Cochrane corner: Physical activity interventions for people with congenital heart disease

Curtis A Wadey[1], Guido E Pieles[2], Graham Stuart[2], Rod S Taylor[3], Linda Long[4], Craig A Williams[1].

1 Children's Health & Exercise Research Centre (CHERC), College of Life and Environmental Sciences, University of Exeter, Exeter, United Kingdom

2 National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Centre, Bristol Heart Institute, Bristol, UK.

3 MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow, Glasgow, UK.

4 Institute of Health Research, University of Exeter Medical School, Exeter, UK.

Corresponding author: Professor Craig A Williams, Children's Health & Exercise Research Centre (CHERC), College of Life and Environmental Sciences, St. Luke's Campus, University of Exeter, Heavitree Road, Exeter EX1 2LU, Devon, UK. Email - C.A.Williams@exeter.ac.uk

Twitter: @CWsport1, @CHERC_UoE, @ag_stuart.

ORCID: CA Wadey 0000-0003-3275-7975, GEP 0000-0003-1203-688X, GS 0000-0003-2789-2216, RST 0000-0002-3043-6011, LL 0000-0001-6889-1426, CA Williams 0000-0002-1740-6248.

Introduction

Congenital heart disease (ConHD) represents 1% of global births (95% confidence interval [CI] 0.86% to 1.02%) and due to improved medical care long-term survival rates have substantially improved, leading to growing ConHD populations across the lifespan (1,2). People with ConHD can have reduced cardiorespiratory fitness (CRF), health-related quality of life (HRQoL), and physical activity (PA) levels when compared to healthy populations. This is important because CRF has been significantly associated with future mortality and morbidity in healthy and ConHD populations (3,4).

Objective: There is currently no high-level evidence evaluating the effect of exercise in ConHD patients. To inform current practice and policy, we therefore sought to undertake a systematic review and meta-analysis of randomised controlled trials (RCTs) to assess the effectiveness and safety of all types of physical activity interventions in people with ConHD (5)

Methods

Searches

A search was performed through to September 2019 in the following databases; Cochrane Central Register of Controlled Trials, MEDLINE, Embase and CINAHL, AMED, BIOSIS, Web of Science, LILACS and DARE.

Study selection

We included any type of RCT that compared a physical activity intervention to a usual care (no physical activity) comparator. We included all types of interventions, all settings (hospital and home) and both paediatric (5-18 years old) and adult (>18 years) populations. Our outcomes of interest were maximal and submaximal CRF, HRQoL, PA, muscular strength, hospital admissions during follow-up, time off work/education, and any adverse events, although these did not limit study inclusion.

Data extraction and risk of bias assessment

Data extraction and risk of bias (RoB) assessment were carried out independently by two authors. We used piloted data extraction templates and assessed study risk of bias using the revised Cochrane RoB 2 tool. Any disagreements were resolved by consensus and decisions were independently checked by a third author.

Data analysis

Where possible, study outcomes were pooled using meta-analysis. Grading of Recommendations Assessment, Development, and Evaluation was used to assess the quality of the evidence.

Results

Study selection

15 RCTs across 39 publications with a total of 924 participants (50 % female) were included, 5 (n=500) of which were paediatric RCTs.

Characteristics of included studies

Three types of intervention were identified: PA promotion (n=3, 435 participants), exercise training (n=11, 435 participants) and inspiratory muscle training (IMT) (n=1, 38 participants).

Based on neonatal diagnoses; 11 RCTs (n=559) comprised severe ConHD, 3 RCTs (n=254) pooled mild, moderate, and severe ConHD and 1 trial (n=111) included mild disease only. Outcomes were measured after the cessation of the intervention, and only one study measured long-term outcome at 36 months.

Risk of bias

Risk of bias judgements were made in relation to five outcomes: maximal and submaximal CRF; HRQoL; PA; and muscular strength. Studies and outcomes were judged predominately to be of 'some concerns' except for the outcome HRQoL, which was judged to be of a 'high' risk of bias. No study or outcome was judged to have a low risk of bias. This was due to a lack of information regarding the blinding of the outcome assessors and the lack of information in pre-registered protocols describing proposed statistical methods.

