Cardiology in the Young

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Peripheral and respiratory muscle strength in children and adolescents with CHD: systematic review and meta-analysis

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Review

Cite this article: Niedermeyer CC, Shizukuishi MLY, Schaan CW, and Lukrafka JL (2022) Peripheral and respiratory muscle strength in children and adolescents with CHD: systematic review and meta-analysis. *Cardiology in the Young* **32**: 1728–1741. doi: 10.1017/S1047951122003092

Received: 2 March 2022
Revised: 1 September 2022
Accepted: 4 September 2022
First published online: 6 October 2022

Keywords:
Heart defects; Congenital; Muscle strength; Child; Adolescent; Review; Meta-analysis

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Abstract

Patients with CHD are less active if compared with controls and have limited functional capacity, related to muscle weakness and fatigue. The aim of this study was to evaluate the peripheral and respiratory muscle strength of children and adolescents with CHD with systematic review and meta-analysis. The review included observational and randomised control trial studies which evaluated peripheral and respiratory muscle strength in children and adolescents with CHD under 18 years old. The peripheral muscle strength was evaluated through dynamometry and respiratory muscle strength through manovacuometry. In studies that compared patients with CHD and respective control groups, it was possible to perform a meta-analysis. A total of 5634 articles met the criteria of eligibility, 15 were included in the systematic review, and 4 were included in the meta-analysis. Twelve studies assessed peripheral muscle strength with a reduction in patients with CHD. In the meta-analysis, patients with CHD had lower muscle strength than controls (−34.07 nm; 95% CI, −67.46 to −0.68; I2 47%; p for heterogeneity = 0.05), and the meta-analysis of the handgrip muscle strength showed no significant difference between patients with CHD and controls (0.08 nm; 95% CI, −6.39 to 6.55; I2 98%; p for heterogeneity <0.00001). The meta-analysis in the present study showed lower limb muscle strength in patients with CHD in comparison to controls. In contrast, no difference was found regarding hand grip strength. Also, the review showed lower respiratory muscle strength in patients with CHD, yet no meta-analysis was possible to perform.

CHD is the most common congenital malformation present from birth, with defects in structure or cardiocirculatory function.[1,2] Most paediatric patients with CHD are less active,[3] have a decrease in functional capacity, and reduced aerobic capacity compared to controls.[4] Moreover, the majority of heart defects require surgical intervention, and impairments have been linked to the severity of CHD, the number of surgical, and complications after the procedures.[5,6]

Muscle strength can be considered a variable that is related to physical fitness and health status, and a decrease can be associated with significant functional limitations.[7] In adults with CHD, peripheral muscle strength can be considered a predictor of overall strength; however, there are a few reports in paediatric patients.[7] Strength in children is directly related to age, sex, height, and weight, with an increase in values according to growth and maturity,[8] and can be reduced in different diseases,[9–11] as well as in patients after lung or heart transplantation.[12] In children with CHD or some type of developmental deficit, muscle strength is usually decreased, generating muscle weakness and fatigue that compromises motor and functional skills in daily living.[13]

Isokinetic dynamometry is used in research and clinical practice to measure strength (isokinetic or isometric), power, and muscular endurance.[14] Isokinetic tests have been considered safe to use in paediatric populations.[14] Handgrip strength is an adequate instrument to measure generalised isometric muscle strength in adults, representing the association of arm, back, and leg strength. There are few studies in the paediatric population, mostly with children with congenital heart disease, so it is difficult to confirm that handgrip can be used as a predictor of general muscle strength.[15]

Patients with CHD also have impaired aerobic capacity compared to age and gender-matched healthy controls.[13] These impairments are multifactorial and result from internal and external influences, such as the severity of disease, number of surgical procedures, hypoactivity, haemodynamic limitations, and pulmonary and musculoskeletal disorders.[13] This reduction in exercise capacity has been widely associated with increased morbidity and mortality in adults.[6,16]

Peripheral muscle strength may be related to exercise capacity and the presence of functional limitations in patients with CHD.[17,18] Cardiocirculatory changes are responsible for the low supply of oxygen to muscle groups, which contributes to exercise intolerance and muscle fatigue.[17,18] The relationship between muscle strength and exercise capacity in children and adolescents with CHD is still poorly explored in the literature. Nevertheless, some studies have already shown an association between strength and muscle endurance in training programmes.[17,18]

Respiratory muscle strength may be affected in patients with CHD presenting muscle weakness and failure may occur.[17] The musculoskeletal dysfunction and the respiratory muscle weakness are common in young adults with CHD associated with exercise capacity reduction.[17] The measurement occurs through the performance of a maximum inspiratory pressure and maximal expiratory pressure effort, evaluating the isometric strength of the inspiratory expiratory muscles.[19] Smith et al.[20] claim that there is a relationship between respiratory muscle strength and peripheral muscle strength in cardiac patients, where each kg of the handgrip was associated with 0.74% higher predicted forced expiratory volume in one second (FEV1) ($p < 0.001$), but it is not possible to extrapolate the data for paediatrics due to the lack of studies in this specific population. Therefore, to the best of our knowledge, there have been no systematic reviews of muscle strength in paediatric populations with CHD. Thus, this systematic review and meta-analysis aimed to evaluate the peripheral and respiratory muscle strength of children and adolescents with CHD.

