People with ConHD have reduced levels of fitness (Amedro 2017); reduced health-related quality of life (HRQoL) (Amedro 2015); and are less physically active (Brudy 2020; Dua 2007; McCrindle 2007; Sandberg 2016). Fitness has also been heavily associated with future health outcomes in this population (Dimopoulos 2006; Giardini 2009; Müller 2015; Udholm 2018). It is crucial, therefore, that people with ConHD lead an active lifestyle, but there is currently no consensus on how best to improve PA, CRF and HRQoL in people with ConHD.

Description of the intervention

Physical activity consists of any bodily movement involving skeletal muscles that results in increased energy expenditure, whereas exercise training is a planned and structured period of PA with the intention of maintaining or improving physical fitness components (Caspersen 1985). The current guidelines for PA are an average of 60 minutes of moderate to vigorous physical activity (MVPA) a day for young people (< 18 years old) and 150 minutes of MVPA a week in adults (Department of Health 2011). Currently within specialist paediatric cardiac clinics physical activity recommendations are not adequately discussed due to a lack of training, time and knowledge of the current exercise recommendations for people with ConHD (Williams 2017).

Interventions that aim to improve CRF, PA and HRQoL typically consist of a PA promotion (goal setting, motivational interviews etc.), or exercise training (aerobic/resistance training, sports participation etc.), or a combination of both. PA promotion interventions aim to increase habitual PA behaviours by using psychological conceptual frameworks in order to promote self-efficacy, goal-setting and intrinsic motivation. Exercise training interventions, on the other hand, usually prescribe a set 'dose' of exercise either within a hospital, centre or at home. Inspiratory muscle training (IMT) is a new method of intervention, recently gaining popularity in people with chronic cardiorespiratory conditions and aiming to improve ventilatory power and efficiency. IMT is distinctly different from PA promotion and exercise training as it involves training the inspiratory chest muscles against a breathing resistance by using a handheld device.

How the intervention might work

The 'gold standard' measure of cardiorespiratory fitness is maximal oxygen consumption, which is explained by the Fick equation where oxygen uptake is the product of the cardiac output and the arteriovenous oxygen difference ($\dot{V}O_2$ = Q * a-$\dot{V}O_2$ diff). Improving cardiorespiratory fitness must target improving oxygen delivery (Q) and/or oxygen extraction at the peripheral sites (a-$\dot{V}O_2$ diff) of the body, namely the muscles. PA and exercise training are known to improve both cardiac output and oxygen extraction through complex molecular interactions improving myocardial contractility, mitochondrial activity, stem cell proliferation, nitric oxide bioavailability and muscle fibre adaptations (Adams 2017; Gielen 2010). There is evidence that supports inspiratory muscle training to improve ventilatory efficiency and fitness in people with chronic cardiorespiratory pathologies and in healthy people, but the adaptation mechanisms are not well understood (Shei 2018; Wong 2011). It is proposed that the increase in ventilatory efficiency is due to a combination of factors, inclusive of, but not limited to, changing motor recruitment 'diaphragm sparing' and the release of inflammatory cytokines (Shei 2018).

Why it is important to do this review

Cardiorespiratory fitness is lower in people with ConHD and deteriorates faster compared to healthy people (Amedro 2017). This has significant implications as CRF has been associated with future mortality and morbidity in several ConHD conditions (Dimopoulos 2006; Giardini 2009; Müller 2015; Udholm 2018). Currently, there is a dearth of evidence to adequately inform the effectiveness of interventions to improve CRF and consequently long-term outcomes.

Recent reviews have included both non-randomised and randomised controlled trials (RCTs), focused on specific types of interventions (e.g. home-based) or have restricted to particular age groups (Gomes-Neto 2016; Li 2019; Meyer 2020). Therefore, we present the first Cochrane Review to assess the effectiveness of all types of physical activity interventions and inclusive of all age groups, using only RCT data in people with ConHD. We hope by conducting this review that we can provide clarity on the effectiveness of physical activity interventions, highlight future avenues for research and inform future healthcare policy.

OBJECTIVES

To assess the effectiveness and safety of all types of physical activity interventions versus standard care in individuals with congenital heart disease.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include all types of randomised controlled trial (RCT), inclusive of but not limited to parallel, cross-over and cluster designs. We included only parallel and randomised cross-over designs: these trials compared all types of physical activity interventions to a 'no physical activity/no exercise' comparator. We included trials irrespective of their duration of follow-up.

Types of participants

We included all individuals with a diagnosis of ConHD, who were deemed suitable for participation in a physical activity or exercise training intervention. We included all types of congenital heart disease, regardless of previous medical care and categorised them as mild, moderate or severe (Hoffman 2002). We also included paediatric (5 to 18 years old) and adult populations (> 18 years old).

Types of interventions

We identified and included three types of intervention: physical activity (PA) promotion; exercise training; and inspiratory muscle training (IMT). PA promotion studies incorporated psychological components to promote and educate participants on the benefits of exercise, whereas exercise training studies 'prescribed' exercise at a set dose either in a hospital or in a home-based setting. IMT was not an anticipated intervention type at the protocol phase; we included it due to its increasing use in clinical care (Pufulete 2019). Furthermore, we included interventions whether they were structured versus unstructured, supervised versus unsupervised, home versus hospital and single versus multicomponent. All interventions were compared to 'no physical activity/physical activity as usual' control; and both the intervention and control group received usual medical care.

Types of outcome measures

Studies should have intended to assess any of the outcomes in both the intervention and the control groups. At the protocol phase we intended to extract outcomes at two time points: at the end of intervention and at long-term follow-up (> 12 months). Due to the lack of long-term follow-up data, we only extracted the data at the end of the intervention. We sought to report the following primary and secondary outcomes, but they did not form the basis of our inclusion/exclusion criteria.

Primary outcomes

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

Secondary outcomes

- Submaximal CRF
- Validated questionnaire-based 'subjective' measures of physical activity
- Return to work or full-time education
- Hospital admissions
- Muscular strength determined by:
  - grip strength
  - isokinetic testing
  - muscular endurance capacity
- Adverse events

We anticipated there would be substantial variability in the reported outcome measures and we approached the primary outcomes as follows.

Cardiorespiratory fitness (CRF)

We pooled peak oxygen consumption (peak $\dot{V}O_2$) measured in millilitres per kilogram per minute ($mL.kg^{-1}.min^{-1}$) as our measure of maximal CRF. Peak $\dot{V}O_2$ was assessed by validated cardiopulmonary exercise test protocols, measuring oxygen consumption directly or indirectly (by estimated oxygen consumption), using either a treadmill or cycle ergometer. The submaximal CRF outcome was oxygen consumption per kilogram of body mass ($\dot{V}O_2$ $mL.kg^{-1}.min^{-1}$) at the gas exchange threshold (GET).

Health-related quality of life (HRQoL)

As anticipated there was large variability in the HRQoL scales used; we pooled HRQoL data in a meta-analysis where appropriate and reported all HRQoL in Table 1 and summarised in text.

Device-worn measures of physical activity

Physical activity was measured by accelerometry only. We pooled data regardless of device (Actigraph GT3X, Actigraph GT1M), device settings (epoch ranged 5 to 60 seconds) and activity parameter measured (time spent in MVPA per day as a percentage (n = 1) and minutes spent in MVPA per day) as per the protocol. There were no heart rate data to analyse. and activity parameter measured (time spent in MVPA per day as a percentage (n = 1) and minutes spent in MVPA per day) as per the protocol. There were no heart rate data to analyse.

Search methods for identification of studies

Electronic searches

We undertook a systematic search of the following databases on 23 September 2019.

- CENTRAL in the Cochrane Library (Issue 9 of 12, 2019)
- Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 19 September 2019)
- Embase (Ovid, 1980 to 2019 week 38)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOHost, 1937 to 23 September 2019)
- Allied and Complementary Medicine Database (AMED) (Ovid, 1985 to September 2019)
- BIOSIS Citation Index (Clarivate Analytics, 1926 to 23 September 2019)
- Web of Science Core Collection (Clarivate Analytics, 1900 to 23 September 2019)
- Latin American and Caribbean Health Sciences Literature (LILACS) (Bireme, 1982 to 23 September 2019)
- DARE (NIHR Centre for Reviews and Dissemination www.crd.york.ac.uk, from inception to 31 March 2015 (when this database stopped adding records)).

We applied the Cochrane sensitivity-maximising RCT filter for MEDLINE and for Embase terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011; Higgins 2011). For CINAHL, we used the Cochrane CINAHL RCT filter (Glanville 2019). For all other databases, except CENTRAL, LILACS and DARE, we applied an adaptation of the Cochrane RCT filter. See Appendix 1 for the search strategies.

Searching other resources

We searched ClinicalTrials.gov on 11 September 2020 for ongoing or unpublished trials.

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

Data collection and analysis

Selection of studies

Two review authors (CAW and CW) independently screened titles and abstracts for inclusion from all the potential trials we identified from the searches. We then sourced full texts and both review authors (CAW and CW) independently read them to confirm eligibility; in the event of exclusion, we documented the reasons. This was facilitated by Covidence systematic review software. Two authors (LL and RST) arbitrated if any disagreements arose that could not be rectified through discussion,. We have recorded the selection process with a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies (Liberati 2009).

Figure 1. Study flow diagram

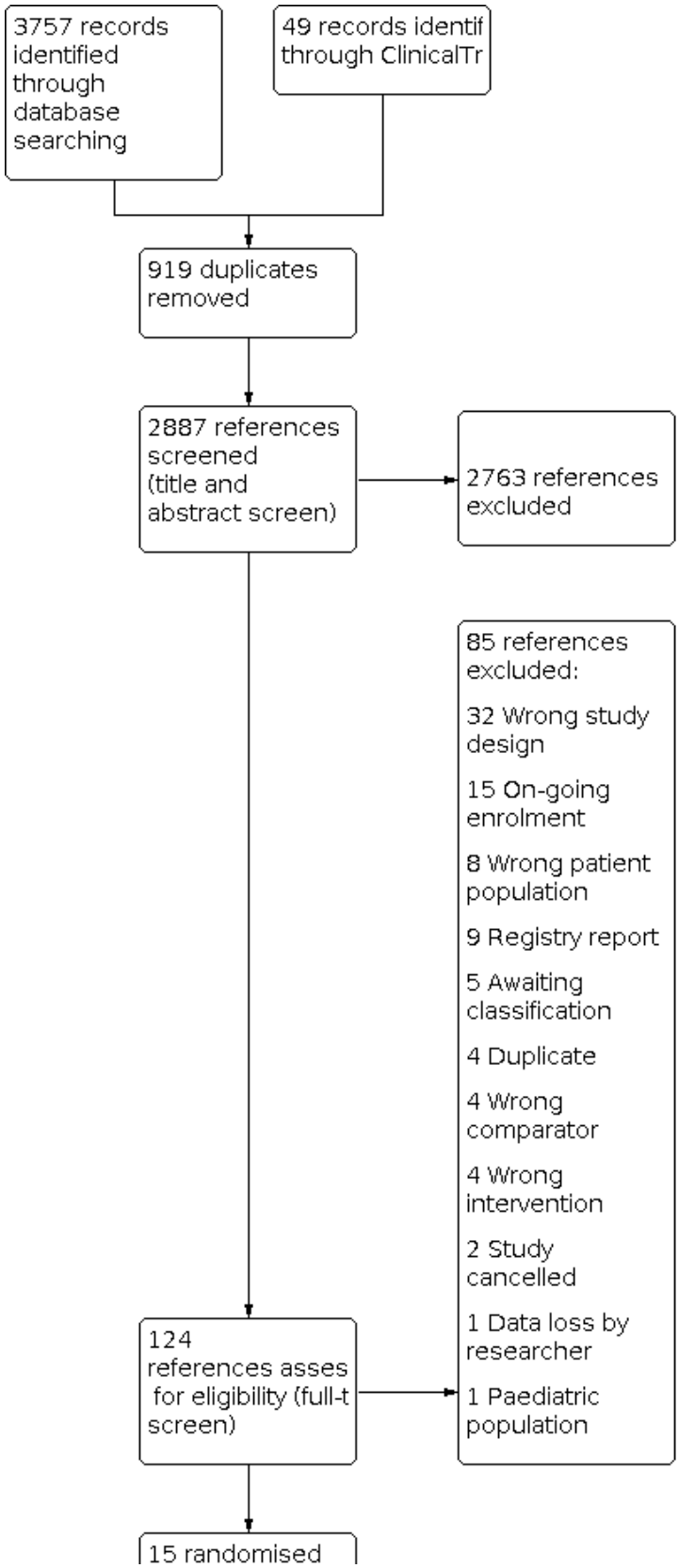
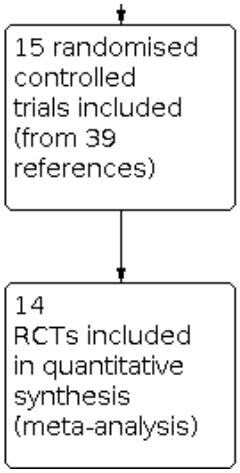


Figure 1. (Continued)



Data extraction and management

Two authors (CAW and CW) independently piloted a data collection form and independently extracted outcome data from included studies. One review author (CW) transferred data into RevMan Web 2019; and CAW checked that the data was entered correctly.

We extracted the following study characteristics.

- Participants: N randomised, N lost to follow-up, N analysed, mean age (± standard deviation), gender, severity of condition*, inclusion criteria, and exclusion criteria.
- Methods: study design, total duration of study, study setting, date of study, withdrawals, number of study centres and location.
- Interventions: intervention description (including the frequency, intensity, duration and modality of the intervention), comparison, and co-interventions.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

*As ConHD is an incredibly varied and complex disease we have classified the severity of the condition 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 have used these criteria to describe the study data (to aid the reader); we have not used it for subgroup analyses.

Assessment of risk of bias in included studies

Two review authors (CAW and CW) independently assessed risk of bias for each study using the recently revised 'Risk of bias in randomised trials (RoB 2)' tool (accessed: 28 January 2020) (Higgins 2019).

We assessed risk of bias for each study outcome using the following Cochrane RoB 2 criteria (Higgins 2019).

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For each domain a series of signalling questions with the answers (yes, probably yes, no information, probably no, no) determine the risk of bias (low risk, some concerns and high risk). We included text alongside the judgements to provide supporting information for our decisions (see Risk of bias in included studies). We decided the risk of bias for an outcome (e.g. health-related quality of life (HRQoL)) by its performance in each domain: if we judged one domain 'some concerns' or 'high risk' this judgement was taken for the whole outcome. We assessed the risk of bias of maximal and submaximal cardiorespiratory fitness (CRF), HRQoL, physical activity (PA) and muscular strength at follow-up. The effect of assignment or 'intention to treat' was our effect of interest and we have summarised the risk of bias in traffic lights on the forest plots, in Table 1 for HRQoL and in text.

Measures of treatment effect

We analysed continuous data as mean difference with 95% confidence intervals (CIs). Where an outcome was measured and reported in more than one way, we report a standardised mean difference (SMD) with 95% CIs. We interpreted the SMD using the two approaches recommended in the *Handbook* (Schünemann 2017). First, we interpreted the mean SMD effect size using the following rule of thumb based on Cohen effect sizes (i.e. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect) (Faraone 2008). In addition, for physical activity data we have converted the SMD back to the original scale units (minutes of moderate to vigorous activity) by multiplying the pooled mean SMD by an among-person standard deviation for a particular trial (Opotowsky 2018). We have corrected for any differences in the direction of the scales for HRQoL (i.e. when some scales have a lower score for a better QoL, a reduction in score would indicate an improvement, whereas a scale that awards higher scores for better QoL would see an increase in score indicating a positive outcome). We included HRQoL data in the meta-analysis only if it was the overall or total HRQoL score. For the outcome 'adverse events' where there was a dichotomous variable (event or no event), we analysed this using count data and summarised in text. Where

data were skewed and reported as medians and interquartile ranges, we converted them to means and standard deviations using validated equations (Wan 2014).

Unit of analysis issues

We only identified studies with individual randomisation. Only one study presented long-term follow-up data (Winter 2012); in this instance we extracted data at the end of the intervention to keep consistency with all the other trials. One trial contained three arm: continuous exercise training; interval exercise training; and a control group (Novakovic 2018). In this case we divided the number randomised to the control group in half to obtain the denominator for data analysis; the means and standard deviation for the control group remained unchanged for both comparisons. One study had a randomised cross-over design, but only contributed data prior to the cross-over (Fritz 2020); it was therefore not necessary to consider a washout period.

Dealing with missing data

We contacted multiple authors to verify key study characteristics (such as randomisation), clarify data queries and obtain missing numerical outcome data. Where data were presented graphically and we were unable to obtain numerical data from the authors, we used WebPlotDigitizer to extract this information.

Assessment of heterogeneity

We explored heterogeneity amongst included studies qualitatively (through visual inspection of forest plots and by comparing the characteristics of included studies), and quantitatively (using the Chi^2 test of heterogeneity and the I^2 statistic). We used a threshold of I^2 greater than 50% to represent substantial heterogeneity for continuous outcomes (Deeks 2017).

Assessment of reporting biases

We were able to pool more than 10 studies in our primary outcome 'maximal cardiorespiratory fitness'. We subsequently created and examined a funnel plot and used the Egger test to explore possible small-study biases for this primary outcome (Egger 1997).

Data synthesis

We performed meta-analyses with 95% CIs including all available studies where appropriate (i.e. when treatments, participants, and the underlying clinical question were similar enough for pooling to be appropriate). We used random-effects meta-analyses for all analyses due to the qualitative (types of interventions and severities of ConHD) and quantitative (statistical) heterogeneity present. Evidence of substantial heterogeneity was confirmed using the I^2 statistic of more than 50%, giving further justification for a random-effects analysis. Random effects provides a more conservative statistical approach, as the confidence interval around a random-effects estimate is wider than a confidence interval around a fixed-effect estimate (Heran 2008a; Heran 2008b). Where an outcome was measured and reported in more than one way, we report a standardised mean difference (SMD) with 95% CI.

We processed data in accordance with guidance in the *Handbook* (Higgins 2011). We completed data synthesis and analyses using RevMan Web software (RevMan Web 2019); and we conducted meta-regression analysis using the “metareg” command in Stata version 14.2 (Stata 2015 [Computer program]). We created additional figures using GraphPad (GraphPad Prism).

We could not pool some HRQoL. In this instance we adopted a modified version of a vote counting table, allowing us to summarise descriptive data, risk of bias and the direction of effect. Whilst this synthesis without meta-analysis (SWiM) method has significant limitations, we believe it to be the only SWiM method that allows us to communicate the results in a transparent and concise format (Campbell 2020).

Subgroup analysis and investigation of heterogeneity

We split the outcome 'maximal cardiorespiratory fitness' into two subgroup analyses: Analysis 1.1 reports the effect of the type of physical activity intervention (i.e. PA promotion, exercise training and inspiratory muscle training (IMT); and Analysis 1.6 reports the effect of the intervention in each group of ConHD (i.e. single ventricle, tetralogy of Fallot and other/mixed ConHD).

We used meta-regression to assess the potential treatment effect modifiers from all interventions (PA promotion, exercise training and IMT) on maximal cardiorespiratory fitness. Due to the limited number of studies to co-variate ratio we limited the meta-regression to univariate analysis only (Higgins 2011). The meta-regression included the following co-variates.

- Type of intervention (PA promotion or exercise training or IMT (categorical variable)).
- ‘Dose’ of exercise intervention (dose = number of weeks of exercise training × average number of sessions/week × average duration of session in minutes) (continuous variable).
- Length of intervention/follow-up period (continuous variable).
- Sample size (continuous variable).
- Setting (home- or centre-based) (categorical variable).
- Study location (North America or Europe or Asia) (categorical variable).
- Age of participants (paediatrics or adults) (categorical variable).
- Percentage of male participants (continuous variable).
- Baseline cardiorespiratory fitness (continuous variable).
- Risk of bias (categorical variable).

Due to the lack of data, we pooled all individual ConHD lesions (Table 2). This has limitations due to the within-condition and between-condition heterogeneity in clinical status (Amedro 2017; Kempny 2012). We therefore used pre-intervention (baseline) cardiorespiratory fitness as a meta-regression covariate to account for the heterogeneity.

Sensitivity analysis

We performed the following sensitivity analyses for the outcome of maximal cardiorespiratory fitness: removal of high risk of bias studies; direct versus indirect methods of measuring/estimating peak $\dot{V}O_2$; the use of a fixed-effect model; insertion of all available change scores; and the removal of computed outcome scores (converting medians and interquartile ranges to means ± standard deviations). We did not perform sensitivity analyses for the other outcomes within the review, due to the lack of studies included in the respective outcomes and the similarity of the studies pooled.

Summary of findings and assessment of the certainty of the evidence

We created the 'Summary of findings 1' using RevMan Web 2019 and reported the following outcomes: maximal cardiorespiratory fitness (CRF), health-related quality of life (HRQoL), device-worn 'objective' measures of physical activity (PA), submaximal CRF, muscular strength, and adverse events.

Two reviewers (CAW & CW) independently conducted GRADE analysis using GRADEpro GDT. Where disagreements arose, we asked co-authors (LL & RST) to arbitrate. We used GRADE to assess the certainty of the available evidence, helping to inform decisions based on this evidence (Schünemann 2017). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence, as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We justified all decisions to downgrade the quality of studies using footnotes.

We used 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). Long-term follow-up (> 12 months) post intervention was our follow-up period of most interest. However, as only one study reported long-term follow-up, we only report short-term follow-up (immediately post intervention) in the 'Summary of findings' table.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies; Characteristics of studies awaiting classification.

Results of the search

We identified 3806 references through our electronic and manual searches. After de-duplication and title and abstract screening, we retrieved 124 references. After screening the full text, we identified 15 RCTs from 39 references (see Figure 1). Searching of the reference lists of eligible publications did not reveal additional publications for inclusion.