Impact of physical activity interventions on outcomes

Maximal CRF

Maximal CRF was measured by peak $\dot{V}O_2$ and when pooled across studies (14 RCTs, 732 participants) showed a mean increase of 1.89 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI -0.22 to 3.99, random effects) compared to control. A subgroup analysis (P=0.07) showed that the exercise training subgroup increased their mean peak $\dot{V}O_2$ by 2.74 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.36 to 5.12), compared to -1.71 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI -4.64 to 1.22) and 0.7 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI -4.83 to 6.23) for PA promotion and IMT respectively. We found no influence of the type of ConHD diagnoses; single ventricle vs. tetralogy of Fallot vs. mixed or other ConHD populations (P=1.00). Univariate meta-regression identified that the duration (P=0.03) and the risk of bias (P<0.01) explained the effect of the intervention (i.e. shorter interventions or a high risk of bias RCTs were more effective). There was no evidence of publication bias (Egger test, p=0.26) and we judged the certainty of the evidence using GRADE as 'moderate' due to imprecision in the estimate as the confidence interval spans 0, so includes both appreciable harm and appreciable benefit.

HRQoL

HRQoL was measured by seven different types of self-reported questionnaires in 8 RCTs. Pooled analysis (3 studies, 163 patients) showed a mean improvement in HRQoL of 0.76 standard deviation units (95% CI -0.13 to 1.65, random effects), compared to control. This was judged using GRADE as very low certainty evidence, because of the high risk of bias, inconsistency and imprecision. We also produced a vote-counting table that summarised all the data from the 8 RCTs, this method reported only 1 study that identified a change in HRQoL.

PA

PA measured by accelerometry was reported in 4 RCTs (328 patients), there was a small increase in pooled mean time spent in moderate to vigorous physical activity (MVPA) of 0.38 standard deviations (95% CI -0.15 to 0.92, random effects) compared to control. This corresponds to an MVPA increase of approximately 10 minutes per day (95% CI -2.5 to 22.2). The certainty of the evidence was judged as low using GRADE, due to inconstancy (i.e. unexplained heterogeneity) and imprecision (<400 patients included in the analysis).

Adverse Events

Adverse event (AE) data were reported by 11 RCTs (501 patients), 6 of which reported 0 AEs. The remaining 5 RCTs reported a total of 11 AEs, 7 (63%) were non cardiac (minor musculoskeletal, minor head injury etc.) and 4 (37%) were cardiac (1 suspected arrhythmia, 1

self-limiting supraventricular arrhythmia, 1 episode of ventricular premature complexes, and 1 episode of non-sustained atrial tachycardia) AEs that could be related to exercise. There were no reported serious adverse events or fatalities. Furthermore, there were no adverse structural or functional myocardial adaptations in 8 studies (377 patients), that used a combination of B-type natriuretic peptide, cardiac magnetic resonance imaging and/or echocardiography pre- and post-intervention. The certainty of the evidence was judged as moderate using GRADE, due to inconsistency, as more than 25% of studies did not report data on AEs.

For further information on our secondary outcomes, questionnaire-based PA, submaximal fitness, hospital admissions, time off work/education, and muscular strength see the full review (5).

Discussion

We present the first Cochrane systematic review and meta-analysis to assess the effectiveness and safety of physical activity interventions in people with ConHD, and the first Cochrane review to utilise the revised RoB 2 tool. We included a total of 15 RCTs (924 patients) within our review that compared three types of intervention (PA promotion, exercise training, or IMT) to usual care. Based on very low to moderate certainty evidence across all outcomes, we found that PA interventions did not produce any serious adverse events and may have a small beneficial effect on CRF and MVPA but little or no effect on HRQoL.

Peak $\dot{V}O_2$ has been associated with future prognosis in ConHD (4) and we report a MD increase of 1.89 $mL \cdot kg^{-1} \cdot min^{-1}$ in peak $\dot{V}O_2$. Interestingly the interventions were equally effective regardless of the type of ConHD included. Research in 4527 healthy adults reported for every one unit increase in a metabolic equivalent task (1 MET = 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$), it reduced the chance of cardiovascular events by 15%; furthermore, the population with the highest CRF quartile was 48% less likely to experience an event compared to the least fit quartile (3). However, due to the lack of long-term follow-up there is no data on what prognostic implication our reported increase of 1.89 $mL \cdot kg^{-1} \cdot min^{-1}$ has on future morbidity and mortality in a ConHD population.

Meta-analysis and GRADE revealed very low certainty evidence for HRQoL. On further analysis, utilising a modified vote-counting table to summarise all the available evidence for HRQoL, only one RCT out of eight reported a substantial increase in HRQoL. To our knowledge this is the first systematic review to quantitatively assess PA using accelerometery after a PA intervention in patients with ConHD. With low certainty evidence it appears PA interventions can have a small beneficial effect increasing MVPA by approximately 10 minutes per day, which could contribute to more people achieving global PA guidelines.