Methods

Protocol and registration

This study was conducted in accordance with the Cochrane Collaboration[21] and is presented as suggested by the Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement.[22] This review with meta-analysis was registered in the PROSPERO - *International prospective register of systematic reviews*, number CRD42021225172.

Eligibility criteria

We included observational studies (cohort and cross-sectional) and data from the first evaluation of randomised or non-randomised clinical trials that investigated children and adolescents under 18 years with CHD, including cardiac septum defects, aortic coarctation, transposition of the great vessels, tetralogy of Fallot, patients submitted to Fontan procedure, and a healthy control group. The outcomes were peripheral muscle strength (isokinetic dynamometer and isometric handgrip dynamometry) and respiratory muscle strength (isometric manovacuometry). Only studies in English were selected, and those with an analysis of the primary outcome were included. We excluded studies that were published before 1990, letters or reviews, thesis or articles published only as abstracts, and conference proceedings.

Strategy of search and selection of studies

We conducted an electronic search in four databases: MEDLINE accessed via PubMed, Embase, PEDro, and Cochrane, to obtain all studies published in the area between 1990 and October 2021. For each database, a specific strategy of descriptors and keywords was applied. A search strategy was performed using the following descriptors in English: *Child or Adolescent* combined with *Heart Defects, Congenital, Heart Septal Defects, Aortic Coarctation, Transposition of Great Vessels, Tetralogy of Fallot, Fontan Procedure*, in addition to *Muscle Strength, Maximal Respiratory Pressures* and *Exercise*. Terms were combined using the Boolean operators "OR" and "AND". The complete search strategy used for PubMed database is shown in the supplementary material.

Two independent authors (CCN and MYS) screened the titles and abstracts of all articles identified by the search strategy. A standard screening checklist based on the eligibility criteria was used. Abstracts that did not provide enough information on the inclusion and exclusion criteria were selected for evaluation of the full text. In this second phase, the same reviewers independently evaluated the full-text articles and made the selection according to the eligibility criteria. A third reviewer (JLL) assessed the studies in cases of disagreement related to the trial eligibility and assisted in the decision to include or exclude studies.

Data extraction

Data extraction was carried out by the same independent reviewers, using a standardised data acquisition form containing information about the study design, participants, and outcomes. The outcomes were isokinetic/isometric muscle strength measured by isokinetic dynamometry, isometric handgrip dynamometry, and respiratory isometric muscle strength measured by manovacuometry.

Risk of bias assessment

The same two reviewers also independently assessed the risk of bias in studies using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies.[23] Cross-sectional studies were evaluated with an adaptation of the same scale.[24] The NOS evaluates the studies on several design-specific criteria: the definition of the exposed and unexposed groups, selection and representativeness of groups, comparability, and outcome variables of interest. The studies were rated individually as "good," "fair," or "poor" quality by the criteria established by Newcastle-Ottawa Scale.[25] Disagreements between reviewers were resolved by consensus.

Data analysis

The quantitative synthesis included studies evaluating patients with CHD and healthy controls. Pooled-effect estimates were obtained by comparing the isometric limb muscle strength and handgrip strength of children and adolescents with CHD and respective healthy control. Combined estimates of effects were generated through the maximum values obtained in the studies reviewed, and the results were presented as weighted mean differences with 95% confidence intervals.

Statistical heterogeneity between the studies was assessed using the Cochrane Q test and the inconsistency test (I^2), in which values below 25% were considered indicative of low heterogeneity, between 25 and 50% moderate heterogeneity, and above 50% high heterogeneity. Heterogeneity among studies was investigated based on the following strategy: the meta-analysis was re-run by removing each study to check if one specific study explained the heterogeneity.

Calculations were performed using the random effects method. A p-value ≤ 0.05 was considered statistically significant. All analyses were performed using the Review Manager 5.1 software (Cochrane Collaboration). Studies that used other measurement units were converted to the same measure, providing

https://doi.org/10.1017/S1047951122003092 Published online by Cambridge University Press

comparability between studies and also performing the meta-analysis. The measurement units adopted were: kilograms (Kg) for handgrip strength and newton meters (Nm) for isokinetic muscle strength. The meta-analysis did not include respiratory muscle strength because the studies did not have a control group.

Results

A total of 5634 articles met the eligibility criteria; 760 were included in the full-text review, and after this stage, 15 studies were included in this review. Figure 1 shows the flow diagram. Of the 15 studies met the eligibility criteria, eigth cross-sectional studies, four cohort studies, and three randomised clinical trials. Table 1 presents the selected articles and their main characteristics. Twelve articles assessed peripheral muscle strength[18,26–36] and three assessed respiratory muscle strength.[5,8,37]

The total sample size of the included studies was 1769.[5,8,18,26–37] The studies comparing patients with CHD and healthy controls included 1202 participants in total,[27,33,34,36] and the studies only included patients with CHD had a total number of 567 participants.[5,8,18,26,28–32,35,37] Regarding the studies with evaluation only of patients with CHD, the majority had undergone at least one surgical procedure and submitted it to cardiac training or rehabilitation. The control group was patients without any intervention. Only one article compared different CHD.[5,8,35,37] In methodological analysis, the majority were classified as “fair” by the quality analysis using the Newcastle-Ottawa Scale scale, representing a medium risk of bias. Only two studies by Ferrer-Sargues et al. reached sufficient scores to be classified as "good", representing a low risk of bias.[5,26]

Descriptive analysis

Peripheral muscle strength

Peripheral muscle strength was assessed by 12 articles.[18,26–36] Of these, seven were cross-sectional, two cohorts, and three randomised clinical trials.