We contacted 18 corresponding authors for further information regarding study inclusion. When we could not reach the authors, we included these studies (n = 5) in the Studies awaiting classification table.

Included studies

Population

We included 15 RCTs with 924 participants (50% ± 12% male) in the review. There were five paediatric RCTs and 10 adult RCTs with 500 participants and 424 participants respectively. All paediatric RCTs were based in Europe, whereas adult trials were based in Europe (n = 6), North America (n = 3) and Asia (n = 1). There were 11 RCTs that included severe classification participants (n = 559); three RCTs that pooled mild, moderate and severe classifications (n = 254); and one RCT that included mild classification participants only (n = 111). Table 2 reports the individual ConHD lesions that we pooled into the meta-analyses.

Intervention

We identified three distinct types of interventions: exercise training (n = 11); physical activity promotion (n = 3); and inspiratory muscle training (IMT) (n = 1). See Table 3 for the characteristics of exercise training trials. Physical activity promotion aims were varied: Morrison 2013 and Klausen 2016 used motivational techniques (interviewing and goal setting vs. text 'e-based' encouragement) to improve physical activity and fitness in children and adolescents; whereas another intervention used a family-based psychological intervention with a subcomponent of physical activity promotion with the aim of improving HRQoL, time/behaviour in school and sports enjoyment in young children (van der Mheen 2019). The only IMT study included within the review aimed to assess the efficacy of IMT in adults with severe ConHD (Fontan circulations). The intervention was a randomised cross-over design using a commercially available inspiratory muscle trainer. The participants completing three sets of 10 to 30 repetitions every day for six months, the intensity could be adjusted from 10 cm H_2O to 90 cm H_2O and was individualised for every training session to maintain an optimal training effect (Fritz 2020).

Comparison

All studies compared to usual care for their region. Only one study had three arms: two intervention arms (interval and continuous training) and a control arm (Novakovic 2018).

Primary Outcomes

Maximal cardiorespiratory fitness (CRF) was measured in 14 out of 15 (93.3%) studies. Health-related quality of life (HRQoL) was reported in 8 out of 15 (53.3%) studies, using a variety of validated questionnaires summarised in Table 1. Device-worn measures of physical activity was reported by four (26.6%) studies, using a range of accelerometers, cut points and parameters such as time spent as a percentage in moderate to very vigorous activity, average minutes of moderate to vigorous activity (MVPA) and total minutes per day spent in MVPA assessed using accelerometer cut-points greater than 2000 counts (Duppen 2015; Klausen 2016; Morrison 2013; Opotowsky 2018). No study used disease-specific cut points.

Secondary Outcomes

Only one study numerically reported questionnaire-based physical activity (Duppen 2015). Klausen 2016 used questionnaires in combination with device-worn measures but did not report the questionnaire data as it reported similar results. No study measured return to work or full-time education. One study reported episodes off school for one or more days, however (van der Mheen 2019). No study reported on hospital admissions. Submaximal CRF was reported in a variety of ways: the most commonly reported was the oxygen consumption at the gas exchange threshold (GET) scaled to body mass ($mL.kg^{-1}.min^{-1}$) (n = 5 studies) and the ventilatory equivalents ($\dot{V}E$) over volume of carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope) (n = 4 studies) (Avila 2016; Duppen 2015; Fritz 2020; Moalla 2006; Novakovic 2018; Opotowsky 2018; van Dissel 2019; Westhoff-Bleck 2013). Absolute oxygen consumption at the GET ($mL.min^{-1}$), power output in watts at the GET, VE at the GET, heart rate at the GET and the oxygen uptake efficiency slope were all reported once. Muscular strength was only reported by one study using isokinetic testing (Moalla 2006); and adverse events were reported by 11 studies, independent of whether an adverse event actually took place (Avila 2016; Duppen 2015; Fritz

2020; Klausen 2016; Novakovic 2018; Opotowsky 2018; Sandberg 2018; Therrien 2003; van Dissel 2019; Westhoff-Bleck 2013; Winter 2012).

Excluded studies

We excluded 85 references during the full-text review, amongst which were 32 due to wrong study design, 15 because they are ongoing trials and 8 because they included the wrong patient population. For more regarding exclusions see Figure 1 and Characteristics of excluded studies.

Risk of bias in included studies

Risk of bias assessments for each outcome, including all domain judgements and support for judgement, is located in the Risk of bias section (located after the Characteristics of included studies), at the side of all forest plots and in Table 1 for HRQoL. To access further detailed risk of bias assessment data, please use the following link (doi.org/10.24378/exe.2363).

Risk of bias of outcomes across all studies was similar and predominately of 'some concerns'. Study authors reported poorly
the details of blinding outcome assessors (patient-facing members of staff conducting the outcome assessments, i.e. the person conducting the exercise test or questionnaire) and pre-agreed statistical analysis plans with sufficient detail.

Across most outcomes risk of bias was similar: we judged it as 'some concerns'. The only exception was HRQoL which we judged to be at high risk of bias due to the nature of self-reported questionnaires, the lack of blinding of the participants and other outcome assessors.

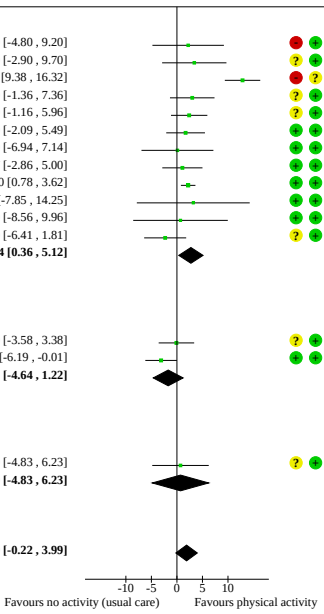
Effects of interventions

See: **Summary of findings 1** Summary of findings for the main comparison. Physical activity and exercise interventions compared to usual care for people with congenital heart disease.

See Summary of findings 1 and forest plots (Figure 2, Figure 3, Figure 4, Figure 5, Figure 6).

Figure 2. Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease. Outcome: Maximal cardiorespiratory fitness ($\dot{V}O_2$ mL.kg^{-1}.min^{-1} at maximal exercise).

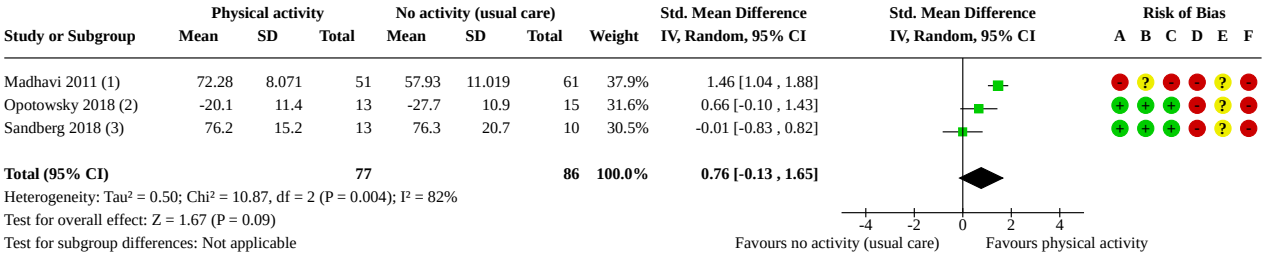
Study or Subgroup	Physical activity Mean [mL/kg/min]	SD [mL/kg/min]	Total	No activity (usual care) Mean [mL/kg/min]	SD [mL/kg/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/kg/min]	Risk of Bias A B C D E F
1.1.1 Exercise training									
Therrien 2003	24.3	8.2	9	22.1	6.5	8	4.8%	2.20 [-4.80 , 9.20]	
Moalla 2006	33	6.2	10	29.6	7.2	8	5.4%	3.40 [-2.90 , 9.70]	
Madhavi 2011	43.84	10.33	51	30.99	7.96	61	8.1%	12.85 [9.38 , 16.32]	
Winter 2012	29	7	24	26	8	22	7.2%	3.00 [-1.36 , 7.36]	
Westhoff-Bleck 2013	25.9	6.1	19	23.5	5.3	21	8.0%	2.40 [-1.16 , 5.96]	
Duppen 2015	35.9	7.4	43	34.2	8.6	30	7.8%	1.70 [-2.09 , 5.49]	
Avila 2016	28.6	7.1	13	28.5	6.01	4	4.8%	0.10 [-6.94 , 7.14]	
Sandberg 2018	25.1	6.16	13	24.03	3.33	10	7.6%	1.07 [-2.86 , 5.00]	
Opotowsky 2018	1	1.5	13	-1.2	2.3	15	9.9%	2.20 [0.78 , 3.62]	
Novakovic 2018 (1)	26.5	12.5	9	23.3	8.5	5	2.7%	3.20 [-7.85 , 14.25]	
Novakovic 2018 (2)	24	6.2	9	23.3	8.5	4	3.5%	0.70 [-8.56 , 9.96]	
van Dissel 2019	25.4	6.6	17	27.7	5.6	17	7.4%	-2.30 [-6.41 , 1.81]	
Subtotal (95% CI)			**230**			**205**	**77.3%**	**2.74 [0.36 , 5.12]**	
Heterogeneity: Tau² = 10.92; Chi² = 40.79, df = 11 (P < 0.0001); I² = 73%									
Test for overall effect: Z = 2.26 (P = 0.02)									
1.1.2 Physical activity promotion									
Morrison 2013	37.4	8.8	62	37.5	8.6	39	8.1%	-0.10 [-3.58 , 3.38]	
Klausen 2016	43.2	9.7	81	46.3	10.1	77	8.5%	-3.10 [-6.19 , -0.01]	
Subtotal (95% CI)			**143**			**116**	**16.6%**	**-1.71 [-4.64 , 1.22]**	
Heterogeneity: Tau² = 1.68; Chi² = 1.60, df = 1 (P = 0.21); I² = 37%									
Test for overall effect: Z = 1.14 (P = 0.25)									
1.1.3 Inspiratory muscle training									
Fritz 2020	24	8.3	18	23.3	9.1	20	6.1%	0.70 [-4.83 , 6.23]	
Subtotal (95% CI)			**18**			**20**	**6.1%**	**0.70 [-4.83 , 6.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.25 (P = 0.80)									
Total (95% CI)			**391**			**341**	**100.0%**	**1.89 [-0.22 , 3.99]**	
Heterogeneity: Tau² = 11.06; Chi² = 55.03, df = 14 (P < 0.00001); I² = 75%									
Test for overall effect: Z = 1.76 (P = 0.08)									
Test for subgroup differences: Chi² = 5.34, df = 2 (P = 0.07), I² = 62.5%									



Footnotes
(1) interval training arm
(2) continuous training arm

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiorespiratory fitness
(C) Bias due to missing outcome data: Cardiorespiratory fitness
(D) Bias in measurement of the outcome: Cardiorespiratory fitness
(E) Bias in selection of the reported result: Cardiorespiratory fitness
(F) Overall bias: Cardiorespiratory fitness

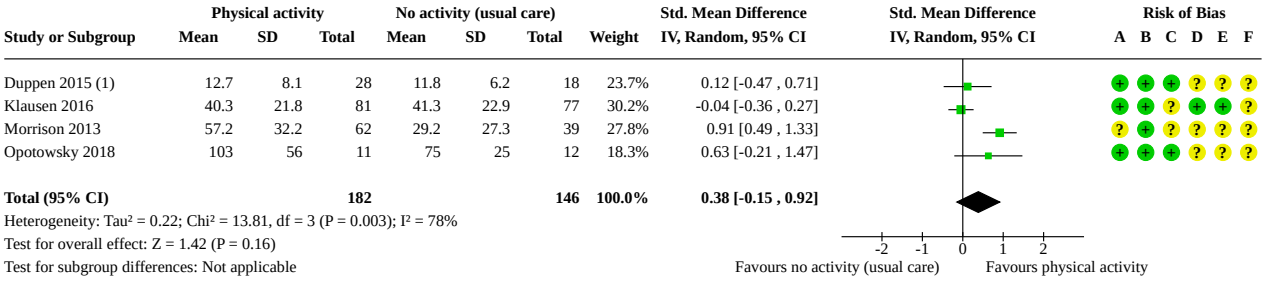
Figure 3. Exercise training versus no activity (usual care) in people with congenital heart disease. Outcome: Health related quality of life.



Footnotes
(1) SF-36 (total score)
(2) MLHFQ
(3) EQ5D VAS

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-related quality of life
(C) Bias due to missing outcome data: Health-related quality of life
(D) Bias in measurement of the outcome: Health-related quality of life
(E) Bias in selection of the reported result: Health-related quality of life
(F) Overall bias: Health-related quality of life

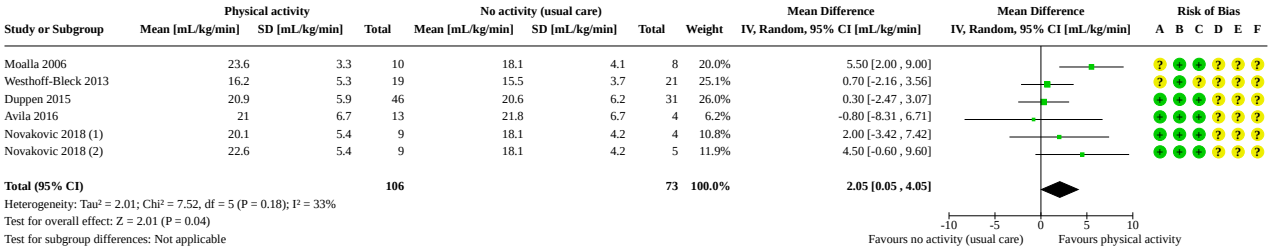
Figure 4. Physical activity promotion and exercise training interventions versus no activity (usual care) in people with congenital heart disease. Outcome: Physical activity (device-worn).



Footnotes
(1) Measure of activity: time spent in moderate-to-very-vigorous activity as a percentage. All other studies report minutes of MVPA per day.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Physical activity (device-worn)
(C) Bias due to missing outcome data: Physical activity (device-worn)
(D) Bias in measurement of the outcome: Physical activity (device-worn)
(E) Bias in selection of the reported result: Physical activity (device-worn)
(F) Overall bias: Physical activity (device-worn)

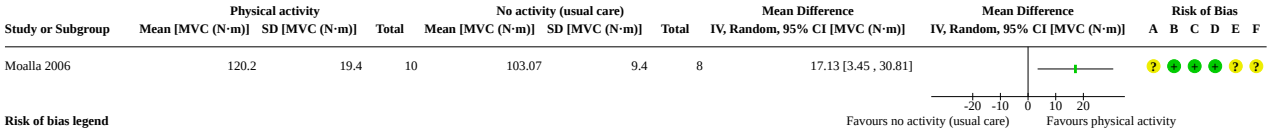
Figure 5. Exercise training interventions versus no activity (usual care) in people with congenital heart disease. . Outcome: Sub-maximal cardiorespiratory fitness ($\dot{V}O_2$ mL.kg^{-1}.min^{-1} at the gas exchange threshold).



Footnotes
(1) continuous training arm.
(2) interval training arm

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Submaximal cardiorespiratory fitness (gas exchange threshold)
(C) Bias due to missing outcome data: Submaximal cardiorespiratory fitness (gas exchange threshold)
(D) Bias in measurement of the outcome: Submaximal cardiorespiratory fitness (gas exchange threshold)
(E) Bias in selection of the reported result: Submaximal cardiorespiratory fitness (gas exchange threshold)
(F) Overall bias: Submaximal cardiorespiratory fitness (gas exchange threshold)

Figure 6. Exercise training interventions versus no activity (usual care) in people with congenital heart disease. Outcome: Muscular strength.



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Muscular strength
(C) Bias due to missing outcome data: Muscular strength
(D) Bias in measurement of the outcome: Muscular strength
(E) Bias in selection of the reported result: Muscular strength
(F) Overall bias: Muscular strength

Maximal cardiorespiratory fitness

A total of 14 studies (15 training arms, 732 participants) reported maximal CRF using peak oxygen consumption (peak $\dot{V}O_2$) scaled to body mass (mL.kg^{-1}.min^{-1}). One study had a long-term follow-up at 36 months post intervention (Winter 2012); all other studies' follow-up was at the cessation of the intervention (median 12, IQR 12 to 26 weeks). Most studies reported the post-score mean and standard deviation. However, van Dissel 2019 reported both a post score and a change score from baseline and Opotowsky 2018 only reported change score from baseline. To ensure consistency, change scores were included only when no post score was reported.

We pooled all available studies into a random-effects meta-analysis, with a subgroup analysis comparing the different types of intervention; we did not consider the result of the subgroup analysis to be significant (Chi² = 5.34, df = 2, P = 0.07, I² = 62.5%). In the pooled analysis there was a mean difference (MD) of 1.89 mL.kg^{-1}.min^{-1} (95% CI −0.22 to 3.99; 14 studies (15 training arms), 732 participants; I² = 75%). The subgroup exercise training consisted of 11 studies (435 participants) and there was a mean difference of 2.74 mL.kg^{-1}.min^{-1} (95% CI 0.36 to 5.12; I² = 73%) versus a mean difference of −1.71 mL.kg^{-1}.min^{-1} (95% CI −4.64 to 1.22, I² = 37%) and 0.70 mL.kg^{-1}.min^{-1} (95% CI −4.83 to 6.23) in physical activity promotion and inspiratory muscle training respectively (Figure 2).

We performed a further subgroup analysis for the type of congenital heart disease, which reported a pooled mean difference of 1.90 mL.kg^{-1}.min^{-1} (95% CI −0.14 to 3.95; 14 studies (15 training arms), 732 participants; I² =73%). The test for subgroup differences revealed no differences between subgroups (P = 1.00); single ventricle (MD 2.06, 95% CI −0.25 to 4.38; n = 153), tetralogy of Fallot (MD 1.97, 95% CI −1.11 to 5.05; n = 104) and other or mixed populations (MD 1.98, 95% CI −1.67 to 5.62; n = 474) all had a similar response to a physical activity intervention (Analysis 1.6).

We performed several separate sensitivity analyses removing high risk of bias studies (MD 0.92, 95% CI −0.27 to 2.11; 12 studies (13 training arms), 603 participants; I² = 18%) (Madhavi 2011; Therrien 2003); and studies that estimated peak $\dot{V}O_2$ using validated protocols (MD 1.07, 95% CI −0.14 to 2.28; 12 studies (13 training arms), 519 participants) (Madhavi 2011; Morrison 2013). We also report the use of fixed-effect meta-analyses (MD 2.00, 95% CI 1.09 to 2.91; 14 studies, 732 participants (15 training arms)); the insertion of all available change scores (MD 1.98, 95% CI 0.09 to 3.86; 14 studies (15 training arms), 732 participants) (Sandberg 2018); and the removal of computed outcome scores (converting medians and interquartile ranges to means ± standard deviations from Avila 2016, Fritz 2020, Klausen 2016, Novakovic 2018, Sandberg 2018 and Winter 2012) (MD 2.84, 95% CI −0.21 to 5.88; 8 studies, 423 participants).

We used univariate meta-regression to assess individual predictors of peak $\dot{V}O_2$. We regressed 10 predictors and the risk of bias and the intervention length produced significant associations (for regression coefficients and P values see Table 4 and Figure 7). This indicates that the shorter the intervention and the higher the risk of bias then the greater the effect on peak $\dot{V}O_2$. There was no evidence of publication bias (P = 0.268) (Figure 8). Using GRADE, we assessed the evidence to be of moderate certainty because of imprecision.

Figure 7. Meta-regression analyses investigating the effect of the 'overall risk of bias' and the 'length of intervention'. Outcome: Maximal cardiorespiratory fitness (see Table 4).