Conclusions

The results of this systematic review and meta-analysis show some likely beneficial effects of PA interventions in some outcomes such as CRF and PA, with no serious adverse events related to the exercise reported. The certainty of this evidence ranges from very low to moderate. Currently, there is insufficient evidence to determine the effectiveness of these interventions in both the short and long-term on patient health. There is an urgent need for further detailed methodologies and appropriately powered high-quality RCTs with longer duration of patient follow-up.

Word count - 1437

References

1. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: Updated systematic review and meta-analysis of 260 studies. Int J Epidemiol. 2019;48(2):455–63.

2. Best KE, Rankin J. Long-term survival of individuals born with congenital heart disease: A systematic review and meta-analysis. J Am Heart Assoc. 2016;5(6):1–16.

3. Letnes JM, Dalen H, Vesterbekkmo EK, Wisløff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: The Hunt Fitness study. Eur Heart J. 2019;40(20):1633–9.

4. Diller GP, Kempny A, Babu-Narayan S V., Henrichs M, Brida M, Uebing A, et al. Machine learning algorithms estimating prognosis and guiding therapy in adult congenital heart disease: Data from a single tertiary centre including 10 019 patients. Eur Heart J. 2019;40(13):1069–77.

5. Williams CA, Wadey C, Pieles G, Stuart G, Taylor RS, Long L. Physical activity interventions for people with congenital heart disease. Cochrane Database Syst Rev. 2020;(10):https://doi.org/10.1002/14651858.CD013400.

Contribution of authors

Abridged version - CA Wadey wrote the manuscript and created the summary figure. All authors contributed to the final version of the manuscript and agreed to its content.

Full review - CA Williams and CA Wadey independently completed title and abstract screening, full text review, risk of bias assessments, data extraction and GRADE. CA Williams co-wrote the manuscript. CA Wadey performed statistical analyses, produced the summary of findings table and co-wrote the manuscript. GEP and GS gave specialist clinical insight into the literature and population with congenital heart disease. RST designed and carried out the statistical analyses 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 the manuscript.

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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.

Patient and public involvement

Patients were not involved in the design of this review

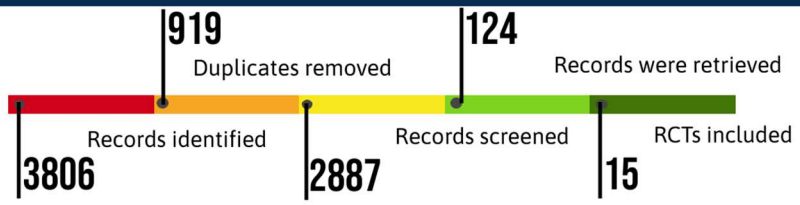
Patient consent for publication

Not required

Disclaimer

This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2020, Issue 10, DOI: https://doi.org/10.1002/14651858.CD013400. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Cochrane review: Physical activity interventions for people with congenital heart disease.



MD
+1.89
RCTs = 14
Patients = 732
Certainty = Moderate

Cardiorespiratory fitness

- Physical activity may increase peak oxygen consumption (mL/kg/min) slightly.
- Lack of long term follow-up; uncertain the prognostic importance this has.

SMD
+0.76
RCTs = 3
Patients = 163
Certainty = V Low

Health-related quality of life (HRQoL)

- The evidence is very uncertain about the effect physical activity has on HRQoL.
- Vote counting revealed only 1 out of 8 studies found a postive effect.

SMD
+0.38
RCTs = 4
Patients = 328
Certainty = Low

Physical activity

- Re-expressing SMD reveals an increase of 10 minutes of moderate to vigorous physical activity per day.

11
(2%)
RCTs = 11
Patients = 501
Certainty = Moderate

Adverse events

- 11 adverse events, of which 4 were cardiac.
- No serious adverse events were reported.
- No evidence of adverse cardiac adaptions.

Conclusion and implications

- There are likely beneficial effects of physical activity interventions.
- Certainty of the evidence ranges from very low to moderate.
- Insufficient evidence and more randomised controlled

Reference

For further information see:
Williams CA, Wadey C, Pieles G, Stuart G, Taylor RS, Long L. Physical activity interventions for people with congenital heart disease. Cochrane Database Syst Rev. 2020; https://doi.org/10.1002/14651