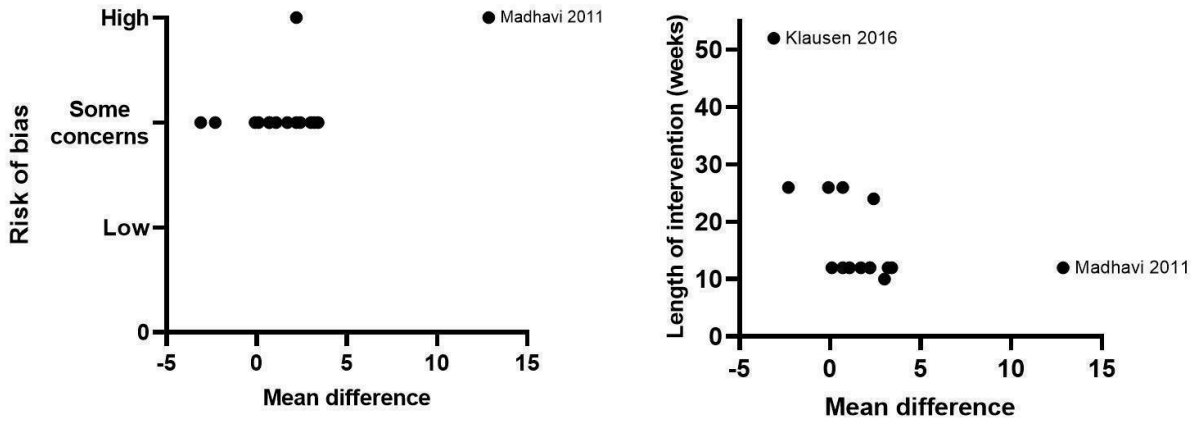
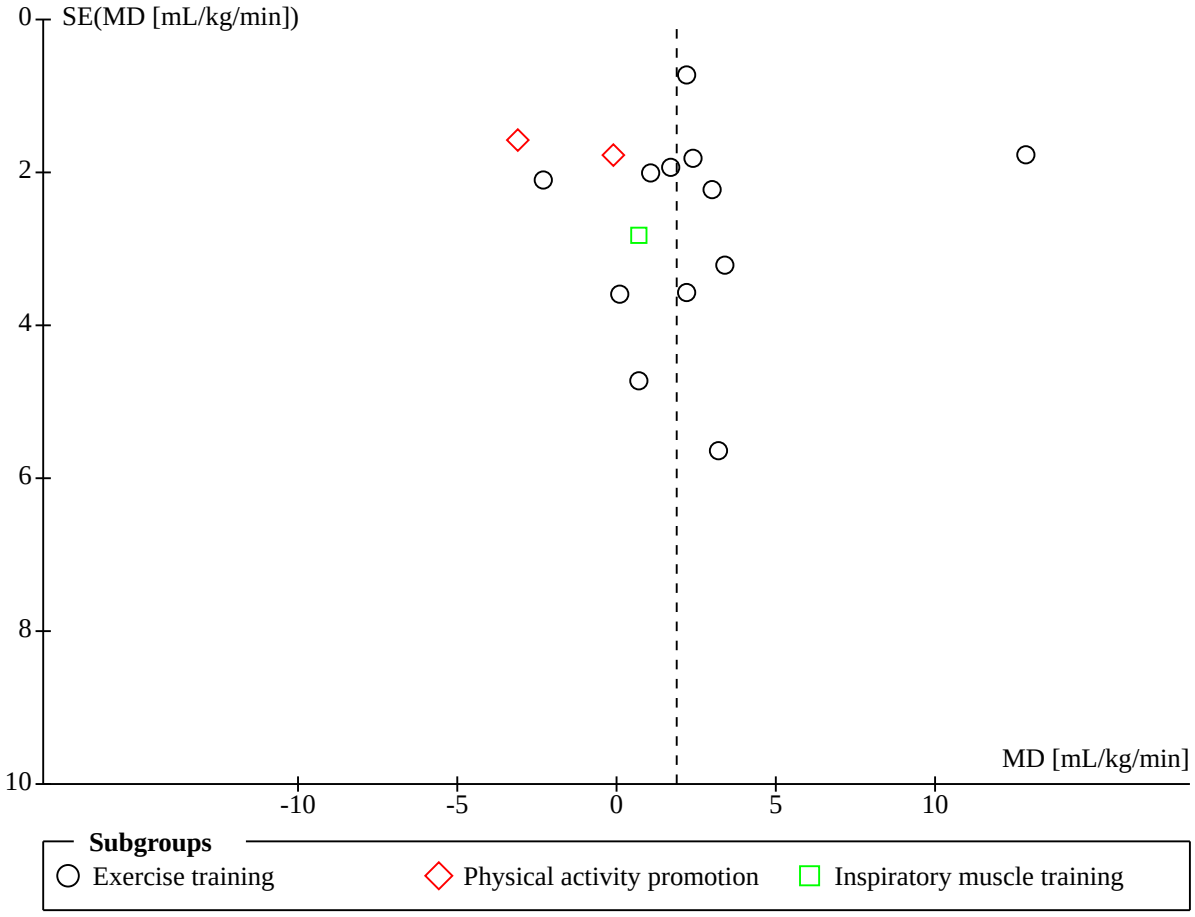


Figure 8. Funnel plot investigating publication bias. Outcome: Maximal cardiorespiratory fitness (Egger 1997 test, P=0.268).



Health-related quality of life (HRQoL)

HRQoL was reported by eight studies using a variety of validated questionnaires and a median follow-up of 12 weeks (Table 1). The '36-item short form health survey' (SF-36) was reported most frequently (n = 5), followed by the 'Congenital heart disease - TNO/AZL adult quality of life questionnaire' (ConHD TAAQoL) which was reported twice. All other questionnaires were reported once. Where possible we pooled HRQoL scores into a random-effects meta-analysis; we could enter only three studies into the analyses due to the variety of measurements reported. The result of the analysis was a standardised mean difference of 0.76 (95% CI −0.13 to 1.65; I^2 = 82%), which suggests a moderate effect size indicating a possibly beneficial effect of interventions on HRQoL (Figure 3). When we summarised all the evidence on HRQoL presented in the vote count table, however, this is not supported (Table 1). The vote count table aims to summarise all studies and instruments used to report HRQoL. Out of the 12 HRQoL questionnaires reported by the eight studies, only one questionnaire found a significant improvement in HRQoL (Madhavi 2011). Using GRADE, we judged the certainty of the evidence to be 'very low' due to serious to very serious concerns regarding risk of bias, inconsistency and imprecision.

Device-worn 'objective' measures of physical activity

Four studies (328 participants) used device-worn measures of physical activity and we entered their data into a random-effects meta-analysis (Figure 4). The median follow-up was 19 weeks (IQR 12 to 39 weeks). There is weak evidence of a small effect on physical activity levels with a standardised mean difference of 0.38 (95% CI −0.15 to 0.92; I^2 = 78%). The small effect size indicates a possibly beneficial albeit small effect of moderate to vigorous physical activity levels. Re-expressing these values into the original scales we can report an approximate 10 minute increase per day in moderate to vigorous physical activity (95% CI −2.50 to 22.20). Using GRADE, we downgraded the certainty of evidence by two levels to low, due to concerns over inconsistency and imprecision.

Validated questionnaire-based ‘subjective’ measures of physical activity

No study measured physical activity using only questionnaire measures of physical activity; two studies used them in combination with device-worn measures (Duppen 2015; Klausen 2016). Active leisure time (sports, walking and cycling) was not different after an exercise intervention; passive leisure time (television and computer) reduced significantly in both the

intervention and control group, making its attribution to the exercise intervention challenging (Duppen 2015). Klausen 2016 did not report their questionnaire results as it did not differ from their device-worn measures.

Return to work or full-time education

van der Mheen 2019 reported days off school for children participating in a multicomponent (physical activity promotion and psychological) intervention. The intervention group had 11 episodes of one or more days off school versus 13 episodes in one month in the control group, reported by school teachers. Interestingly when this was reported by mothers there was no effect (15 vs. 15) and the direction of effect was the other direction when reported by fathers (13 vs. 11).

Hospital admissions

No study reported this outcome.

Submaximal cardiorespiratory fitness

A total of nine studies (10 training arms) reported a measure of submaximal CRF, with a median follow-up of 12 weeks. As previously described in the Characteristics of included studies there was a large variety of submaximal CRF parameters. Oxygen consumption scaled to body mass ($mL.kg^{-1}.min^{-1}$) at the gas exchange threshold (GET) was reported most often and was subsequently entered into a random-effects meta-analysis, showing a likely increase in favour of the intervention with a mean difference of 2.05 (95% CI 0.05 to 4.05; 5 studies (6 training arms), 179 participants; I^2 = 33%) $mL.kg^{-1}.min^{-1}$ (Figure 5). All of the studies that contributed data to this meta-analysis were exercise training interventions (i.e. not PA promotion or IMT). Using GRADE, we judged the certainty of evidence as moderate—we downgraded the certainty of the evidence one level due to concerns over imprecision (< 200 participants).

Muscular strength

One study (18 participants) reported muscular strength measured by maximal voluntary contraction (N·m) of knee extensions in paediatrics with congenital heart disease. At the end of the exercise (cycling) intervention (12 weeks) there was a mean difference of 17.13 (95% CI 3.45 to 30.81) N·m in favour of exercise training (Figure 6). Using GRADE, we downgraded the certainty of evidence one level to moderate due to imprecision (only 18 participants).

Adverse events (AEs)

Eleven studies (501 participants) reported on the outcome of adverse events, over a median follow-up period of 12 weeks (IQR 12 to 26 weeks) (Avila 2016; Duppen 2015; Fritz 2020; Klausen 2016; Novakovic 2018; Opotowsky 2018; Sandberg 2018; Therrien 2003; van Dissel 2019; Westhoff-Bleck 2013; Winter 2012). Of the eleven studies, six studies reported zero adverse events and five studies reported a total of eleven adverse events. Of the 11 AEs, seven were non-cardiac (63%), characterised by dizziness, discomfort, minor musculoskeletal and minor head injuries. The remaining four cardiac AEs were inclusive of one suspected arrhythmia, one self-limiting supraventricular arrhythmia (beta-blocker administered), one episode of ventricular premature complexes (managed conservatively) and one episode of non-sustained atrial tachycardia that could be related to exercise. There were no reported serious adverse events or fatality.

Eight studies (377 participants) reported no adverse myocardial changes; seven studies reported no adverse changes to cardiac biomarker B-type natriuretic peptide (NT-proBNP), with a further four studies reporting no structural or functional cardiac effects using medical imaging (cardiac magnetic resonance and echocardiography) post intervention. There were no major adverse events reported. Our judgement of the certainty of evidence using the GRADE approach was moderate due to concerns over inconsistency.

DISCUSSION

Summary of main results

We identified 15 studies (with 924 participants) that were eligible for inclusion in this review. This review shows that based on moderate to very low certainty of evidence that all types of physical activity interventions (physical activity promotion, exercise training and inspiratory muscle training) when compared to usual care may have a small effect on cardiorespiratory fitness and physical activity level but little or no effect on HRQoL. It should be noted that there was high statistical heterogeneity amongst studies assessing cardiorespiratory fitness, physical activity and HRQoL. Seventy-three per cent of studies reported adverse events (six studies reported zero adverse events and five studies reported a total of eleven adverse events), of which seven of 11 events were of a non-cardiac nature, and there were no reported serious adverse events or fatalities related to the physical activity interventions. We were unable to find any data related to secondary outcomes on return to work or hospital admissions. The risk of bias under the outcomes of cardiorespiratory fitness and physical activity was predominantly of 'some concerns', for the outcome of health-related quality of life it was judged to be a high risk of bias.

Overall completeness and applicability of evidence

The generalisability of previous systematic reviews was either limited to only adults (Li 2019), to a specific type of intervention (Meyer 2020), or to a specific population (Scheffers 2020). This review is the first to include only randomised controlled trial data, of all age groups, types of ConHD and types of physical activity intervention. The findings of this review have potentially better external and ecological validity. Many studies have small sample sizes and all studies were published in the last 17 years. We also report 15 ongoing studies, which indicates there is continuing interest in this area. The quality of the evidence was moderate to very low for all outcomes, indicating further research is very likely to have an important impact on our confidence in the estimate of effect.

Quality of the evidence

Overall, there was a general lack of reporting details of the actual intervention. Using GRADE we assessed the quality of evidence to range from moderate to very low across all outcomes.

We downgraded the certainty of evidence for cardiorespiratory fitness to moderate using GRADE, as the confidence interval includes both appreciable harm and appreciable benefit (i.e. 95% CI spans 0). Therefore, we downgraded the certainty of evidence by one level due to imprecision.

We downgraded the certainty of evidence for health-related quality of life included in the meta-analysis to very low using GRADE. This

was due to an inconsistent directions of effect (i.e. 95% CI spans 0), considerable heterogeneity (HRQoL, I^2 = 82%), a high risk of bias across all studies and impression due to the low numbers of participants (< 400). We therefore downgraded the certainty of evidence by three levels due to inconsistency, methodological limitations (risk of bias) and imprecision.

We downgraded the certainty of evidence for physical activity to low using GRADE. This was due to an inconsistent direction of effect and considerable heterogeneity (i.e. 95% CI spans 0; I^2 = 77%); there was also a low number of participants (< 400). We therefore downgraded the certainty of evidence by two levels due to inconsistency and imprecision.

We downgraded the certainty of evidence for submaximal cardiorespiratory fitness and muscular strength to moderate using GRADE. This was due to the small numbers of events/participants (< 400). We therefore downgraded the certainty of evidence by one level due to imprecision.

The certainty of evidence for adverse events was downgraded to moderate using GRADE. This is due to over 25% of studies not reporting data on adverse events. We therefore downgraded the certainty of evidence by one level due to publication bias.

Potential biases in the review process

We have documented and justified alterations to our methods from the published protocol in the Differences between protocol and review section (Williams 2019).

We believe this is the most comprehensive systematic review to date of RCTs in people with ConHD. However, it has some limitations as the overall risk of bias for the included studies was predominately of 'some concerns'. Specifically, blinding of outcome assessors and statistical analysis plans were poorly reported. It is impossible to blind a physical activity/exercise intervention; there were, however, very few reported attempts to blind trial staff to the allocation of participants during randomisation, assessing the outcomes and statistical analysis of the outcomes.

All included studies reported a 'no formal exercise training' intervention comparator. However, there were three active types of intervention and the amount of data is unequally distributed between these types (PA promotion n = 3; exercise training n = 11; and IMT n = 1). This reduces the certainty of evidence in the less well represented types of interventions; they may have a significant potential for improving primary and secondary outcomes, but it could not be assessed with the limited data.

A limitation of the current data is that studies group patients using their individual ConHD lesion (diagnosis) or group multiple different types of ConHD together in a single cohort. Previous studies have reported large variations in fitness and health status between patients who have the same condition. Future studies should adopt a function-based assessments/interventions approach, which will enable scientists to observe which types of patients respond better to interventions, improving the evidence base for individualising physical activity interventions (Budts 2013; Budts 2020; Cedars 2020; Moons 2020).

Agreements and disagreements with other studies or reviews

Cardiorespiratory fitness

Both maximal and submaximal measures of CRF have been shown to be prognostic of future mortality and morbidity in congenital heart disease (Dimopoulos 2006; Giardini 2009; Müller 2015; Udholm 2018). In the current review maximal cardiorespiratory fitness increased by a mean difference of 1.89 $mL.kg^{-1}.min^{-1}$ (95% CI −0.22 to 3.99). In a healthy population an increase of 3.5 $mL.kg^{-1}.min^{-1}$ (one MET) reduces the chance of cardiovascular diagnosis or event by approximately 15% (Letnes 2019); and in patients with cardiovascular disease a one MET increase is associated with a 8% to 35% (median 16%) reduction in mortality (Franklin 2013). Currently, in ConHD there is no consensus regarding what the prognostic implication is of an increase of 1.89 $mL.kg^{-1}.min^{-1}$. A recent systematic review in exercise training in patients with Fontan circulations reported a similar estimate of effect to the current study of 1.73 $mL.kg^{-1}.min^{-1}$ although this was not conducted using a meta-analysis (Scheffers 2020).

Our ConHD subgroup analysis reported no difference in the response to the intervention between single ventricle, tetralogy of Fallot and other/mixed ConHD populations (P = 1.0). All subgroups responded similarly to the intervention; this may suggest that a functional-based classification (over the traditional diagnosis/lesion-based approach), may help to identify groups who respond better to interventions.

This was the first systematic review and meta-analysis that assessed submaximal fitness parameters. The oxygen consumption at the gas exchange threshold (GET) improved modestly (MD 2.05, 95% CI 0.05 to 4.05); this has also been accompanied with an increase in power output (watts) at the GET (Moalla 2006; Westhoff-Bleck 2013). Participants therefore had a greater period of time where they could operate in a predominantly aerobic state, which is an indicator of improved fitness.

Health-related quality of life

Health-related quality of life was reported in a variety of ways making pooling difficult: we pooled only three studies and there was a standardised mean difference indicating a moderate effect size (SMD 0.76, 95% CI −0.13 to 1.65), which we judged as very low certainty of evidence. However, using a modified vote-counting table (Table 1), only one study out of eight showed a significant and positive effect on health-related quality of life (Madhavi 2011). Gratz 2009 and Amedro 2015 reported that people with ConHD had a significantly poorer health-related quality of life in the domains of physical functioning/physical well-being and general health. Gratz 2009 also stated that the ConHD population dangerously overestimate their exercise capacity and this could explain the small to no increase in HRQoL within this review.

Physical activity

Re-calculating the effect estimate into the original scales (minutes of moderate to vigorous physical activity (MVPA)), we can report an approximate 10-minute increase per day in MVPA (95% CI −2.50 to 22.20). Whilst this is a small increase of MVPA, accumulatively over the course of a week more participants will be achieving the physical activity guidelines. To our knowledge this is the

first review to quantitatively analyse the effects of physical activity interventions on physical activity in people with ConHD. However, were unable to perform a meta-regression on this outcome, due to the lack of studies contributing to the analyses.

This review summarises the latest evidence on CRF, HRQoL and PA. Although there were only small improvements in CRF and PA and small to no improvements in HRQoL, there were no serious adverse events related to the interventions or adverse cardiac remodelling. These observations support the proposition that physical activity and exercise is safe and the benefits outweigh the potential risks (Koyak 2012). Although these data are promising, there is currently insufficient evidence to definitively determine the impact of physical activity interventions in ConHD. Therefore, further high-quality randomised control trials are needed utilising a longer duration of follow-up.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there are no guidelines outlined by the National Institute for Health and Care Excellence (NICE) for physical activity and exercise training in congenital heart disease. Moreover, in the UK there is no provision for cardiac rehabilitation (inclusive of physical activity interventions) for children and adolescents with congenital heart disease and clinical teams are encouraged to develop pathways to increase exercise and physical activity habits. By targeting young people it is suggested that good health and health behaviours will track into adulthood, subsequently reducing hospital admissions, reducing future morbidity and contributing to increasing survival rates.

Implications for research

This review reports small and modest improvements in maximal and submaximal cardiorespiratory fitness, but there is uncertainty in the prognostic implications of this improvement over a long-term follow-up. We require an international effort to produce a large and long-term randomised multicentre trial of physical activity and exercise interventions with long-term outcomes of mortality, morbidity, cost effectiveness, cardiorespiratory fitness and health-related quality of life. Future interventions should classify their patients (and modify the interventions) based on their functional capacity over their lesion-specific diagnoses—this should help define what types of populations respond to interventions the best (Budts 2013; Budts 2020; Cedars 2020; Moons 2020). A prognostic factors systematic review is also required to assess the current evidence of the prognostic power of cardiorespiratory fitness for patients with congenital heart disease, as it will enable physical activity and exercise interventions to be individualised and evaluated more effectively.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Avila 2016

Study characteristics

Avila 2016 *(Continued)*

Methods	**Aim of study:** to assess the impact of exercise on ventricular arrhythmias in adults with tetralogy of Fallot **Study design:** parallel-group randomised controlled trial (2:1 randomisation) **No. of centres:** 1 (Montreal Heart Institute Adult Congenital Centre) **Country:** Canada
Participants	**N randomised:** 17 (exercise 13; control 4) **Diagnosis** (% of pts): **ConHD total:** 17 (100%); intervention: 13 (100%); comparator 4 (100%) **Severity of condition** (corrected tetralogy of Fallot): **Exercise:** severe = 13 (100%); Control: severe = 4 (100%) **Age (mean ± SD)**, years: total: 35 ± 11.3; exercise: 35 ± 11.3: control: 34 ± 14.5 (converted from median and IQR). **Percentage male:** total 65%; exercise 69%; control 50% **Percentage white:** not reported **Inclusion criteria:** adults (≥ 18 years of age) with surgically repaired tetralogy of Fallot **Exclusion criteria:** non-cardiac contraindications to exercising, prior sustained ventricular arrhythmias, aborted sudden death, or New York Heart Association (NYHA) functional class III or IV symptoms. Pregnant women and patients unable to provide informed consent.
Interventions	**Exercise:** • Total duration: 12 weeks • Aerobic/resistance/mix: combined dynamic and resistance training • Frequency: 1 to 2 training sessions per week (for 12 weeks) • Duration: I hour (including 10-min warm-up and 10-min cool-down period) • Intensity: tailored to the individual in order to achieve 70% to 80% of the maximum heart rate. Exercise intensity adjusted periodically (every month) and increased gradually according to progress and tolerance. • Modality: combined dynamic and resistance training (e.g. jogging, rowing, swimming and weight-bearing exercises). • Settings: hospital • Other: supervised exercise (by physiologist and physician) **Control group/Comparison** Usual care (standard clinical care with encouragement to perform moderate-intensity aerobic activities for at least 30 minutes a minimum of 3 days per week, in conjunction with moderate intensity muscle-strengthening activities at least 2 days per week).
Outcomes	Maximal and submaximal CRF Adverse events
Notes	Adults randomised in a 2:1 ratio All patients randomised to the exercise program were required to wear a portable 2-lead Holter monitor (Quark 12, Cosmed, Rome, Italy) during each exercise session. But compliance to target heart rate not reported.

Avila 2016 *(Continued)*

	Country and settings: Canada; single centre Follow-up: 3 months

Duppen 2015

Study characteristics	
Methods	**Aim of study:** assess effects of an exercise training program on cardiopulmonary fitness and daily physical activity in patients with corrected tetralogy of Fallot (ToF) or Fontan circulation. **Study design:** RCT **No. of centres:** 5 **Country:** the Netherlands
Participants	**N randomised** total: 93; intervention: 56; comparator: 37 **Diagnosis of ConHD** total: 93; intervention: 56; comparator: 37 **Severity of condition** (corrected tetralogy of Fallot or Fontan): • **intervention:** severe = 56 (100%) • **comparator:** severe = 37 (100%) **Age (mean ± SD)** total 15 ± 3; intervention 15 ± 3; control 16 ± 3 **Percentage male** total: 66 (73%); intervention 40 (76%); control 26 (70) **N lost to follow-up** total: intervention: 1 refused; comparator: 0 **N analysed** total: 90; intervention: 53; comparator: 37 **Inclusion criteria:** correction of ToF, using the transatrial-transpulmonary approach, had to be performed before the age of 3.5 years. The Fontan circulation had to be completed before the age of 6 years. All participants had to be able, both mentally as well as physically, to adhere to a training programme. **Exclusion criteria:** excluded were patients with contraindications for exercise, mental retardation, standard contraindications for magnetic resonance imaging, or a ventricular outflow obstruction (peak Doppler gradient > 60 mm Hg).

Interventions	**Description:** standardised exercise training programme, aerobic dynamic cardiovascular training
	
	Setting: hospital
	
	Supervision: supervised
	
	Detail of exercise
	
	• **Modality:** aerobic dynamic
	• **Intensity:** resting heart rate plus 60–70% of the heart rate reserve
	• **Resistance training included?** No
	• **Dose**
	  ◦ 1 - Length of session: 12 weeks
	  ◦ 2 - Frequency/no. of sessions a week: 2 to 3 (2.5)
	  ◦ 3 - Duration of session: 60 minutes
	  ◦ Dose of exercise: 1*2*3 = 1800

Duppen 2015 *(Continued)*

Outcomes	• Maximal and submaximal CRF • Physical activity • HRQoL
Notes	**No. of centres:** 5 **Country:** the Netherlands **Comparator:** **Description:** regular medical care **Co-interventions:** none

Fritz 2020

Study characteristics	
Methods	**Aim of study:** the aims of the current study were (1) to investigate the effect of a telephone supervised, daily inspiratory muscle training for six months on exercise capacity and 2) on lung volumes in adult patients with Fontan circulation. **Study design:** RCT **No. of centres:** 1 **Country:** Germany
Participants	**N randomised** total: 42; intervention: 20; comparator: 22 **Age (mean ± SD)** total: 28.6 (24.7; 36.5); intervention 28.8 (25.3; 38.3); control 27.7 (23.7; 36.0) **Percentage male** total: 21 (50%); intervention: 11(55%); comparator: 10(45%) **Severity of condition:** • **intervention:** severe = 20 (100%); • **comparator:** severe = 22 (100%); **Inclusion criteria:** 18 years and older, Fontan physiology **Exclusion criteria:** patients who underwent cardiac catheter examination in the last 6 months or heart surgery in the last 12 months were excluded from the study. Further exclusion criteria were a change in drug administration in the last 3 months, planned intervention in the near future, neuromuscular or mental disorders, moderate to severe ventricular dysfunction as well as an unstable general state of health.
Interventions	**Setting: home/hospital/internet delivery or combination:** home **Supervision: supervised/unsupervised/not reported:** telephone semi-supervised **Detail of exercise:** • 3 sets with 10 to 30 reps daily. An adjustment from 10 cm H_2O to 90 cm H_2O was possible; inspiratory load was adjusted individually until maximum for every training session to maintain an optimal training effect. • **Modality**: inspiratory muscle training • **Resistance training included?** No

Fritz 2020 *(Continued)*

Outcomes	• CRF • Adverse events Other outcomes measured: • FVC FEV1 • Oxygen saturation
Notes	

Klausen 2016

Study characteristics	
Methods	**Aim of study:** to assess benefit and harms of adding an eHealth intervention to health education and individual counselling in adolescents with congenital heart disease **Study design:** randomised clinical trial. **No. of centres:** (nationwide?) **Country:** Denmark
Participants	**N randomised** total: 158; intervention: 81; comparator: 77 **N lost to follow-up** total: 39; intervention: 23; comparator: 16 **N analysed** total: intervention: 81; comparator: 77 **Severity of condition:** • **intervention:** severe = 81; • **comparator:** severe = 77; (Other reported – impossible to know so assumed severe; furthermore, included criteria state complex, albeit not referencing Hoffman 2002 criteria). **Inclusion criteria:** age between 13 and 16 years, previous repair for a complex CHD, and assignment to lifelong medical follow-up **Exclusion criteria:** residual defects significant for physical activity restrictions, assessed by the participants' regular cardiologist
Interventions	**Description**: 52-week internet, mobile application, and SMS-based programme delivering individually tailored text messages to encourage physical activity. Patients recorded exercise duration and type in a mobile application that translated intensity into virtual points, a system designed to provide motivation. **Setting:** home/internet delivery **Supervision:** unsupervised but self-reported adherence using an app. **Detail of exercise:** activity encouragement. **Modality :** text/technology based PA encouragement **Intensity:** text encouraged 'high intensity' but this it is probably more appropriate to state MVPA due to a loose definition of high intensity. **Resistance training included?** NR

Klausen 2016 *(Continued)*

	Impossible to assess dose
Outcomes	• CRF • Physical activity (accelerometer)
Notes	Adherence to the eHealth program was assessed by patient registration of physical activities via the eHealth application for at least two consecutive weeks during the trial. Not statistically powered (needed 216 randomised)

Madhavi 2011

Study characteristics	
Methods	**Aim of study:** to find out the influence of graded aerobic exercise on post-surgical adult acyanotic congenital heart diseases. **Study design:** RCT **Country:** India
Participants	**N randomised** total: 111; intervention: 60; comparator: 51 **N analysed** total: NR; intervention: NR; comparator: NR **Severity of condition:** • **intervention:** mild = 60; moderate = 0; severe = 0 • **comparator:** mild = 51; moderate = 0; severe = 0 **Inclusion criteria:** atrial septal defect (ASD) with pulmonary stenosis, ventricular septal defect (VSD), patent ductus arteriosus (PDA), left to right shunts. **Exclusion criteria:** cyanotic heart disease; severe pulmonary vascular disease; cardiomyopathy; severe atrioventricular valve regurgitation; exercise-induced ventricular arrhythmia; samples with moderate to severe obstructive lesions
Interventions	**Description**: individualized structured exercise protocol and were modified weekly as per the individual tolerance **Setting: home/hospital/internet delivery or combination:** NR assumed hospital based **Supervision: supervised/unsupervised/not reported –** assumed supervised **Detail of exercise:** • **Modality :** NR • **Intensity:** NR • **Resistance training included?** NR • **1 - Length of session:** 12 weeks • **2 - Frequency/no. of sessions a week:** NR • **3 - Duration of session:** NR
Outcomes	• HRQoL • CRF
Notes	

Moalla 2006

Study characteristics	
Methods	**Aim of study:** to assess exercise tolerance, and to investigate how the 6'WT could be a useful test in the follow-up of rehabilitation programme in children with CHD **Study design:** RCT **Country:** France
Participants	**N randomised** total: 18; intervention: 10; comparator: 8 • **intervention:** mild = 3; severe = 7 • **comparator:** mild = 1; severe = 7 Age (mean ± SD); intervention: 13.0 ± 1.4; comparator: 12.8 ± 1.3 **Inclusion criteria:** the left ventricle ejection fraction (LVEF) of CHD group was < 40%. All patients had undergone cardiac surgery reconstruction for complex heart disease. The CHD subjects had to be stabilized with drug treatment for at least 3 months; their medication was the same during the training period. Medical therapy included diuretics, cardiotonics, antivitamins K, and angiotensin-converting enzyme inhibitor. **Exclusion criteria:** subjects with additional diagnoses of locomotor or mental disorders or other diseases that could limit muscle performance were excluded from the study. Beta-blockers, pacemaker.
Interventions	**Description**: cycling 12 week intervention **Setting:** home **Supervision:** unsupervised – pulse monitors checked weekly for compliance **Detail of exercise:** • **Modality :** cycling • **Intensity:** Hr at the VT/GET • **Resistance training included?** No • **1 - Length of session:** 12 weeks • **2 - Frequency/no. of sessions a week:** 3 • **3 - Duration of session:** 60 mins • **Dose of exercise:** 1*2*3 = 2160
Outcomes	• CRF maximal and submaximal • Strength • NIRS
Notes	

Morrison 2013

Study characteristics	
Methods	**Aim of study:** to ascertain if motivational techniques and a structured exercise programme can increase activity in adolescents afflicted with congenital heart disease **Study design:** RCT

Morrison 2013 *(Continued)*

	Country: Northern Ireland
Participants	**N randomised** total: 143; intervention: 72; comparator: 71 **N lost to follow-up** total: 42; intervention: 10; comparator: 32 **N analysed** total: 101; intervention: 62; comparator: 39 **Severity of condition:** mild = 39; moderate = 61; severe = 43 **Age (mean ± SD)** intervention: 15.24; comparator: 15.89 **Percentage male** total: 60%; intervention: 66.7%; comparator: 53.5% **Inclusion criteria:** people with ConHD 12 to 20 years old **Exclusion criteria: p**atients were excluded if they had a syndromic diagnosis, major learning difficulty, or if exercise was contraindicated (i.e. severe left ventricular outflow tract obstruction, severe aortic stenosis).
Interventions	**Description**: 6 activity interventions days. Motivational interviewing techniques promoting exercise/activity. Given bespoke training plan to implement at home. **Setting: home/hospital combination:** home-based **Supervision:** unsupervised – patients were contacted 1 month into 6-month intervention to check problems **Detail of exercise:** programme suitable for their diagnosis no specifics reported Not possible to calculate exercise dosage.
Outcomes	• CRF • Physical activity
Notes	

Novakovic 2018

Study characteristics	
Methods	**Aim of study:** the aim of the study was to compare high-interval exercise training with moderate continuous training in terms of improving exercise capacity, vascular function, disease-specific biomarkers, cardiac autonomic function (heart rate variability (HRV)) and post-exercise heart rate recovery (HRR)) and HRQoL, in patients with repaired ToF. **Study design:** RCT with 3 parallel groups **No. of centres:** 1 **Country:** Slovenia
Participants	**N randomised** total; HIE intervention: 10; CIE intervention: 10; comparator: 10 **N lost to follow-up** total: 3; HIE intervention: 1; CIE intervention: 1; comparator: 1 **N analysed** total: 27; HIE intervention: 9; CIE intervention: 9; comparator: 9 **Severity of condition:**

Novakovic 2018 *(Continued)*

- **HIE intervention:** severe = 10
- **CIE intervention:** severe = 10
- **comparator:** severe = 10

Age (mean ± SD) total: 38.5 (8.7); HIE intervention: 36.2 (6.8); 7 CIE intervention: 40.1 (10.4); comparator: 38.4 (8.9)

Percentage male total: 37; HIE intervention: 22; CIE intervention: 44; comparator: 44

Inclusion criteria: adults with surgically repaired ToF in childhood

Exclusion criteria: exclusion criteria included known or symptomatic atherosclerotic disease, unstable cardiovascular disease or recent (< 3 months prior to inclusion) cardiovascular events, acute illness or recent (< 3 months prior to inclusion) non-cardiovascular diseases requiring hospitalisations, emergency or unplanned specialist management, unstable or poorly controlled dysrhythmias, permanent atrial fibrillation, pregnancy and intellectual development disorder.

Interventions	**High intensity interval training vs. continuous intensity exercise vs. Control group** **Setting: h ome/hospital/Internet delivery or combination:** not reported assumed hospital-based **Supervision: supervised/unsupervised/not reported:** not reported assumed supervised **Detail of exercise:** • **Modality :** cycling or speed walking • **Intensity:** 80 of HR peak (intensity increased 5% HR peak-points at 12th and 24th training session) • **Resistance training included?** No • **1 - Length of session:** 36 sessions (12 weeks) • **2 - Frequency/no. of sessions a week:** 2/3 (2.5) • **3 - Duration of session:** 42 • **Dose of exercise:** 1*2*3 = 1260
Outcomes	• CRF • HRQoL Other: • Echocardiography • Disease specific biomarkers (NT-proBNP etc.) • Heart rate variability • Blood pressure • Vascular function
Notes	

Opotowsky 2018

Study characteristics	
Methods	**Aim of study:** compare the effects of standard of care to SOC plus participant in a typical clinical CR program in ACHD. **Study design:** RCT **No. of centres:** 4

Opotowsky 2018 *(Continued)*

	Country: USA
Participants	**N randomised** total: 33; intervention: 18; comparator: 15 **Diagnosis of ConHD** total: 33; intervention: 18; comparator: 15 **Severity of condition:** • **intervention:** mild = 0; moderate to severe = 18 • **comparator:** mild = 0; moderate to severe = 5 **N analysed** total: 28; intervention: 13; comparator: 15 (5 did not receive intervention due to geographical reasons) **Age (mean ± SD)** total: 41.1 (12.1); intervention: 47.5 (9.0); comparator: 35.7 (11.9) **Percentage male** total: 50; intervention: 53.9; comparator: 46.7 **Inclusion criteria:** age > 16 years, ability to provide informed consent, ability and willingness to participate in a 12-week CR program and repeated cardiopulmonary exercise testing (CPET), impaired aerobic capacity defined as peak _VO_2 < 80% predicted on baseline exercise test, baseline resting oxygen saturation (sO_2%) > 92%, and CHD of at least moderate complexity. **Exclusion criteria:** cardiac intervention (catheterization or surgery) within the prior 6 months or planned cardiac intervention within 12 months of enrolment, formal CR within 24 months prior to enrolment, current or recent pregnancy (delivery < 90 days prior to enrolment), pregnancy planned within 12 months, active heart failure or hospitalization or other major clinical change during the 30 days prior to enrolment, and other recent or planned events expected to substantially impact exercise capacity.
Interventions	**Setting: hospital** **Supervision: supervised** **Detail of exercise** • **Modality :** walking, cycling, rowing, resistance • **Intensity:** HR at gas exchange threshold • **Resistance training included?** Yes • **1 - Length of session:** 12 weeks • **2 - Frequency/no. of sessions a week:** 2 • **3 - Duration of session:** 1 hour • **Dose of exercise:** 1*2*3 = 1440
Outcomes	• CRF • HRQoL • Activity
Notes	

Sandberg 2018

Study characteristics	
Methods	**Aim of study:** effect of a home-based exercise training programme on fitness and HRQoL **Study design:** RCT **No. of centres:** 1

Sandberg 2018 *(Continued)*

	Country: Sweden
Participants	**N randomised** total: 26; intervention: 16; comparator: 10 **N analysed** total: 23; intervention: 13; comparator: 10 **Severity of condition:** • **intervention:** severe = 13 • **comparator:** severe = 10 **Age (median (IQR))** total: 30.1 (22.9 to 36.6); intervention: 31.3 (26.9 to 36.6); comparator: 26.3 (22.9 to 35.6) **Percentage male** total: 52; intervention: 62; comparator: 40 **Inclusion criteria:** complex ConHD e.g. Fontan, TGA ToF > 18yrs old **Exclusion criteria:** the exclusion criteria were present exercise training > times/week aimed at increasing or sustaining exercise capacity, arrhythmia or other adverse events (e.g. important symptoms, drop in blood pressure) at CPET, clinically relevant arrhythmia, intellectual disability or mental illness affecting independent decision making, extracardiac disease affecting physical activity, peak VO_2 > 30ml/kg/min at run-in CPET, or no internet access.
Interventions	**Description**: home-based cycling intervention **Setting:** home **Supervision:** semi-supervised **Detail of exercise:** • **Modality :** cycling • **Intensity:** training heart rate (THR) was calculated according to the Karvonen method and to achieve BORG 15 to 16. • **Resistance training included?** No • **1 - Length of session:** 12 weeks • **2 - Frequency/no. of sessions a week:** 3 • **3 - Duration of session:** 31 mins (avg interval of 3.5 min and including work and rest unloaded intervals) • **Dose of exercise:** 1*2*3 = 1116 (individualised)
Outcomes	• Cardiorespiratory fitness • Health-related quality of life
Notes	Compliance 79% (median 83%, 47% to 100%). Range of session completed 17 to 36. Comparator: usual care

Therrien 2003

Study characteristics	
Methods	**Aim of study:** assess impact of exercise training on aerobic capacity in repaired tetralogy of Fallot (ToF) patients. **Study design:** RCT **No. of centres:** 1

Therrien 2003 *(Continued)*

	Country: Canada
Participants	**Diagnosis of ConHD** total: 18; intervention: 9 ; comparator: 9 **Severity of condition:** repaired ToF • **intervention:** severe = 9 • **comparator:** severe = 8 **Age (mean ± SD)** intervention: 35 (9.5); comparator: 43.3 (7.3) **Percentage male %:** total @ randomisation: 55; intervention: 55; comparator: 55 **N randomised** total: 18; intervention: 9; comparator: 9 **N lost to follow-up** total: 1; intervention: 0; comparator: 1 **N analysed** total: 17; intervention: 9; comparator: 8 **Inclusion criteria:** adult patients with repaired ToF **Exclusion criteria:** recent surgery, syncope or malignant arrhythmia
Interventions	**Description**: 12-week structured exercise programme, patients in the exercise group were evaluated by an exercise physiologist (MW) and given an individualized aerobic training programme. Exercise sessions were held once a week at the Toronto General Hospital Cardiac Rehabilitation Department under the direct supervision of the exercise physiologist. **Setting:** combination of home (2* weekly walking) and hospital based **Supervision:** both supervised and unsupervised **Detail of exercise:** • **Modality :** cycling and walking • **Intensity:** 60% to 85% of baseline peak VO_2 • **Resistance training included?** No • **1 - Length of session:** 12 weeks • **2 - Frequency/no. of sessions a week:** 3 (1 hospital and 2 home) • **3 - Duration of session:** 50 mins • **Dose of exercise:** 1*2*3 =1800 **Comparator:** **Description:** usual care; regular daily exercise **Co-interventions:**
Outcomes	**CRF** **Adverse events**
Notes	No deaths or morbid events occurred in either group, nor were any symptoms reported during the study period. Occasional premature ventricular and atrial beats were recorded in 4 patients during exercise testing (at baseline study in 2 patients and follow-up study in 2 patients). None of these episodes required any intervention or discontinuation of testing. Furthermore, no significant ST segment shift was observed in any patient during the exercise or recovery period of either the baseline or follow-up cardiopulmonary testing. Of note: patients were not on telemetry during hospital training sessions.

van der Mheen 2019

Study characteristics	
Methods	**Aim:** does participating in the CHIP-Family intervention improve the psychosocial well-being of children with CHD and their parents, family functioning, and parents' disease-specific knowledge? **Study Design:** single-blinded parallel randomised controlled trial **No. of centres:** 1 **Country:** the Netherlands
Participants	**N randomised total:** 93; intervention: 49; comparator: 44 **Diagnosis of ConHD:** total 90; intervention: 47; comparator: 43 **Severity of condition:** limited to 1: atrial septal defect, patent ductus arteriosus, pulmonary valve stenosis, total anomalous pulmonary venous connection, ventricular septal defect. Mild, moderate, severe: anomalous left coronary artery from the pulmonary artery, atrioventricular septal defect, coarctation of the aorta, complex biventricular (e.g. truncus arteriosus, aortic arch defects with ventricular septal defect), univentricular heart defects – Fontan circulation, Ebstein's anomaly (sub)valvular aortic stenosis, tetralogy of Fallot (ToF) including main aorta to pulmonary connecting artery, transposition of the great arteries • **intervention:** limited to none: 14; mild to severe = 33 • **comparator:** limited to none: 12; mild to moderate to severe = 31 **Age (mean ± SD)** intervention: 5.43 ± 1.30; comparator: 5.21 ± 1.26 **Percentage male** total: 50%; intervention: 53.2%; comparator: 46.5% **N lost to follow-up** total: parents of three children did not complete any questionnaires after randomisation. **N analysed** total: 90; **intervention**: 45 (Baseline assessment data: n = 47 families; Follow-up assessment data: n = 45 families; Excluded from analyses: n = 2 (no complete questionnaires)); **comparator:** 40 (Baseline assessment data: n = 40 families; Follow-up assessment data: n = 40 families; Excluded from analyses: n = 1 (no complete questionnaires)). **Inclusion criteria:** underwent at least one invasive medical procedure for CHD (i.e. cardiac catheterisation or open heart surgery or both); and (2) were attending kindergarten or first or second year of primary school at the time of first assessment and were eligible for participation. Can speak Dutch. **Exclusion criteria:** children with known intellectual impairment (intelligence quotient ≤ 70) were excluded, as a sufficient level of intelligence was required to participate in the child intervention programme. Moreover, prematurely born children (i.e. gestational age at birth < 37 weeks) with no CHD other than a patent ductus arteriosus were excluded, as families of prematurely born children experience different psychosocial problems
Interventions	**Description:** the CHIP-Family is an adaptation and extension of the CHIP-School intervention. 36 CHIP-Family consisted of a 6-hour group workshop (3 to 5 families per workshop) for parents and children and an individual 1-hour follow-up session per parent couple. The 1-day parent workshop consisted of problem prevention therapy, psychoeducation, general parenting skills, skills specific to parenting a child with CHD (provided by 2 senior clinical psychologists for 4 hours), and medical issues (provided by a paediatric cardiologist supported by a senior clinical psychologist for 1 hour). Approximately 4 weeks after the workshop, each parent couple received an individual follow-up session provided by a senior psychologist who was present at the parent workshop and a psychologist who was present at the child workshop. The CHIP-Family module also comprised a specific child module. The child module consisted of a workshop that was held concurrently with the parent workshop. The child workshop consisted of cognitive behavioural exercises based on the evidence-based 'Fun FRIENDS' protocol and focused on strengthening self-esteem, regulating emotions, relaxation, problem-solving skills, and positive thinking (provided by 2 junior psychologists who were supervised by 2 senior clinical psychol-

van der Mheen 2019 *(Continued)*

	ogists for 4 hours). The children also did sport exercises based on a standardised exercise programme specifically developed for children with CHD and their siblings (provided by a physiotherapist and assistant for 1 hour). Each child was allowed to bring a 4- to 10-year-old sibling or friend to normalise participation and to stimulate practice at home. **Setting:** hospital **Supervision:** supervised **Detail of exercise:** as above • **Modality:** range of dynamic sports exercises • **Intensity:** moderate • **Resistance training included?** No • **Dose:** 1 day • **1 - Length of session:** 1 to 4 hours • **2 - Frequency/no. of sessions a week:** 3 • **3 - Duration of session:** 1 × 240 mins and 2 × 60 mins • **Dose of session:** 1*2*3 = 720 (calculated as average 2 hours × 3 sessions × 120 min)
Outcomes	• HRQoL • Days off school
Notes	Due to logistical reasons in the starting phase of the project, the first 4 families who consented to participate were allocated to the CHIP-Family group without randomisation.

van Dissel 2019

Study characteristics	
Methods	**Aim of the study:** physical activity promotion and exercise training interventions for people with congenital heart disease **Study design:** RCT **No. of centres:** 1 **Country:** the Netherlands
Participants	**N randomised** total: 40; intervention: 20; comparator: 20 **Diagnosis of ConHD** total: 40; intervention: 20; comparator: 20 **Severity of condition:** eligible patients were adults with CHD and New York Heart Association (NYHA) class II or III symptoms: tetralogy of Fallot; transposition of the great arteries; Fontan circulation; pulmonary atresia; other • **intervention:** moderate = 2; severe = 18 • **comparator:** moderate = 1; severe = 19 **Age (mean ± SD)** total; intervention: 39.9 ± 8.6; comparator: 40.0 ± 15.4 **Percentage male** total: 55%; intervention: 9 (45%); comparator: 13 (65%) **N lost to follow-up** total: 6; intervention: 3; comparator: 3 **N analysed** total: 34; intervention: 17; comparator: 17

van Dissel 2019 *(Continued)*

	Inclusion criteria: eligible patients were adults with CHD and New York Heart Association (NYHA) class II or III symptoms, included in the CONgenital CORvitia database, the Dutch nationwide registry and DNA-bank for adults with CHD **Exclusion criteria:** exclusion criteria were NYHA class I or IV, presence of exercise-induced arrhythmia, major comorbidities or limitations that could interfere with exercise training, recent (≤ 6 months) major cardiovascular events or procedures, cyanosis at rest, a resting blood pressure N200 mm Hg or diastolic blood pressure N110 mm Hg, pregnancy (wish) or mental or physical incapability to participate in a home-based exercise training programme.
Interventions	**Description:** home-based exercise training programme, with a target training regimen of minimum 3 sessions of 45 min per week for the duration of 6 consecutive months. **Setting:** home **Supervision:** unsupervised - compliance and adherence monitored. **Detail of exercise:** • **Modality:** self-selected • **Intensity:** 80% max HR achieved in CPET • **Resistance training included?** No • **1 - Length of session:** 26 weeks • **2 - Frequency/no. of sessions a week:** 3 • **3 - Duration of session:** 45mins • **Dose of exercise: 1*2*3 =** 3510 **Control group/Comparator:** patients randomised to the control group did not receive any formal advice on exercise training, and were neither encouraged, nor discouraged to participate in sports. All patients were asked to continue habitual daily activities, even if these included regular physical exercise.
Outcomes	• Maximal and submaximal CRF • HRQoL
Notes	Patients in the exercise training group reportedly exercised for a median of 2.5 h per week. 13 of the 17 patients in the exercise training group exercised at or above the target training level of 2¼ h per week. The remaining 4 patients exercised at least 1 h per week. The main reason patients could not fully adhere to the training regimen was lack of time related to work or family commitments. The types of sports performed by patients in the exercise group are high-dynamic sports (76%) and a small subset of those patients (23%) practised sports both at the highest static and dynamic level, such as rowing, cycling and ice-skating.

Westhoff-Bleck 2013

Study characteristics	
Methods	**Aim of study:** investigated the effect of 6-month aerobic exercise training on cardiorespiratory and subaortic RV function in a prospective randomised trial. **Study design:** RCT **No. of centres:** 1 **Country:** Germany
Participants	**N randomised** total: 48; intervention: 24; comparator: 24 **Diagnosis of ConHD: total** 48; intervention: 24; comparator: 24

Westhoff-Bleck 2013 *(Continued)*

Severity of condition: adult patients with previous atrial redirection surgery for D-TGA were eligible for the study. At our institution all patients underwent the Mustard procedure.

- **intervention:** mild = 0; moderate = 0; severe = 24
- **comparator:** mild = 0; moderate = 0; severe = 24

Age (mean ± SD) total: 29.3 ± 3.4 ; intervention: 29.9 ± 3.1 ; comparator: 28.6 ± 3.1

Percentage male total: 31; intervention: 13; comparator: 18

N lost to follow-up total: 8; intervention: 5; comparator: 3

N analysed total: 40; intervention: 19; comparator: 21

Inclusion criteria: adult patients with previous atrial redirection surgery for D-TGA were eligible for the study (mustard procedure). Additional inclusion criteria were: stable heart failure according to classification of New York Heart association (NYHA) class I/II, unchanged medication angiotensin-converting enzyme inhibitors, beta-blockers) for the last 6 months, no physical training programme at inclusion, and the physical and mental ability to follow a controlled training programme.

Exclusion criteria: exclusion criteria were: clinical diagnosis of NYHA functional class III–IV, known pulmonary vascular disease, significant baffle-obstruction, recent onset or change of heart failure medication within the last 6 months, pregnancy, pacemaker or defibrillator implantation, history of ventricular arrhythmias, renal/liver insufficiency, claustrophobia, and mental retardation.

Interventions

Description: patients randomised to training participated in a structured exercise programme with a goal of improved exercise capacity over a period of 24 weeks. As home equipment, patients received a bicycle ergometer and heart rate monitors (Polar USA Inc. New York, New York). Patients in the training group were advised to document heart rate and number and duration of training units.

Setting: home

Supervision: unsupervised weekly phone calls to monitor adherence.

Detail of exercise:

- **Modality :** cycling
- **Intensity:** heart rate corresponding to 50% of peak oxygen uptake
- **Resistance training included?** No
- **1** - **Length of session**:
- **2 - Frequency/no. of sessions a week:**
- **3 - Duration of session:**
- **Dose of exercise:** 1*2*3 **=** 2550 (see calculation below)
  - No Weeks * Frequency per * Duration of session
  - 3*3*10 = 90
  - 3*3*15 = 135
  - 3*5*15 = 225
  - 3*5*20 = 300
  - 12*5*30 = 1800
  - 1800+300+225+135+90 = **2550**

Comparator:

Description: usual care

Co-interventions:

Outcomes

Other outcomes measured:

- MRI

Westhoff-Bleck 2013 *(Continued)*

- Bloods

Notes	During the study, 2 patients in the training and 1 patient in the control group experienced an episode of supra-ventricular tachycardia, which was terminated by cardioversion. None of these episodes were timely related to physical training or to cardiac decompensation.

Winter 2012

Study characteristics	
Methods	**Aim of study:** the primary aim of our study was to determine whether exercise training improves maximal exercise capacity in adult patient with a systemic RV. Additionally, we aimed to determine whether exercise training decreases serum N-terminal pro hormone brain natriuretic peptide (NT-proBNP) levels and improves quality of life in these patients **Study design:** RCT **No. of centres:** 4 **Country:** the Netherlands (3 sites) Italy (1 site)
Participants	**N randomised** total: 54; intervention: 28; comparator: 26 **Diagnosis of ConHD** total: 54; intervention: 28; comparator: 26 **Severity of condition:** adults with a systemic RV due to a congenitally or surgically corrected TGA. • **intervention:** mild = moderate = severe = 28 • **comparator:** mild = moderate = severe = 26 **Age (mean ± SD)** total: 32 ± 11; intervention: 31 ± 10; comparator: 34 ± 11 **Percentage male** total: 23; intervention: 9; comparator: 14 **N lost to follow-up** total: 8; intervention: 4; comparator: 4 **N analysed** total: 46; intervention: 24; comparator: 22 **N randomised** total: 54; intervention: 28; comparator: 26 **N lost to follow-up** total: 8; intervention: 6; comparator: 8 **N analysed** total: 40; intervention: 22; comparator: 18 **Inclusion criteria:** eligible participants were adults with a systemic RV due to a congenitally or surgically corrected TGA **Exclusion criteria:** exclusion criteria were mental or physical incapability to participate in a home-based exercise training programme, the presence of exercise-induced arrhythmia, symptomatic myocardial ischaemia, a resting systolic blood pressure .200 mm Hg and/or diastolic blood pressure.110 mm Hg, New York Heart Association (NYHA) class III or IV, pregnancy during the training period, and non-cardiac co-morbidity that could affect exercise performance or that could aggravate by exercise.
Interventions	**Description**: the training protocol was home-based, and consisted of 3 sessions of steps aerobics per week for the duration of 10 consecutive weeks. **Setting:** home **Supervision:** unsupervised but compliance followed up through email and calls **Detail of exercise:**

Winter 2012 *(Continued)*	• **Modality :** step aerobics • **Intensity:** 75% to 90% of max heart rate (target HR increased with intervention length). • **Resistance training included?** No • **1 - Length of session:** 10 weeks • **2 - Frequency/no. of sessions a week:** 3 • **3 - Duration of session:** 42 mins • **Dose of exercise:** 1*2*3 = 1260 **Comparator:** **Description:** usual care **Co-interventions:** none
Outcomes	**Other outcomes measured:** • BP • BNP
Notes	Exercise tests could be performed without complications in all patients. One baseline exercise test was aborted due to nausea of the patient, but was repeated successfully 6 h later. As stated above, 1 patient developed ventricular bigeminy in the recovery phase, and was excluded from participation in the study. During the training protocol, 1 patient sustained calf injury during exercise, and had to discontinue the protocol for 2 weeks. No other complaints or complications were reported.

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

Study	Reason for exclusion
Ali Faisal 2016	Wrong intervention
Altamirano Diaz 2017	Wrong study design
Amedro 2019	Wrong study design
Babu 2013	Wrong study design
Babu 2017	Wrong study design
Becker Gruenig 2012	Wrong study design
Bhasipol 2018	Wrong study design
Bhasipol 2018a	Wrong study design
BoaSorteSilva 2017	Wrong patient population
Callaghan 2018	Duplicate
Camargo 2007	Wrong comparator
Chen 2017	Wrong intervention
Coats 1992	Wrong patient population

Study	Reason for exclusion
Cordina 2013	Wrong study design
Curnier 2012	Wrong study design
DRKS00011363	Registry Report
Du 2015	Wrong study design
Du 2017	Wrong study design
Dua 2010	Wrong study design
Fredriksen 2000	Wrong study design
Fredriksen 2000a	Wrong study design
Gierat Haponiuk 2014	Wrong study design
Goldbeck 2011	Wrong study design
Gomes Neto 2016	Wrong study design
Gotink 2017	Wrong intervention
Hedlund 2018	Wrong study design
Hooglugt 2018a	Wrong study design
IlarrazaLomel 2008	Wrong study design
IoannisLaoutaris 2015	Wrong patient population
IRCT20180417039341N1	Registry report
ISRCTN74393113	Registry report
Joshi 2019	Wrong study design
Kobashigawa 1999	Data loss by researcher
Lalonde 2014	Wrong study design
Lam 2014	Wrong patient population
Longmuir 1985	Wrong study design
Longmuir 2013	Wrong study design
Lozada 2017	Wrong comparator
Marra 2015	Wrong study design
McKillop 2018	Wrong comparator
NCT00930800	Registry report

Study	Reason for exclusion
NCT01463800	Study cancelled
NCT01671566	Registry report
NCT01822769	Registry report
NCT02632253	Study cancelled
NCT02643810	Registry report
NCT02980393	Wrong study design
NCT03297918	Registry report
Nehyba 2009	Wrong patient population
NTR2527	Wrong patient population
NTR3041	Wrong patient population
Rhodes 2006	Wrong study design
Rowland 2016	Wrong study design
Ruttenberg 1983	Wrong study design
Stefani 2014	Wrong study design
Sutherland 2018	Wrong comparator
Tan 1996	Wrong intervention
Tikkanen 2016	Duplicate
Zhou 2017a	Duplicate
Zhou 2017b	Paediatric population

Characteristics of studies awaiting classification *[ordered by study ID]*

Ali 2018

Methods	
Participants	Fontan patients
Interventions	Controlled respiratory training
Outcomes	CPET
Notes	

Callaghan 2017

Methods	
Participants	ConHD
Interventions	Physical activity
Outcomes	Potentially HRQoL
Notes	

Morrison 2015

Methods	
Participants	ConHD
Interventions	PA promotion
Outcomes	Physical activity
Notes	

Neidenbach 2017

Methods	
Participants	Fontan patients
Interventions	Inspiratory muscle training
Outcomes	Oxygen saturations
Notes	

Nilsson 2019

Methods	RCT
Participants	Patients following aortic valve replacement
Interventions	Exercise training
Outcomes	Cardiopulmonary exercise testing
Notes	

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

Ganzoni 2019

Study name	Impact of a structural phonation training on respiratory muscle function in patients with structural heart disease - HeartChoir (Study NCT03297918)
Methods	RCT
Participants	Inclusion criteria: • Informed consent as documented by signature (Appendix Informed Consent Form) • Age ≥ 18 years • Known cardiomyopathy from acquired heart disease (ischemic or dilated) or patients with complex CHD (cyanotic congenital heart disease, Fontan palliation, subaortic right ventricle or repaired tetralogy of Fallot)
Interventions	**Active comparator:** intervention group - patients will be asked to participate in a structured singing and respiratory training for 12 weeks vs. no activity control.

Outcomes	**Primary outcome measures**:
	• Change of MIP (% predicted)
	  ◦ Change of maximal inspiratory pressure after the intervention
	Secondary outcome measures:
	• Change of MEP
	  ◦ Change of maximal expiratory pressure after the intervention
	• Change of MVO2
	  ◦ Change of maximal VO_2 after the intervention
	• Change of QoL
	  ◦ Change of Quality of life

Starting date	December 2017
Contact information	Principal Investigator: Daniel Tobler
Notes	Unpublished. Author team contacted and they were unable to share data.

ISRCTN74643496

Study name	Improving the effectiveness of psychological interventions for depression and anxiety in the cardiac rehabilitation pathway: a single blind randomised controlled trial with four month and twelve month follow up comparing GroupMCT plus usual CR (intervention) with usual CR (control).
Methods	RCT. Metacognitive therapy vs. usual care control.
Participants	Inclusion: • Competent level of English language skills (able to read, understand and complete questionnaires in English). • Acute coronary syndrome used for any condition brought on by sudden, reduced blood flow to the heart • Following revascularisation is the restoration of perfusion to a body part or organ that has suffered ischaemia • Stable heart failure

ISRCTN74643496 *(Continued)*

	• Stable angina is chest pain or discomfort that most often occurs with activity or stress • Following implantation of cardioverter defibrillators/cardiac resynchronisation devices • Heart valve repair/replacement • Heart transplantation and ventricular assist devices • Adult congenital heart disease identified in adulthood • A score of = 8 on either the depression or anxiety subscale of the HADS.
Interventions	Experimental: metacognitive therapy plus CR Group psychological treatment focused on reducing worry and rumination and modifying beliefs about thinking in addition to treatment as usual (standard cardiac rehabilitation). Metacognitive therapy (MCT) helps clients to identify episodes of worry and rumination in response to negative thoughts and bring these responses under control. This process is facilitated by exercises that enhance the flexibility of attention control, challenge unhelpful beliefs about thinking and enable new relationships with thoughts 2. Active Comparator: Usual group-based cardiac rehabilitation (treatment as usual) involving stress management, exercise, education.
Outcomes	**Primary** • Change in Hospital Anxiety and Depression Scale (HADS) (time frame: baseline pre treatment, four-month post baseline, 12 months' follow-up) **Secondary** • Metacognitions Questionnaire • Cognitive Attentional Syndrome • Impact of Event Scale-Revised • Health-related quality of life • Economic Patient Questionnaire (EPQ)
Starting date	1 June 2015
Contact information	Jane Garnett, University of Manchester 5th Floor (Research) St. Mary's Hospital Oxford Road M13 9WL Manchester United Kingdom
Notes	Control group are exercise training. Mixed population of Non congenital heart as well as congenital heart patients. Would not be eligible for inclusion into this review unless the intervention group underwent no exercise/physical activity .

NCT01397110

Study name	Influence of respiratory and exercise therapy on oxygen uptake, quality of life in patients with severe associated pulmonary arterial hypertension (apah) as part of a congenital heart defect with/without Eisenmenger's syndrome
Methods	Randomized parallel assignment
Participants	Inclusion Criteria: • signed consent form • men and women> 18 years <80 years • APAH with congenital heart defects with/without Eisenmenger syndrome (WHO functional class II-IV), invasively diagnosed by right heart and left heart catheterization: mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, with targeted PAH medication for at least two months stable before study inclusion (exception: compensated WHO class II without vasodilating drug therapy)
Interventions	Active comparator: respiratory and exercise therapy

NCT01397110 *(Continued)*

	Randomized, prospective, controlled, blinded study of three-week inpatient rehabilitation and subsequent continuing of the training at home for 12 weeks. The control group received conventional rehabilitation without a specific training program. After 15 weeks training is also offered to patients in the control group. No Intervention: Control group without exercise training Patients of the control group continue their sedentary lifestyle without given advice for exercise training. The time before start of rehabilitation (three months) serves as control group. Afterwards patients take part in the training program as well.
Outcomes	**Primary outcomes** • Changes in the maximum 6-minute walk distance (6MGT) (time frame: up to 15 weeks) • Changes in quality of life (time frame: up to 15 weeks) **Secondary outcomes** • Changes in maximum oxygen uptake • Changes in exercise capacity: 6-minute walk distance, recumbent bike (watts), respiratory economy (EQO_2, $EQCO_2$) • Improved condition(NYHA class, Borg scale) • Changes in magnetic resonance tomography and echocardiographic parameters of right and left ventricle: size and pump function • Change of laboratory parameters, which are markers of right heart failure as NTproBNP, interleukins • Changes in haemodynamics (time frame: up to 15 weeks)
Starting date	January 2012
Contact information	Ekkehard Gruenig, MD+49 6221 396 8053 ekkehard.gruenig@med.uni-heidelberg.de
Notes	

NCT02240147

Study name	Start-to-sport - feasibility and efficacy of individualized, telemonitored, home-based exercise for adolescents and adults with congenital heart disease
Methods	Randomized parallel assignment
Participants	Inclusion Criteria: • adolescents and adults with congenital heart disease • 16 to 65 years Exclusion Criteria: • congenital rhythm or conduction disorders • isolated congenital coronary artery anomalies • pregnancy • being listed for heart transplantation • inability to perform standard physical activities due to mental/physical disability.

NCT02240147 *(Continued)*

Interventions	During a 30 minute face-to-face motivational interview with an exercise specialist, the patient will be advised and coached about his exercise prescription, on how to implement it in his own daily life and on how to prevent relapse. Furthermore, the patients will receive instructions on how to monitor their exercise intensity and on recognising adverse signals. During the following 12 weeks, patients will be asked to exercise 4.5 hours per week within the prescribed exercise intensity range according to the guidelines
Outcomes	peak oxygen uptake (time frame: baseline, post-intervention, after 1 year) physical activity (time frame: baseline, post-intervention and after 1 year)
Starting date	1 January 2015
Contact information	Principal investigator: Roselien Buys, PhD KU Leuven Principal investigator: Werner Budts, PhD KU Leuven
Notes	Unpublished. Author team contacted and they were unable to share data.

NCT02283255

Study name	Cardiovascular, Pulmonary and Skeletal Muscle Evaluation in Late Postoperative Period of the Fontan Surgery
Methods	A long-term randomized clinical study that will include 60 patients between 12 and 30 years, submitted to total cavopulmonary connection for at least 5 years post operative at the Heart Institute, University of São Paulo Medical School. The patients will be divided into four groups: 1) Exercise training with aerobic exercise + lower and upper limb strength exercise (GTF-I); 2) Respiratory training with respiratory muscle exercise (GTF-II); 3) Exercise training with aerobic exercise + lower and upper limb strength exercise + Respiratory training with respiratory muscle exercise (GTF-III); and A non-exercise group as control group (GNTF-IV). The patients will be revaluated after the 4-month period of intervention.
Participants	**Inclusion criteria:** • Both gender, aged between 12 and 30 years • Patients undergoing the Fontan operation with time postoperatively ≥ 5 years • Clinically stable patients, no arrhythmia in the last electrocardiogram or clinical assessment • Consent by the cardiologist • Patients who voluntarily signed the consent form. **Exclusion criteria:** • Patients with hypoplastic left heart syndrome • Changes that reduce musculoskeletal walking skills • Neurological sequelae, patients with associated genetic syndrome, disturbance cognitive or psychiatric • Patients with a history of ventricular arrhythmias, cardio respiratory arrest, users of anti-arrhythmic drugs and/or underwent implantation of pacemaker • Atrial arrhythmia requiring treatment in the last 6 months • Patients with heart failure not controlled by medications and lung hypertension • Patients with protein-losing enteropathy • Severe hypoxemia (oxygen saturation <80% at rest) • Symptomatic patients with a diagnosis of diaphragmatic paresis or paralysis postoperative patients, with or without plication • Patients with moderate to severe asthma

NCT02283255 *(Continued)*

	• Patients who live outside the area of Sao Paulo
Interventions	Aerobic training: Aerobic training and muscle strength exercise for upper and lower limbs, 3 times a week for 4 months. Respiratory training: muscle training using POWERbreathe device, 7 times a week, 3 series of 30 repetitions per day, for 4 months. Aerobic and respiratory training: aerobic training and muscle strength exercise for upper and lower limbs, 3 times a week for 4 months and respiratory muscle training using POWERbreathe device, 7 times a week, 3 series of 30 repetitions per day, for 4 months. No physical activity: control group (usual care)
Outcomes	• Improvement exercise tolerance and physical capacity (time frame: baseline and 4 months) • Improvement in the functional capacity post exercise training programme (time frame: baseline and 4 months) • Improvement in pulmonary function post physical exercise programme (time frame: baseline and 4 months) • Change in autonomic function post exercise training programme (time frame: baseline and 4 months) • Improvement in peripheral blood flow post exercise training programme (time frame: baseline and 4 months) • Change in the plasma epinephrine level post exercise training programme (time frame: baseline and 4 months) • Change in muscle metabolism post exercise training programme (time frame: baseline and 4 months)
Starting date	2014
Contact information	Contact: Aida LR Turquetto, Researcher +55 11 26615399 ext +5511981140723 aidaturquetto@me.com Contact: Marcelo B Jatene, Researcher +551126615399 ext +551126615399 marcelo.jatene@incor.usp.br
Notes	

NCT02658266

Study name	Effect of resistance training in adults with complex congenital heart disease
Methods	RCT Behavioural: home-based resistance training
Participants	Inclusion criteria: • Complex congenital heart disease (e.g. tetralogy of Fallot, transposition of the great arteries, pulmonary atresia, patients palliated with Fontan procedure or total cavo-pulmonary connection). • Clinically stable without significant change the last 3 months. • Adult (> 18 years of age). • Informed consent. Exclusion criteria: • Cognitive impairment affecting the ability of independent decision making.

NCT02658266 *(Continued)*

	• Present strategy of regularly executing resistance training > 2times per week in purpose to increase muscle strength. • Other comorbidity affecting physical activity. • Other circumstance making participation unsuitable.
Interventions	Home-based resistance training 12 weeks home based resistance training 3 times per week, 10 to 12 reps, 2 sets
Outcomes	• Change in muscle endurance (number of repetitions) (time frame: change from baseline muscle endurance at 12 weeks' follow-up) • Change in total body skeletal muscle mass (kg) (time frame: change from baseline total body skeletal muscle mass at 12 weeks' follow-up) • Change in appendicular skeletal muscle mass (kg) (time frame: change from baseline appendicular skeletal muscle mass at 12 weeks' follow-up) • Change in body fat percentage (time frame: change from baseline body fat percentage at 12 weeks' follow-up) • Change in bone mineral density (g/cm^2) (time frame: change from baseline bone mineral density at 12 weeks' follow-up) • Muscle metabolism (time frame: change from baseline muscle metabolism at 12 weeks' follow-up) • Compliance to study protocol (time frame: at completion of study protocol 12 weeks) • Adverse events (time frame: once a week from the date of onset of the home based exercise regimen until the follow-up at 12 weeks)
Starting date	2017
Contact information	Contact: Bengt Johansson, MD, PhD +46907852782 bengt.johansson@medicin.umu.se Contact: Camilla Sandberg, RPT, PhD +46907858441 camilla.sandberg@medicin.umu.se
Notes	

NCT03335475

Study name	Congenital Heart Disease Physical Activity Lifestyle Study (CHD-PALS)
Methods	Randomized. Study includes 2 possible conditions to which participants are randomized: (1) Fitbit only and (2) Fitbit + coaching sessions.
Participants	Inclusion Criteria: • Between the ages of 15 and 18 (if 18, must be in high school and/or still living at home) • Are diagnosed with moderate or complex structural congenital heart disease • Live within 120 miles of Nationwide Children's Hospital • Able to complete an exercise stress test on a treadmill
Interventions	Intervention: In the Fitbit + Coaching Sessions arm, participant will receive their exercise prescription, as devised from their baseline exercise stress test results, a Fitbit, and will have 8 sessions with a coach (interventionist) over the course of 20 weeks. They will undergo a 9 week (interim) and a 22 week assessment (follow-up). Control: In the Fitbit Only arm, participants will receive their exercise prescription, as devised from their baseline exercise stress test results, and a Fitbit. They will undergo a 9 week (interim) and a 22 week assessment (follow-up).
Outcomes	**Primary outcome measures:**

NCT03335475 *(Continued)*

	• Number of minutes spent in moderate to vigorous physical activity as measured by an accelerometer ◦ Moderate to vigorous physical activity (time frame: from baseline to follow-up (approximately 22 weeks)) **Secondary outcome measures:** • Number of minutes spent being sedentary as measured by an accelerometer. • Maximal oxygen utilization during physical activity as measured by V02max during an exercise stress test. • Sedentary behaviour (time frame: from baseline to follow-up (approximately 22 weeks)) • Exercise tolerance (time frame: from baseline to follow-up (approximately 22 weeks))
Starting date	7 November 2017
Contact information	Principal investigator: Jamie L Jackson, PhD Nationwide Children's Hospital
Notes	

NCT03435354

Study name	Impacting child physical and mental health outcomes in congenital heart disease: a randomized, controlled trial of enhanced physical activity support in clinical care
Methods	Cluster-randomized trial, with randomization by within each site by week (i.e. site-week)
Participants	**Inclusion criteria:** • All patients 5 to 17 years with CHD diagnoses classified as moderate or severe in complexity by the American College of Cardiology/American Heart Association joint guidelines. **Exclusion criteria:** • Cardiac intervention (catheterization or surgery) in preceding 6 months. Syndrome/diagnosis affecting physical activity (e.g., developmental disability) or the ability to complete the assessment questionnaires.
Interventions	Clinician counselling about physical activity using standardised tools to promote daily physical activity.

Outcomes	**Primary outcome:**
	
	• Pedometer step counts per day
	  ◦ Change in daily physical activity (time frame: baseline then first week of each month for 6 months)
	
	Secondary outcomes:
	
	• Children's Self-Perceived Adequacy and Predilection for Physical Activity Scale
	• Paediatric Quality of Life Inventory (PedsQL),
	• PLAY Tools Run2 and screening question
	  ◦ Change in physical activity adequacy and predilection (time frame: baseline, 6 months)(time frame: baseline, 6 months)
	  ◦ Change in quality of life (time frame: baseline, 6 months)
	  ◦ Change in physical literacy (time frame: baseline, 6 months)

Starting date	March 5, 2018

NCT03435354 *(Continued)*

Contact information	Principal Investigator: Patricia Longmuir, PhD Scientist
Notes	

NCT03479957

Study name	Remotely monitored and coached exercise based cardiac rehabilitation in northern Sweden
Methods	RCT
Participants	**Inclusion criteria:** • Scheduled appointment with physiotherapist for follow-up after cardiac event: myocardial infarction (MI) • Per cutaneous coronary intervention (PCI) due to MI or angina pectoris • Open heart surgery due to coronary artery disease or valvar disease • Living in the catchment area of Heart centre, University Hospital of Umeå.
Interventions	Remotely monitored and coached exercise training in real time using the REMOTE-CR system. The patients randomized to remotely monitored exercise can either work out with self-selected activities e.g. Nordic-walking, cycling, skiing or participate in supervised exercise session via video link. The patients randomized to be controls will receive individualized information and instructions regarding current exercise recommendations but will not be monitored or coached during their exercise sessions (usual care).
Outcomes	**Primary outcome:** The aerobic exercise capacity (W) will be evaluated using a standardised submaximal exercise test on cycle ergometer • Change in submaximal aerobic exercise capacity (time frame: baseline and 12 weeks) **Secondary outcome:** • Number of repetitions achieved during test of Unilateral isotonic shoulder flexion and Unilateral isotonic heel-lift • Isometric grip strength • International Physical Activity Questionnaire • The Swedish version of the Tampa scale for Kinesiophobia Heart (TSK-SV Heart) The scale comprises 17 items assessing subjective rating of kinesiophobia. The total score varies between 17-68 and a score > 37 defines a high level of kinesofobia.
Starting date	3 September 2019
Contact information	Camilla Sandberg, PhD+46907858441 camilla.sandberg@umu.se
Notes	Most likely will not meet participant inclusion criteria

NCT03690518

Study name	Impact of cardiovascular rehabilitation on the quality of life of adolescents and young adults with congenital heart disease: a randomized controlled multicentre trial

NCT03690518 *(Continued)*

Methods	
Participants	Inclusion Criteria: • Patient aged 13 to 25 years included • With a congenital heart diseases (CHD) as defined in the international CHD classification. • Recent (< 3 months) cardio-pulmonary exercise test (CPET)with maximum oxygen uptake (VO2max) <80% of theoretical values and/or first ventilatory anaerovic threshold (VAT) <55% of VO2max. • Consent of the adult patient or the parents or legal guardians of the minor patient. • Beneficiary of the social security scheme.
Interventions	Cardiac rehabilitation: rehabilitation will have a regular follow-up with intervention (rehabilitation program)

Outcomes	**Primary outcomes:**
	• Evolution of the PedsQL 4.0 self-reported scores from month 0 to month 12
	• Quality of life score (PedsQL, 24 items), range score from 0 to 100, higher score indicating better quality of life. (time frame: follow-up of patients over 12 months)
	Secondary outcomes:
	• Disease knowledge questionnaire (Leuven questionnaire, 34 items, total range score from 0 to 100, a higher score indicating better knowledge)
	• Number of consultation in cardiology, number of hospitalization in cardiology, number of cardio-vascular events
	• Score of physical activity (Ricci and Gagnon questionnaire, 9 items, total range score from 6 to 45, higher score indicating a higher level of physical activity)
	• NYHA functional class= New York Association functional class from the World Health Organization
	• Variation of cardiac output during exercise tests measured by impedance measurement (Physioflow)
	  ◦ Peak oxygen uptake (VO_2max, ml/kg/min) (time frame: Month 0 and Month 12)
	  ◦ Ventilatory anaerobic threshold (VAT, ml/kg/min) (time frame: Month 0 and Month 12)
	  ◦ Knowledge of the disease (time frame: Month 0 and Month 12)
	  ◦ Cardiac events (time frame: Month 0 and Month 12)
	  ◦ Physical activity scoring (time frame: Month 0 and Month 12)
	  ◦ Functional NYHA class (time frame: Month 0 and Month 12)
	  ◦ Cardiac output during exercise (time frame: Month 0 and Month 12)

Starting date	27 July 2018
Contact information	Contact: Sophie GUILLAUMONT0467336632 s-guillaumont@chu-montpellier.fr Contact: Pascal AMEDRO0467336632 p-amedro@chu-montpellier.fr
Notes	Amedro P, Gavotto A, Legendre A, Lavastre K, Bredy C, De La Villeon G, Matecki S, Vandenberghe D, Ladeveze M, Bajolle F, Bosser G, Bouvaist H, Brosset P, Cohen L, Cohen S, Corone S, Dauphin C, Dulac Y, Hascoet S, Iriart X, Ladouceur M, Mace L, Neagu OA, Ovaert C, Picot MC, Poirette L, Sidney F, Soullier C, Thambo JB, Combes N, Bonnet D, Guillaumont S. Impact of a centre and home-based cardiac rehabilitation program on the quality of life of teenagers and young adults with congenital heart disease: The QUALI-REHAB study rationale, design and methods. Int J Cardiol. 2019 May 15;283:112-118. doi: 10.1016/j.ijcard.2018.12.050. Epub 2018 Dec 20.

NCT03999320

Study name	Sophrology and congenital heart disease (SOPHRO CARE)
Methods	RCT
Participants	**Inclusion criteria:** • Patient aged 13 to 25 years old • With a congenital heart disease (CHD) as defined in the international anatomic and clinical classification (ACC) - CHD classification • Informed consent from adult patients or parents/legal guardians for minor patients
Interventions	Sophrology sessions

Outcomes	**Primary outcome:**
	VO_2max Variation
	1. Maximum oxygen uptake (VO2 max) (time frame: variation between baseline (M0) and at 12 months (M12))
	Secondary outcomes:
	• Quality of life score variation (PedsQL, 24 items), range score from 0 to 100, higher score indicating better quality of life.
	• Score of physical activity (Ricci and Gagnon questionnaire, 9 items, total range score from 6 to 45, higher score indicating a higher level of physical activity)
	  ◦ Quality of life score (time frame: evolution of the PedsQL 4.0 self-reported scores from month 0 to month 12)
	  ◦ Physical activity score (time frame: variation between Baseline (M0) and at 12 months (M12))

Starting date	19 July 2019
Contact information	Pascal AMEDRO, MD0467336632 p-amedro@chu-montpellier.fr
Notes	

NCT04135859 (YACHD-PALS)

Study name	Young Adult Congenital Heart Disease Physical Activity Lifestyle Study (YACHD-PALS)
Methods	This study will adapt a physical activity lifestyle intervention to emerging adult congenital heart disease (CHD) survivors with the primary goal of increasing physical activity levels. The study will be split into 2 phases. In Phase 1, participants will be asked to complete questionnaires, wear an accelerometer around the waist for 7 days, and undergo an exercise stress test. The accelerometer and exercise stress test will be used to determine whether participants are eligible to be randomized for the intervention study. In Phase 2, participants will be randomized to one of two conditions: 1) receiving a physical activity tracker (a Fitbit) or 2) receiving a Fitbit AND engaging in videoconferencing sessions with a physical activity coach. During Phase 2, participants will also be asked to complete 3 assessments (weeks 9 and 22, and a 6-month follow-up). The week 9 assessment will consist of completing questionnaires and wearing an accelerometer for 7 days. Week 22 will be similar to week 9 with the addition of a final exercise stress test. The 6-month follow-up will mirror the week 9 assessment.
Participants	**Inclusion Criteria:** • Between the ages of 18 and 25 (if 18, must no longer be in high school and no longer living at home)

NCT04135859 (YACHD-PALS) *(Continued)*

- Diagnosed with moderate or complex structural congenital heart disease
- Live within 120 miles of Nationwide Children's Hospital
- Able to complete an exercise stress test on a treadmill

Exclusion Criteria:

- Do no speak or write proficiently in English
- Have cognitive impairments that would interfere with the completion of study procedures
- Are diagnosed with a genetic syndrome (e.g. Downs, Marfans)
- Have been engaged in a formal exercise program within the past 6 months
- Underwent open-heart surgery or have had a transcatheter valve replacement in the last 3 months
- Are otherwise prohibited by their cardiologist to engage in at least moderate levels of physical activity
- Are unable to complete a treadmill-based exercise stress test
- Are currently pregnant
- Have contraindications for exercise based on an exercise stress test (e.g., exercise-induced arrhythmias or evidence of cardiac ischaemia)
- > 150 min/weekday of moderate-to-vigorous physical activity per the accelerometer
- Do not have access or a device for videoconferencing with the coach

Interventions	In the Fitbit Only arm, participants will receive their exercise prescription, as devised from their baseline exercise stress test results, and a Fitbit. They will undergo a 9 week (interim) and a 22 week assessment (follow-up). Intervention: Behavioral: Physical Activity Monitoring In the Fitbit + Coaching Sessions arm, participants will receive their exercise prescription, as devised from their baseline exercise stress test results, a Fitbit, and will have 8 sessions with a coach (interventionist) over the course of 20 weeks. They will undergo a 9 week (interim) and a 22 week assessment (follow-up). Interventions: • Behavioral: physical activity lifestyle intervention • Behavioral: physical activity monitoring • Active Comparator: Fitbit only • Experimental: Fibit + coaching sessions
Outcomes	Number of minutes spent in moderate to vigorous physical activity as measured by an accelerometer.
Starting date	2019
Contact information	Jamie Jackson, Nationwide Children's Hospital
Notes	

NCT04208893

Study name	Exercise training strategies for children with repaired tetralogy of Fallot
Methods	RCT
Participants	Paediatrics with repaired tetralogy of Fallot

NCT04208893 *(Continued)*

Interventions	The aerobic training intervention will include 60 minutes/session, 3 times/week for 12 weeks at an intensity of 65% to 85% of participants' heart rate reserve (HRR), as determined by the CPET. Patients will be asked to wear a fitness-tracking device to monitor their heart rate response and in order to comply with the prescribed training intensity. All training sessions will start with a 10-minute warm up, 40-minute aerobic interventions, and ends with a 10-minutes cool down. One study doctor will be on call during in-hospital training. Onsite supervised aerobic interventions will include play-based activities, whereas home-based aerobic activities will include stationary bikes and exercise activities that would target desired heart rate ranges. Home exercise equipment will be provided.
Outcomes	Primary • Consent rate (time frame: 1 year) • Enrolment rate (time frame: 1 year) • Adherence rate (time frame: 1 year) • Completion rate (time frame: 1 year) • Attrition rate (time frame: 1 year) • Acceptability questionnaire Secondary • The effect of aerobic training only versus combined aerobic and strength training on exercise capacity using cardiopulmonary exercise test in children with repaired tetralogy of Fallot (ToF) (peak exercise ml/kg/min) (time frame: from baseline to 3 months post intervention) • The effect of aerobic training only versus combined aerobic and strength training on pulmonary measures using pulmonary function test in children with repaired tetralogy of Fallot (ToF) (Change in time in force vital capacity (FVC) (litres)) (time frame: from baseline to 3 months post intervention). • Many others planned outcomes see registry
Starting date	2019
Contact information	Brian McCrindle, MDThe Hospital for Sick Children, Toronto, Canada
Notes	

NCT04264650

Study name	Long-term effectiveness of an mHealth intervention for improving the disease knowledge and physical activity of youth With congenital heart disease: a randomized controlled trial
Methods	• No Intervention: control group • Experimental: one active intervention group • Experimental: the other active intervention group
Participants	**Inclusion criteria**: • being diagnosed with CHD by a paediatric cardiologist and qualifying as having simple or moderate CHD complexity according to the 2008 American College of Cardiology/American Heart Association guidelines; • having a regular pulse; • being 15 to 24 years of age; • being conversant in Mandarin and Taiwanese; • possessing a smartphone with Internet connection; • agreeing to wear an exercise-monitoring wristband to record physiological data;

NCT04264650 *(Continued)*

	• agreeing to engage in exercises designed to test cardiopulmonary endurance; • agreeing to participate in the study and sign an informed consent form for a relevant interview. For participants under 20 years of age, guardian approval by signing a written consent form was required. **Exclusion criteria:** • having cognitive impairment to the extent of being noncommunicative; • having CHD complicated with other congenital abnormalities; • having undergone a cardiac catheter-related intervention or surgery within the past 6 months; • being pregnant
Interventions	The COOL program is a 12-month randomized controlled trial that compared two active intervention groups to a standard-care control group (n = 47). Participants with simple and moderate CHD aged 15-24 years were recruited from paediatric or adult CHD outpatient departments. Participants in one active intervention group (n = 49) were provided with COOL Passport, a mobile healthcare application. Those in the other group (n = 47) were provided with access to the Health Promotion Cloud system and use of game-based interactive platforms along with COOL Passport. Outcomes were the Leuven Knowledge Questionnaire for CHD and the International Physical Activity Questionnaire-Taiwan Show-Card Version.
Outcomes	Cardiac disease knowledge and physical activity
Starting date	2020
Contact information	Chi-Wen Chen, PhD National Yang Ming University
Notes	

UMIN000021661

Study name	Evaluation test about safety and efficacy of the respiratory muscle training therapy by abdominal respiratory weight exercises in chronic cardiovascular disease patients
Methods	Parallel randomized
Participants	**Inclusion criteria:** • Patients with chronic cardiovascular disease in outpatient or in hospital of Kurume University hospital • Patients with informed consent • Patients with chronic cardiovascular disease shown in the following • Ischaemic heart disease • Valvular heart disease • Hypertensive heart disease • Cardiomyopathy • Arrhythmia • Adult congenital heart disease • Pulmonary hypertension • Exclusion criteria: Patients with obstructive respiratory disease • Patients with the device planted • Patients with difficult musculoskeletal disease • Patients with symptoms at rest • Patients with pulmonary hypertension of the WHO classification 3 more

UMIN000021661 *(Continued)*	• Patients with hypoxaemia in spite of the use of breathing ancillary equipment • Patients with uncontrolled high blood pressure • Patients with poor control of arrhythmia, such as adverse effects on haemodynamics • Patients that may be in or pregnancy • Others, patients who are judged that this study is unsuitable by physician
Interventions	The respiratory muscle training therapy is performed in addition to performing conventional cardiac rehabilitation. The respiratory muscle training therapy is abdominal muscle training method. Intervention period is 6 months
Outcomes	• Cardiac function • Respiratory function • Exercise capacity • Relief of symptoms • Autonomic function • Body composition • Physical function • Carbohydrate metabolism • Lipid metabolism
Starting date	4 April 2016
Contact information	Miki Biwa biwa_miki@med.kurume-u.ac.jp
Notes	

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Maximal cardiorespiratory fitness

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Exercise training						
Therrien 2003	✗	✓	✓	~	~	✗
Moalla 2006	~	✓	✓	~	~	~
Madhavi 2011	✗	~	✗	✗	~	✗
Winter 2012	~	✓	~	~	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Westhoff-Bleck 2013	~	✓	~	~	~	~
Duppen 2015	✓	✓	✓	~	~	~
Avila 2016	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Opotowsky 2018	✓	✓	✓	~	~	~
Sandberg 2018	✓	✓	✓	✓	~	~
van Dissel 2019	~	✓	~	~	~	~
Subgroup 1.1.2 Physical activity promotion						
Morrison 2013	~	✓	~	~	~	~
Klausen 2016	✓	✓	~	✓	✓	~
Subgroup 1.1.3 Inspiratory muscle training						
Fritz 2020	~	✓	✓	~	~	~

Risk of bias for analysis 1.2 Health-related quality of life

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Madhavi 2011	✗	~	✗	✗	~	✗
Opotowsky 2018	✓	✓	✓	✗	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Sandberg 2018	✓	✓	✓	✗	~	✗

Risk of bias for analysis 1.3 Physical activity (device-worn)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Duppen 2015	✓	✓	✓	~	~	~
Klausen 2016	✓	✓	~	✓	✓	~
Morrison 2013	~	✓	~	~	~	~
Opotowsky 2018	✓	✓	✓	~	~	~

Risk of bias for analysis 1.4 Submaximal cardiorespiratory fitness (gas exchange threshold)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Moalla 2006	~	✓	✓	~	~	~
Westhoff-Bleck 2013	~	✓	~	~	~	~
Duppen 2015	✓	✓	✓	~	~	~
Avila 2016	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~

Risk of bias for analysis 1.5 Muscular strength

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Moalla 2006	~	✓	✓	✓	~	~

Risk of bias for analysis 1.6 Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 Population with a single ventricle						
Winter 2012	~	✓	~	~	~	~
Westhoff-Bleck 2013	~	✓	~	~	~	~
Duppen 2015	✓	✓	✓	~	~	~
Fritz 2020	~	✓	✓	~	~	~
Subgroup 1.6.2 Population with repaired Tetralogy of Fallot						
Therrien 2003	✗	✓	✓	~	~	✗
Duppen 2015	✓	✓	✓	~	~	~
Avila 2016	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Novakovic 2018	✓	✓	✓	~	~	~
Subgroup 1.6.3 Other or mixed ConHD populations						
Moalla 2006	~	✓	✓	~	~	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Madhavi 2011	✗	~	✗	✗	~	✗
Morrison 2013	~	✓	~	~	~	~
Klausen 2016	✓	✓	~	✓	✓	~
Opotowsky 2018	✓	✓	✓	~	~	~
Sandberg 2018	✓	✓	✓	✓	~	~
van Dissel 2019	~	✓	~	~	~	~

DATA AND ANALYSES

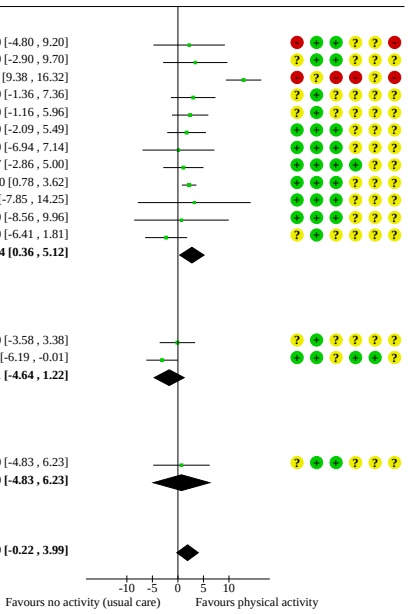
Comparison 1. Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Maximal cardiorespiratory fitness	14	732	Mean Difference (IV, Random, 95% CI)	1.89 [-0.22, 3.99]
1.1.1 Exercise training	11	435	Mean Difference (IV, Random, 95% CI)	2.74 [0.36, 5.12]
1.1.2 Physical activity promotion	2	259	Mean Difference (IV, Random, 95% CI)	-1.71 [-4.64, 1.22]
1.1.3 Inspiratory muscle training	1	38	Mean Difference (IV, Random, 95% CI)	0.70 [-4.83, 6.23]
1.2 Health-related quality of life	3	163	Std. Mean Difference (IV, Random, 95% CI)	0.76 [-0.13, 1.65]
1.3 Physical activity (device-worn)	4	328	Std. Mean Difference (IV, Random, 95% CI)	0.38 [-0.15, 0.92]
1.4 Submaximal cardiorespiratory fitness (gas exchange threshold)	5	179	Mean Difference (IV, Random, 95% CI)	2.05 [0.05, 4.05]
1.5 Muscular strength	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)	14	732	Mean Difference (IV, Random, 95% CI)	1.90 [-0.14, 3.95]
1.6.1 Population with a single ventricle	4	154	Mean Difference (IV, Random, 95% CI)	2.05 [-0.25, 4.35]
1.6.2 Population with repaired Tetralogy of Fallot	4	104	Mean Difference (IV, Random, 95% CI)	1.97 [-1.11, 5.05]
1.6.3 Other or mixed ConHD populations	7	474	Mean Difference (IV, Random, 95% CI)	1.98 [-1.67, 5.62]

Analysis 1.1. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 1: Maximal cardiorespiratory fitness

Study or Subgroup	Physical activity Mean [mL/kg/min]	SD [mL/kg/min]	Total	No activity (usual care) Mean [mL/kg/min]	SD [mL/kg/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/kg/min]	Risk of Bias A B C D E F
1.1.1 Exercise training									
Therrien 2003	24.3	8.2	9	22.1	6.5	8	4.8%	2.20 [-4.80 , 9.20]	
Moalla 2006	33	6.2	10	29.6	7.2	8	5.4%	3.40 [-2.90 , 9.70]	
Madhavi 2011	43.84	10.33	51	30.99	7.96	61	8.1%	12.85 [9.38 , 16.32]	
Winter 2012	29	7	24	26	8	22	7.2%	3.00 [-1.36 , 7.36]	
Westhoff-Bleck 2013	25.9	6.1	19	23.5	5.3	21	8.0%	2.40 [-1.16 , 5.96]	
Duppen 2015	35.9	7.4	43	34.2	8.6	30	7.8%	1.70 [-2.09 , 5.49]	
Avila 2016	28.6	7.1	13	28.5	6.01	4	4.8%	0.10 [-6.94 , 7.14]	
Sandberg 2018	25.1	6.16	13	24.03	3.33	10	7.6%	1.07 [-2.86 , 5.00]	
Opotowsky 2018	1	1.5	13	-1.2	2.3	15	9.9%	2.20 [0.78 , 3.62]	
Novakovic 2018 (1)	26.5	12.5	9	23.3	8.5	5	2.7%	3.20 [-7.85 , 14.25]	
Novakovic 2018 (2)	24	6.2	9	23.3	8.5	4	3.5%	0.70 [-8.56 , 9.96]	
van Dissel 2019	25.4	6.6	17	27.7	5.6	17	7.4%	-2.30 [-6.41 , 1.81]	
Subtotal (95% CI)			**230**			**205**	**77.3%**	**2.74 [0.36 , 5.12]**	
Heterogeneity: Tau² = 10.92; Chi² = 40.79, df = 11 (P < 0.0001); I² = 73%									
Test for overall effect: Z = 2.26 (P = 0.02)									
1.1.2 Physical activity promotion									
Morrison 2013	37.4	8.8	62	37.5	8.6	39	8.1%	-0.10 [-3.58 , 3.38]	
Klausen 2016	43.2	9.7	81	46.3	10.1	77	8.5%	-3.10 [-6.19 , -0.01]	
Subtotal (95% CI)			**143**			**116**	**16.6%**	**-1.71 [-4.64 , 1.22]**	
Heterogeneity: Tau² = 1.68; Chi² = 1.60, df = 1 (P = 0.21); I² = 37%									
Test for overall effect: Z = 1.14 (P = 0.25)									
1.1.3 Inspiratory muscle training									
Fritz 2020	24	8.3	18	23.3	9.1	20	6.1%	0.70 [-4.83 , 6.23]	
Subtotal (95% CI)			**18**			**20**	**6.1%**	**0.70 [-4.83 , 6.23]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.25 (P = 0.80)									
Total (95% CI)			**391**			**341**	**100.0%**	**1.89 [-0.22 , 3.99]**	
Heterogeneity: Tau² = 11.06; Chi² = 55.03, df = 14 (P < 0.00001); I² = 75%									
Test for overall effect: Z = 1.76 (P = 0.08)									
Test for subgroup differences: Chi² = 5.34, df = 2 (P = 0.07), I² = 62.5%									



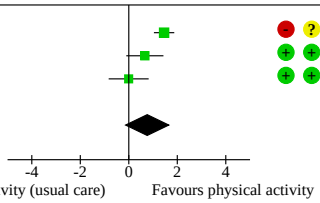
Footnotes
(1) interval training arm
(2) continuous training arm

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Cardiorespiratory fitness
(C) Bias due to missing outcome data: Cardiorespiratory fitness
(D) Bias in measurement of the outcome: Cardiorespiratory fitness
(E) Bias in selection of the reported result: Cardiorespiratory fitness
(F) Overall bias: Cardiorespiratory fitness

Analysis 1.2. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 2: Health-related quality of life

Study or Subgroup	Physical activity Mean	SD	Total	No activity (usual care) Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Madhavi 2011 (1)	72.28	8.071	51	57.93	11.019	61	37.9%	1.46 [1.04 , 1.88]		- ? - - ? -
Opotowsky 2018 (2)	-20.1	11.4	13	-27.7	10.9	15	31.6%	0.66 [-0.10 , 1.43]		+ + + - ? -
Sandberg 2018 (3)	76.2	15.2	13	76.3	20.7	10	30.5%	-0.01 [-0.83 , 0.82]		+ + + - ? -
Total (95% CI)			**77**			**86**	**100.0%**	**0.76 [-0.13 , 1.65]**		

Heterogeneity: Tau² = 0.50; Chi² = 10.87, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 1.67 (P = 0.09)
Test for subgroup differences: Not applicable



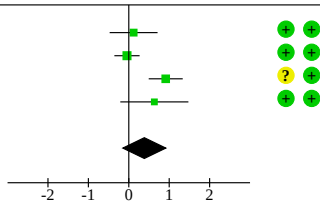
Footnotes
(1) SF-36 (total score)
(2) MLHFQ
(3) EQ5D VAS

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Health-related quality of life
(C) Bias due to missing outcome data: Health-related quality of life
(D) Bias in measurement of the outcome: Health-related quality of life
(E) Bias in selection of the reported result: Health-related quality of life
(F) Overall bias: Health-related quality of life

Analysis 1.3. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 3: Physical activity (device-worn)

Study or Subgroup	Physical activity Mean	SD	Total	No activity (usual care) Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F
Duppen 2015 (1)	12.7	8.1	28	11.8	6.2	18	23.7%	0.12 [-0.47 , 0.71]		+ + + ? ? ?
Klausen 2016	40.3	21.8	81	41.3	22.9	77	30.2%	-0.04 [-0.36 , 0.27]		+ + ? + + ?
Morrison 2013	57.2	32.2	62	29.2	27.3	39	27.8%	0.91 [0.49 , 1.33]		? + ? ? ? ?
Opotowsky 2018	103	56	11	75	25	12	18.3%	0.63 [-0.21 , 1.47]		+ + + ? ? ?
Total (95% CI)			**182**			**146**	**100.0%**	**0.38 [-0.15 , 0.92]**		

Heterogeneity: Tau² = 0.22; Chi² = 13.81, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



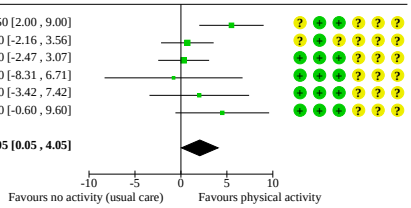
Footnotes
(1) Measure of activity: time spent in moderate-to-very-vigorous activity as a percentage. All other studies report minutes of MVPA per day.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Physical activity (device-worn)
(C) Bias due to missing outcome data: Physical activity (device-worn)
(D) Bias in measurement of the outcome: Physical activity (device-worn)
(E) Bias in selection of the reported result: Physical activity (device-worn)
(F) Overall bias: Physical activity (device-worn)

Analysis 1.4. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 4: Submaximal cardiorespiratory fitness (gas exchange threshold)

Study or Subgroup	Physical activity Mean [mL/kg/min]	SD [mL/kg/min]	Total	No activity (usual care) Mean [mL/kg/min]	SD [mL/kg/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/kg/min]	Risk of Bias A B C D E F
Moalla 2006	23.6	3.3	10	18.1	4.1	8	20.0%	5.50 [2.00 , 9.00]	? + + ? ? ?
Westhoff-Bleck 2013	16.2	5.3	19	15.5	3.7	21	25.1%	0.70 [-2.16 , 3.56]	? + ? ? ? ?
Duppen 2015	20.9	5.9	46	20.6	6.2	31	26.0%	0.30 [-2.47 , 3.07]	+ + + ? ? ?
Avila 2016	21	6.7	13	21.8	6.7	4	6.2%	-0.80 [-8.31 , 6.71]	+ + + ? ? ?
Novakovic 2018 (1)	20.1	5.4	9	18.1	4.2	4	10.8%	2.00 [-3.42 , 7.42]	+ + + ? ? ?
Novakovic 2018 (2)	22.6	5.4	9	18.1	4.2	5	11.9%	4.50 [-0.60 , 9.60]	+ + + ? ? ?
Total (95% CI)			**106**			**73**	**100.0%**	**2.05 [0.05 , 4.05]**	

Heterogeneity: Tau² = 2.01; Chi² = 7.52, df = 5 (P = 0.18); I² = 33%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable

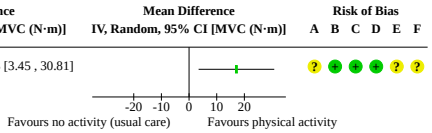


Footnotes
(1) continuous training arm.
(2) interval training arm

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Submaximal cardiorespiratory fitness (gas exchange threshold)
(C) Bias due to missing outcome data: Submaximal cardiorespiratory fitness (gas exchange threshold)
(D) Bias in measurement of the outcome: Submaximal cardiorespiratory fitness (gas exchange threshold)
(E) Bias in selection of the reported result: Submaximal cardiorespiratory fitness (gas exchange threshold)
(F) Overall bias: Submaximal cardiorespiratory fitness (gas exchange threshold)

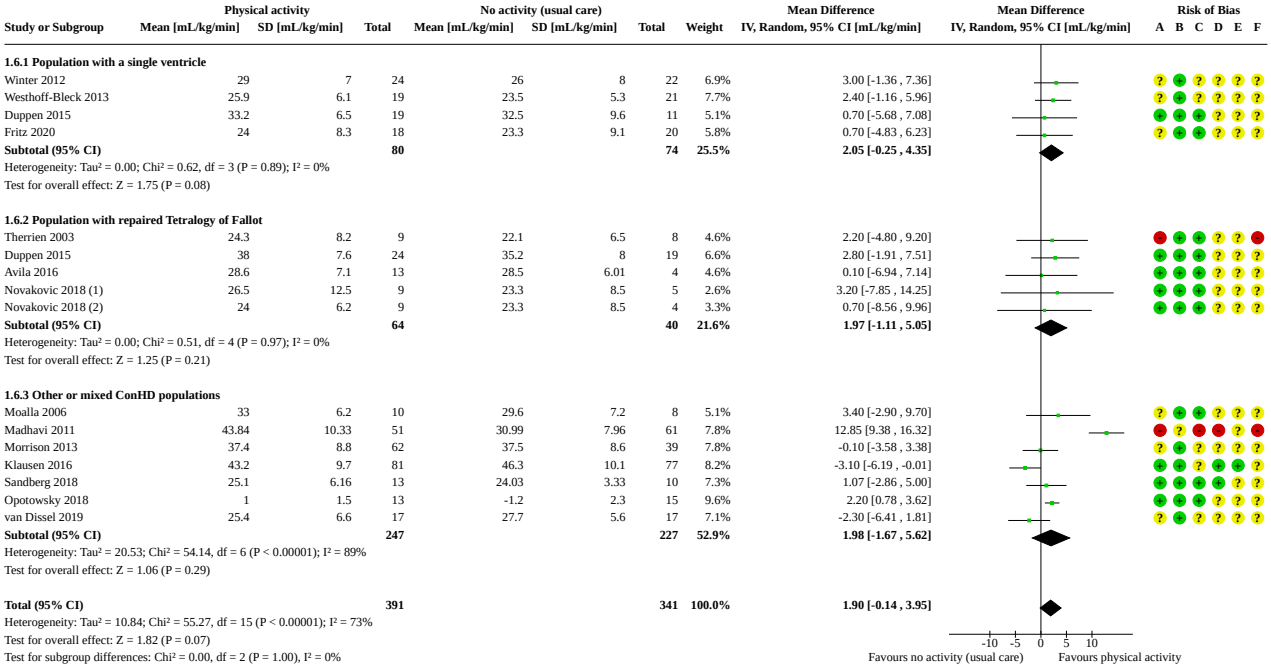
Analysis 1.5. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 5: Muscular strength

Study or Subgroup	Physical activity Mean [MVC (N·m)]	SD [MVC (N·m)]	Total	No activity (usual care) Mean [MVC (N·m)]	SD [MVC (N·m)]	Total	Mean Difference IV, Random, 95% CI [MVC (N·m)]	Risk of Bias A B C D E F
Moalla 2006	120.2	19.4	10	103.07	9.4	8	17.13 [3.45 , 30.81]	? + + + ? ?



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Muscular strength
(C) Bias due to missing outcome data: Muscular strength
(D) Bias in measurement of the outcome: Muscular strength
(E) Bias in selection of the reported result: Muscular strength
(F) Overall bias: Muscular strength

Analysis 1.6. Comparison 1: Physical activity promotion, exercise training and inspiratory muscle training interventions versus no activity (usual care) in people with congenital heart disease, Outcome 6: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)



Study or Subgroup	Physical activity Mean [mL/kg/min]	SD [mL/kg/min]	Total	No activity (usual care) Mean [mL/kg/min]	SD [mL/kg/min]	Total	Weight	Mean Difference IV, Random, 95% CI [mL/kg/min]	Risk of Bias A B C D E F
1.6.1 Population with a single ventricle									
Winter 2012	29	7	24	26	8	22	6.9%	3.00 [-1.36 , 7.36]	
Westhoff-Bleck 2013	25.9	6.1	19	23.5	5.3	21	7.7%	2.40 [-1.16 , 5.96]	
Duppen 2015	33.2	6.5	19	32.5	9.6	11	5.1%	0.70 [-5.68 , 7.08]	
Fritz 2020	24	8.3	18	23.3	9.1	20	5.8%	0.70 [-4.83 , 6.23]	
Subtotal (95% CI)			**80**			**74**	**25.5%**	**2.05 [-0.25 , 4.35]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 3 (P = 0.89); I² = 0%									
Test for overall effect: Z = 1.75 (P = 0.08)									
1.6.2 Population with repaired Tetralogy of Fallot									
Therrien 2003	24.3	8.2	9	22.1	6.5	8	4.6%	2.20 [-4.80 , 9.20]	
Duppen 2015	38	7.6	24	35.2	8	19	6.6%	2.80 [-1.91 , 7.51]	
Avila 2016	28.6	7.1	13	28.5	6.01	4	4.6%	0.10 [-6.94 , 7.14]	
Novakovic 2018 (1)	26.5	12.5	9	23.3	8.5	5	2.6%	3.20 [-7.85 , 14.25]	
Novakovic 2018 (2)	24	6.2	9	23.3	8.5	4	3.3%	0.70 [-8.56 , 9.96]	
Subtotal (95% CI)			**64**			**40**	**21.6%**	**1.97 [-1.11 , 5.05]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 4 (P = 0.97); I² = 0%									
Test for overall effect: Z = 1.25 (P = 0.21)									
1.6.3 Other or mixed ConHD populations									
Moalla 2006	33	6.2	10	29.6	7.2	8	5.1%	3.40 [-2.90 , 9.70]	
Madhavi 2011	43.84	10.33	51	30.99	7.96	61	7.8%	12.85 [9.38 , 16.32]	
Morrison 2013	37.4	8.8	62	37.5	8.6	39	7.8%	-0.10 [-3.58 , 3.38]	
Klausen 2016	43.2	9.7	81	46.3	10.1	77	8.2%	-3.10 [-6.19 , -0.01]	
Sandberg 2018	25.1	6.16	13	24.03	3.33	10	7.3%	1.07 [-2.86 , 5.00]	
Opotowsky 2018	1	1.5	13	-1.2	2.3	15	9.6%	2.20 [0.78 , 3.62]	
van Dissel 2019	25.4	6.6	17	27.7	5.6	17	7.1%	-2.30 [-6.41 , 1.81]	
Subtotal (95% CI)			**247**			**227**	**52.9%**	**1.98 [-1.67 , 5.62]**	
Heterogeneity: Tau² = 20.53; Chi² = 54.14, df = 6 (P < 0.00001); I² = 89%									
Test for overall effect: Z = 1.06 (P = 0.29)									
Total (95% CI)			**391**			**341**	**100.0%**	**1.90 [-0.14 , 3.95]**	
Heterogeneity: Tau² = 10.84; Chi² = 55.27, df = 15 (P < 0.00001); I² = 73%									
Test for overall effect: Z = 1.82 (P = 0.07)									
Test for subgroup differences: Chi² = 0.00, df = 2 (P = 1.00), I² = 0%									

Footnotes

(1) interval training arm
(2) continuous training arm

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)
(C) Bias due to missing outcome data: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)
(D) Bias in measurement of the outcome: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)
(E) Bias in selection of the reported result: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)
(F) Overall bias: Maximal cardiorespiratory fitness (type of ConHD subgroup analysis)

ADDITIONAL TABLES

Table 1. Health-related quality of life

Author	Sample size	Type of intervention	Questionnaire	Domain	Intervention vs. control at follow up Mean (Standard deviation) & between group P value	Direction of effect	Overall risk of bias
Duppen 2015	73	Exercise training	SF-36 (8 domains) +	Physical functioning	94.6 (10.9) 95.0 (8.5) P = 0.71	Exercise = control	High
			SF-36 (8 domains) +	Bodily pain	96.6 (8.1) 93.2 (17.3) P = 0.96	Exercise = control	High
			SF-36 (8 domains) +	General health	68.3 (27.9) 67.5 (19.1) P = 0.94	Exercise = control	High
			SF-36 (8 domains) +	Vitality	71.7 (18.0) 70 (17.0) P = 0.56	Exercise = control	High
			SF-36 (8 domains) +	Role limitations due to physical limitations	100 (0.0) 91.7 (21.2) P = 0.16	Exercise = control	High
			SF-36 (8 domains) +	Social functioning	95.8 (10.0) 100.0 (0.0)P = 0.09	Exercise = control	High
			SF-36 (8 domains) +	Role limitations due to emotional problems	100 (0.0) 100 (0.0) P = 0.72	Exercise = control	High
			SF-36 (8 domains) +	Mental health	85.0 (16.8) 81.3 (10.2) P = 0.65	Exercise = control	High
			TACQOL +	Symptoms	95.6 (7.90) 97.8 (3.7) P = 0.16	Exercise = control	High
			TACQOL +	Impact of cardiac surveillance	85 (6.30) 85.7 (4.80) P = 0.07	Exercise = control	High
			TACQOL +	Worries	95.7 (8.70) 88.6 (270) P = 0.67	Exercise = control	High
			TACQOL-CF +	Pain and physical symptoms	26.3 (6.2) 24 (7.15) P = 0.21	Exercise = control	High

Table 1. Health-related quality of life *(Continued)*

			TACQOL-CF +	Motor functioning	30.1 (1.9) 29.5 (4.37) P = 0.51	Exercise = control	High
			TACQOL-CF +	Cognitive functioning	28.6 (6.2) 29.7 (6.9) P = 0.05	Exercise = control	High
			TACQOL-CF +	Social functioning	31.5 (1.2) 32 (0) P = 0.45	Exercise = control	High
			TACQOL-CF +	Positive emotional functional	14.2 (3.5) 14.43 (2.9) P = 0.39	Exercise = control	High
			TACQOL-CF +	Negative emotional functioning	12.7 (2.12) 14.2 (2.2) P = 0.34	Exercise = control	High
Madhavi 2011	112	Exercise training	SF-36 +	SF36 total score	23.3 (13.2) 11.3 (14.3) P < 0.001	Exercise > control	High
Klausen 2016	158	Physical activity promotion	Danish Paediatric QoL Inventory +	Generic	NR	Exercise = control	High
			Danish Paediatric QoL Inventory +	Disease specific	NR	Exercise = control	High
Opotowsky 2018	28	Exercise training	MLHFQ -	MLHFQ	20.1 (11.4) 27.7 (10.9) P = 0.13	Exercise = control	High
Sandberg 2018	23	Exercise training	EQ5D VAS +	EQ5D VAS	76.2 (15.2) 76.3 (20.7) P = 0.31	Exercise = control	High
Novakovic 2018	14	Exercise training (Interval)	SF36 +	Physical component	86.7 (40.2) 101.0 (16.6) P > 0.05	Exercise = control	High
			SF36 +	Mental component	80.0 (21.0) 87.3 (21.9) P > 0.05	Exercise = control	High
Novakovic 2018	13	Exercise training (Continuous)	SF36 +	Physical component	103 (5.2) 101.0 (16.6) P > 0.05	Exercise = control	High
			SF36 +	Mental component	89.3 (18.4) 87.3 (21.9) P > 0.05	Exercise = control	High
Westhoff-Bleck 2013	40	Exercise training	KCCQ +	KCCQ	NR	Exercise = control	High

Table 1. Health-related quality of life *(Continued)*

Winter 2012	46	Exercise training	SF-36 +	Mental component	P = 0.17	Exercise = control	High
			SF-36 +	Physical component	P = 0.20	Exercise = control	High
			ConHD-TAAQOL +	Symptoms	85 (10.79) 83 (10.47) P = 0.31	Exercise = control	High
			ConHD-TAAQOL +	Worries	77 (15.4) 84.5 (9.21) P = 0.30	Exercise = control	High
			ConHD-TAAQOL +	Impact	84 (7.19) 85.25 (6.20) P = 0.91	Exercise = control	High

Each study's outcome of health related quality of life was individually assessed using risk of bias 2; all studies were judged as a high risk of bias under the domain 'Measurement of the outcome'. **'+'** = a higher score represents better health; **'-'** = a lower score represents better health; HRQoL, Health related quality of life; SF-36, 36-Item Short Form Health Survey; MLHFQ, Minnesota living with heart failure questionnaire; TACQOL, TNO/AZL child quality of life questionnaire; ConHD TAAQOL, The congenital heart disease - TNO/AZL adult quality of life questionnaire; EQ5D VAS, EuroQol Vertical Visual Analogue Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire.

Table 2. Individual ConHD lesions pooled into the meta-analyses

Study	Age	Type of ConHD and (sample size, %)	Classification
Avila 2016	35 ± 11	Repaired ToF (17, 100%)	Severe
Duppen 2015	15 ± 3	Fontan circulation (43, 48%) [Intra-atrial lateral tunnel 47%; extracardiac conduit 44%; other 9%]	Severe
		Repaired ToF (47, 52%)	
Fritz 2020	30 ± 9	Fontan circulations (42, 100%) [Atrioventricular Anastomosis 19%; Atriopulmonary Anastomosis 21%; Total Cavopulmonary Connection 60%]	Severe
Klausen 2016	15 ± 1	Coarctation of the aorta (52, 33%)	Severe
		TGA (35, 22%)	
		Steno–Fallot tetralogy (21, 13%)	
		Double outlet right ventricle (7, 4%)	
		Truncus arteriosus (4, 3%)	
		Atrioventricular septal defect (9, 6%)	
		TCPC (6, 4%)	
		Other (24, 15%)	
Madhavi 2011	29 ± 11	Acyanotic Congenital Heart Disease (112, 100%)	Mild
Moalla 2006	13 ± 1	Fontan (4, 22%)	Mild to Severe
		TGA (Senning/Mustard procedure) (5, 28%)	
		Repaired ToF (5, 28%)	
		Repaired ASD (4, 22%)	
Morrison 2013	15 ± 2	Minor CHD (no surgical intervention) (39, 27%)	Mild to Severe
		Acyanotic corrected ConHD (61, 43%)	
		Cyanotic corrected (30, 21%)	
		Cyanotic palliated (13, 9%)	
Novakovic 2018	38 ± 8	Repaired ToF (30, 100%)	Severe
Opotowsky 2018	41 ±12	ToF with pulmonary stenosis or atresia or, DORV (13, 46%)	Severe
		TGA with a systemic RV, (9, 32%)	

Table 2. Individual ConHD lesions pooled into the meta-analyses *(Continued)*

		Fontan (2, 7%)	
		Pulmonary atresia with intact ventricular septum with biventricular repair (2, 7%)	
		Truncus arteriosus (1, 4%)	
		Ebstein anomaly (1, 4%)	
Sandberg 2018	30 ± 11	ToF (5, 22%)	Severe
		ccTGA & d-TGA (8, 35%)	
		TCPC (5, 22%)	
		PA (2, 9%)	
		Complete AV-septal defect (1, 4%)	
		Ebstein anomaly (1, 4%)	
		Miscellaneous (1, 4%)	
Therrien 2003	35 ± 9	Repaired ToF (18, 100%)	Severe
Westhoff-Bleck 2013	29 ± 3	Systemic right ventricle - TGA [Mustard] (48, 100%)	Severe
Winter 2012	32 + 11	Systemic right ventricle - TGA and ccTGA (46, 100%)	Severe
van Dissel 2019	40 ± 9	ToF (12, 30%)	Severe
		TGA (13, 33%)	
		Fontan circulation (9, 22%)	
		Pulmonary atresia (3, 7.5%)	
		Other (3, 7.5%)	

ToF, tetralogy of Fallot; TGA, transposition of the great arteries; ccTGA, congenitally corrected transposition of the great arteries; d-TGA, dextro-transposition of the great arteries; ASD, atrial septal defect; TCPC, Total cavopulmonary connection; DORV, double-outlet right ventricle; RV, right ventricle.

Table 3. Characteristics of exercise training interventions

Study	Age group & severity	Location & supervision	Frequency[a] (sessions per week)	Intensity	Time[b] (minutes)	Type	Duration[c] (Weeks)	Dose (a*b*c)
Avila 2016	Adult & severe (ToF)	Hospital & supervised	1 to 2	70% to 80% of the maximum HR (increased throughout intervention)	60	Combination of resistance and aerobic dynamic (running, rowing etc.) exercise	12	1080
Duppen 2015	Paediatric & severe (ToF and Fontan)	Hospital & supervised	2 to 3	Resting heart rate plus 60% to 70% of the HR reserve	60	Aerobic dynamic	12	1800
Madhavi 2011	Adult & mild	NR	NR	Individualised (NR)	NR	NR	12	N/A
Moalla 2006	Paediatric & mild/severe	Home & semi-supervised	3	HR at the gas exchange threshold	60	Cycling	12	2160
Novakovic 2018	Adult & severe (ToF)	NR	2 to 3	80% of HRpeak in high intensity exercise	42	Cycling or speed walking	12	1260
				70% of HRpeak in continuous intensity exercise				
Opotowsky 2018	Adult & severe	Hospital & supervised	2	HR at Gas Exchange Threshold	60	Combination of resistance and aerobic dynamic	12	1440
Sandberg 2018	Adult & severe	Home & semi-supervised	3	HR was calculated according to the Karvonen method and to achieve BORG 15 to 16	31	Cycling	12	1116
Therrien 2003	Adult & severe (ToF)	Hospital and home (1:2 ratio) & supervised	3	60% to 85% of pre training peak VO_2	50	Cycling and walking	12	1800
Westhoff-Bleck 2013	Adult & severe (Mustard procedure)	Home & semi-supervised	3-5	HR corresponding to 50% of peak VO_2	10 to 30	Cycling	24	2550[d]

Table 3. Characteristics of exercise training interventions *(Continued)*

Winter 2012	Adult & severe	Home & semi-supervised	3	75% to 90% of max heart rate (increased throughout intervention)	42	Step aerobics	10	1260
van Dissel 2019	Adult & Moderate and Severe	Home & semi-supervised	3	80% of the maximum HR	45	Self-selected	26	3510

ToF, Tetralogy of Fallot; HR, Heart Rate; NR, Not Reported; [d] See dose calculations in Characteristics of included studies

Table 4. Univariate meta-regression analysis

Potential effect modifiers	Regression coefficient and (Standard error)	P value
Age (adult vs. paediatric)	2.5 (2.2)	0.262
Baseline CRF (peak $\dot{V}O_2$ mL.kg^{-1}.min^{-1})	−0.2 (0.1)	0.186
Dose (intervention length*no. sessions per week*session length)	−0.2 (0.3)	0.614
Follow-up period/intervention length (weeks)	−0.18 (0.1)	**0.031**
Percentage of male	−0.5 (0.3)	0.083
Risk of bias	9.1 (2.2)	**< 0.01**
Sample size	−0.001 (0.02)	0.963
Setting (home or hospital based)	−2.3 (1.6)	0.171
Study location (Continent)	−3.5 (1.8)	0.070
Type of intervention (exercise training, PA promotion, IMT)	−2.3 (1.7)	0.208

Bold = statistically significant; CRF, Cardiorespiratory fitness;

APPENDICES

Appendix 1. Search strategy

CENTRAL

#1 MeSH descriptor: [Exercise] explode all trees

#2 MeSH descriptor: [Physical Fitness] this term only

#3 MeSH descriptor: [Sports] explode all trees

#4 MeSH descriptor: [Rehabilitation] this term only

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

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

#7 MeSH descriptor: [Recreation Therapy] this term only

#8 MeSH descriptor: [Physical Exertion] this term only

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

#10 MeSH descriptor: [Dancing] this term only

#11 exercis*

#12 aerobic*

#13 sport*

#14 walk*

#15 bicycle*

#16 ((lifestyle or life-style) NEAR/5 activ*)

#17 ((lifestyle or life-style) NEAR/5 physical*).tw.

#18 (physical* NEAR/5 (fit* or train* or activ* or endur* or exert* or perform* or inact*))

#19 anaerobic

#20 rehabilitat*

#21 heart rate recovery

#22 danc*

#23 (run* or jog*)

#24 #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

#25 MeSH descriptor: [Heart Defects, Congenital] explode all trees

#26 MeSH descriptor: [Heart Diseases] explode all trees and with qualifier(s): [congenital - CN]

#27 (heart NEAR/2 (defect* or abnormal* or malform*))

#28 (congenital NEAR/2 (heart or cardiac or cardio*))

#29 #25 or #26 or #27 or #28

#30 #24 and #29

MEDLINE Ovid

1 exp Exercise/

2 Physical Fitness/

3 exp Sports/

4 Rehabilitation/

5 Dance Therapy/

6 exp Exercise Therapy/

7 Recreation Therapy/

8 Physical Exertion/

9 exp "Physical Education and Training"/

10 Dancing/

11 exercis*.tw.

12 aerobic$.tw.

13 sport$.tw.

14 walk$.tw.

15 bicycle$.tw.

16 ((lifestyle or life-style) adj5 activ$).tw.

17 ((lifestyle or life-style) adj5 physical$).tw.

18 (physical$ adj5 (fit$ or train$ or activ$ or endur$ or exert$ or perform* or inact*)).tw.

19 anaerobic.tw.

20 rehabilitat$.tw.

21 heart rate recovery.tw.

22 danc*.tw.

23 (run* or jog*).tw.

24 or/1-23

25 exp Heart Defects, Congenital/

26 exp Heart Diseases/cn [Congenital]

27 (heart adj2 (defect* or abnormal* or malform*)).tw.

28 (congenital adj2 (heart or cardiac or cardio*)).tw.

29 or/25-28

30 24 and 29

31 randomized controlled trial.pt.

32 controlled clinical trial.pt.

33 randomized.ab.

34 placebo.ab.

35 drug therapy.fs.

36 randomly.ab.

37 trial.ab.

38 groups.ab.

39 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38

40 exp animals/ not humans.sh.

41 39 not 40

42 30 and 41

Embase Ovid

1 exp exercise/

2 fitness/

3 exp sport/

4 rehabilitation/

5 dance therapy/

6 exp kinesiotherapy/

7 recreational therapy/

8 exp physical education/

9 dancing/

10 exercis*.tw.

11 aerobic$.tw.

12 sport$.tw.

13 walk$.tw.

14 bicycle$.tw.

15 ((lifestyle or life-style) adj5 activ$).tw.

16 ((lifestyle or life-style) adj5 physical$).tw.

17 (physical$ adj5 (fit$ or train$ or activ$ or endur$ or exert$ or perform* or inact*)).tw.

18 anaerobic.tw.

19 rehabilitat$.tw.

20 heart rate recovery.tw.

21 danc*.tw.

22 (run* or jog*).tw.

23 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

24 exp congenital heart malformation/

25 heart disease/cn [Congenital Disorder]

26 (heart adj2 (defect* or abnormal* or malform*)).tw.

27 (congenital adj2 (heart or cardiac or cardio*)).tw.

28 24 or 25 or 26 or 27

29 23 and 28

30 random$.tw.

31 factorial$.tw.

32 crossover$.tw.

33 cross over$.tw.

34 cross-over$.tw.

35 placebo$.tw.

36 (doubl$ adj blind$).tw.

37 (singl$ adj blind$).tw.

38 assign$.tw.

39 allocat$.tw.

40 volunteer$.tw.

41 crossover procedure/

42 double blind procedure/

43 randomized controlled trial/

44 single blind procedure/

45 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46 (animal/ or nonhuman/) not human/

47 45 not 46

48 29 and 47

CINAHL

S52 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

S51 S49 not S50

S50 MH (human)

S49 S46 OR S47 OR S48

S48 TI (animal model*)

S47 MH (animal studies) S46 MH animals+

S45 AB (cluster W3 RCT)

S44 MH (crossover design) OR MH (comparative studies)

S43 AB (control W5 group)

S42 PT (randomized controlled trial)

S41 MH (placebos)

S40 MH (sample size) AND AB (assigned OR allocated OR control)

S39 TI (trial)

S38 AB (random*)

S37 TI (randomised OR randomized)

S36 MH cluster sample

S35 MH pretest-posttest design

S34 MH random assignment

S33 MH single-blind studies

S32 MH double-blind studies

S31 MH randomized controlled trials

S30 S24 AND S29

S29 S25 OR S26 OR S27 OR S28

S28 TX (congenital n2 (heart or cardiac or cardio*))

S27 TX (heart n2 (defect* or abnormal* or malform*))

S26 (MH "Heart Diseases+/FG")

S25 (MH "Heart Defects, Congenital+")

S24 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

S23 TX (run* or jog*)

S22 TX danc*

S21 TX heart rate recovery

S20 TX rehabilitat*

S19 TX anaerobic

S18 TX (physical* n5 (fit* or train* or activ* or endur* or exert* or perform* or inact*))

S17 TX ((lifestyle or life-style) n5 physical*)

S16 TX ((lifestyle or life-style) n5 activ*)

S15 TX bicycle*

S14 TX walk*

S13 TX sport*

S12 TX aerobic*

S11 TX exercis*

S10 (MH "Dancing")

S9 (MH "Physical Education and Training+")

S8 (MH "Exertion")

S7 (MH "Recreational Therapy")

S6 (MH "Therapeutic Exercise+")

S5 (MH "Dance Therapy")

S4 (MH "Rehabilitation")

S3 (MH "Sports+")

S2 (MH "Physical Fitness")

S1 (MH "Exercise+")

AMED

1 exp Exercise/

2 Physical fitness/

3 exp Sports/

4 Rehabilitation/

5 Dance therapy/

6 exp Exercise therapy/

7 Recreation/

8 Exertion/

9 exp Physical education/

10 Dancing/

11 exercis*.tw.

12 aerobic$.tw.

13 sport$.tw.

14 walk$.tw.

15 bicycle$.tw.

16 ((lifestyle or life-style) adj5 activ$).tw.

17 ((lifestyle or life-style) adj5 physical$).tw.

18 (physical$ adj5 (fit$ or train$ or activ$ or endur$ or exert$ or perform* or inact*)).tw.

19 anaerobic.tw.

20 rehabilitat$.tw.

21 heart rate recovery.tw.

22 danc*.tw.

23 (run* or jog*).tw.

24 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

25 exp Heart defects congenital/

26 (heart adj2 (defect* or abnormal* or malform*)).tw.

27 (congenital adj2 (heart or cardiac or cardio*)).tw.

28 25 or 26 or 27

29 24 and 28

30 randomized controlled trial.pt.

31 controlled clinical trial.pt.

32 randomized.ab.

33 placebo.ab.

34 randomly.ab.

35 trial.ab.

36 groups.ab.

37 30 or 31 or 32 or 33 or 34 or 35 or 36

38 exp animals/ not humans.sh.

39 37 not 38

40 29 and 39

Web of Science and BIOSIS

20 #19 AND #18

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

18 #17 AND #14

17 #16 OR #15

16 TS=(congenital NEAR/2 (heart or cardiac or cardio*))

15 TS=(heart NEAR/2 (defect* or abnormal* or malform*))

14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

13 TS=(run* or jog*)

12 TS=danc*

11 TS=heart rate recovery

10 TS=rehabilitat*

9 TS=anaerobic

8 TS=(physical* NEAR/5 (fit* or train* or activ* or endur* or exert* or perform* or inact*))

7 TS=((lifestyle or life-style) NEAR/5 physical*)

6 TS=((lifestyle or life-style) NEAR/5 activ*)

5 TS=bicycle*

4 TS=walk*

3 TS=sport*

2 TS=aerobic*

1 TS=exercis*

LILACS

(heart or cardiac$ or cardio$) AND (defect or congenital or malform$ or abnormal$) [Words] and Exercise$ or aerobic$ or sport$ or walk$ or bicycle$ or anaerobic$ or rehabilitat$ or heart rate recovery$ or danc$ or run$ or jog$ or active$ or train$ or fit$ [Words]

DARE

heart or cardiac* or cardio* AND defect or congenital or malform* or abnormal* AND exercise* or aerobic* or sport* or walk* or bicycle* or anaerobic* or rehabilitat* or heart rate recovery* or danc* or run* or jog* or active* or train* or fit*

ClinicalTrials.gov

Condition or disease: Congenital Heart Disease
Other terms: exercise
Study type: Interventional studies (Clinical Trials)

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; Budts 2020).

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 atrioventicular 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.

WHAT'S NEW

Date	Event	Description
21 May 2021	Amended	Link to Table in in Results section corrected.

HISTORY

Protocol first published: Issue 8, 2019
Review first published: Issue 10, 2020

Date	Event	Description
8 February 2021	Amended	Technical issue with risk of bias tables resolved
26 January 2021	Amended	Minor edits to abstract and summary of findings table.

CONTRIBUTIONS OF AUTHORS

CAW and CW independently completed title and abstract screening, full text review, risk of bias assessments, data extraction and GRADE.

CAW had overall control of the design of the study and co-wrote the manuscript.

CW assisted data analysis, produced the SoF table and co-wrote the manuscript.

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

GS gave specialist clinical insight into the literature and population with congenital heart disease

RST designed and carried out the statistical analysis and arbitrated any discrepancies.

LL was the lead author overseeing the project and arbitrated any discrepancies.

All authors contributed to the peer review and agreed on the final version of this manuscript.

DECLARATIONS OF INTEREST

CAW has received funding from Heart Research UK and Canon Medical Systems Ltd 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. Neither of these organisations have a financial interest in this review.
CW has a funded PhD scholarship from the University of Exeter and Canon Medical. Canon Medical Systems Ltd does not have a financial interest in this review.
GEP is lead researcher in a contractual research partnership between the University of Bristol and Canon Medical Systems UK Ltd. Canon Medical Systems Ltd does not have a financial interest in this review.
GS is Medical Director of Sports Cardiology UK. Research grant from Heart research UK to evaluate an exercise prescription programme in congenital heart patients. Fee for lecturing at scientific meetings and financial support for educational arrhythmia meeting in February 2019 from Medtronic Actelion. None of the organisations named have a financial interest in this review.
LL has no known conflicts of interest.
RST has no known conflicts of interest.

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Internal sources

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  C Wadey was funded by an industrial PhD studentship from the University of Exeter and Canon Medical Systems UK Ltd.

  GE Pieles 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.

  Authors had full control of the design of the study, methods used, outcome parameters, analysis of the data and production of any manuscripts.

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- WHO ICTRP was unavailable due to increased traffic to the site because of COVID 19, therefore it was not searched. Clinical trials.gov was searched.
- Two studies estimated cardiorespiratory fitness (CRF) using validated CPET protocols, these were pooled with direct measures (gas analysis) of CRF
- Baseline CRF and risk of bias were added to the univariate meta regression.
- A vote counting table was used to synthesise all the information regarding health related quality of life.
- Sensitivity analysis was changed from 'all studies versus only including those studies we judge to have overall low risk of bias (low risk in all domains)' to all studies versus exclusion of high risk studies. This was changed as only one study had a low risk of bias in all domains.

NOTES

None

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; *Breathing Exercises; Cardiorespiratory Fitness [*physiology]; Exercise [*physiology]; Heart Defects, Congenital [*rehabilitation]; Muscle Strength; Oxygen Consumption [physiology]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male