Of the 12 studies, five evaluated only upper limb strength[28–32] through handgrip dynamometry, four evaluated only lower limb strength[18,27,33,34] using hydraulic or isokinetic dynamometers, and three assessed upper and lower limb strength together.[26,35,36]

The reduction of muscle strength was described in four studies, three cross-sectional and one cohort. Moalla et al.,[33] Holm et al.[27], and Sandberg et al.[34] evaluated the strength (isometric and isokinetic) of lower limbs and observed a reduction of this variable in patients with CHD when compared to healthy controls. Zaqout et al.[36] also showed a reduction in upper-limb isometric strength (handgrip) in boys and an increase in lower-limb explosive strength (long jump test) in girls with CHD compared to healthy controls.

Four articles described no change in muscle strength in heart disease patients, two cross-sectional,[30,31] and two randomised clinical trials[6,32]. Longmuir et al reported no difference in grip strength between children with CHD and healthy peers.[6,30] Regarding randomised clinical trials, the study of Longmuir et al.[6] evaluated peripheral muscle strength as a secondary outcome in relation to the increment in physical activity. They found that older patients obtained higher scores in grip strength, but there’s no difference between types of intervention. McKillop et al.,[32] in another randomised clinical trial in adolescents with prior surgical repair of CHD, patients were submitted to a regular individualised exercise programme (control group) or exercise programme plus adapted motivational interviewing (intervention group). After 12 weeks, the authors did not find any difference in muscle strength between the groups.

The study of Klausen et al.[28] classified adolescents with CHD into three groups according to clusters based on health-related fitness: “robust” (very fit and physically strong), “moderately robust” (fitness level close to the mean), and “less robust” (nonathletic body composition and lack of muscle strength). The isometric peripheral handgrip muscle strength differed between clusters, and children “less robust” showed the lowest means of muscle strength. In addition, this study revealed that variability in health-related fitness was unrelated to diagnoses. Zaqout et al.[35] evaluated patients with CHD and stratified them into groups according to the type of defect. They also did not observe any differences ($p = 0.651$) in handgrip strength between groups of ventricular septal disease (17.3 ± 4.4 kg), aortic coarctation (15.8 ± 6.3 kg), transposition of the great vessels (16.0 ± 6.6 kg) and tetralogy of Fallot (4.7 ± 6.0 kg).

Two articles evaluated muscle strength associated with a training programme, one randomised clinical trial[18] and one cohort study.[26] The study of Moalla et al.[18] randomised patients into a control or intervention group, submitted to a 12-week training with an evaluation of lower limb muscle strength through isokinetic dynamometry. As a result, the study showed that the training promoted an increase in strength and muscle endurance in patients with CHD. The study by Ferrer-Sargues et al.[26] evaluated the muscular strength of the upper limbs through handgrip dynamometry in patients with heart diseases submitted to a cardiopulmonary rehabilitation programme. They showed an increase in muscular strength after rehabilitation.

Respiratory muscle strength

Respiratory muscle strength was assessed in three studies[5,8,37]; two studies were cohort and one cross-sectional. All articles used a manovacuometer as an instrument to obtain values of the isometric strength of the maximum inspiratory and expiratory pressure The three articles included only patients with CHD without healthy controls, and the values obtained were compared to reference values available in the paediatric population. Two studies presented a respiratory muscle training protocol[5,37] and, the third study[8] only presented values regarding the assessment of inspiratory and expiratory muscle strength without proposing a muscle training protocol.

Ferrer-Sargues et al.[5] proposed a paediatric cardiopulmonary rehabilitation programme lasting 70 minutes in a total of 24 supervised sessions. The sessions were structured in five different phases, with respiratory muscle training beginning with a minimum load of 30% of the maximum inspiratory pressure. It was evidenced by an increase in maximum inspiratory pressure in absolute value and percentage predicted after cardiac rehabilitation, as well as its maintenance of values after 6 months of follow-up. On the other hand, the maximal expiratory pressure did not show statistically significant variation after rehabilitation.

The study by Feltez et al.[8] used only the respiratory muscle strength evaluation without intervention or training, finding higher maximum inspiratory pressure and lower maximal expiratory pressure than predicted values in patients with CHD after cardiac surgery. Furthermore, the study cites a relationship between reduced expiratory pressure with impaired left ventricular ejection fraction and low cardiac output, as well as the fact that the low oxygen supply during exercise in patients with CHD can affect muscle strength.

https://doi.org/10.1017/S1047951122003092 Published online by Cambridge University Press

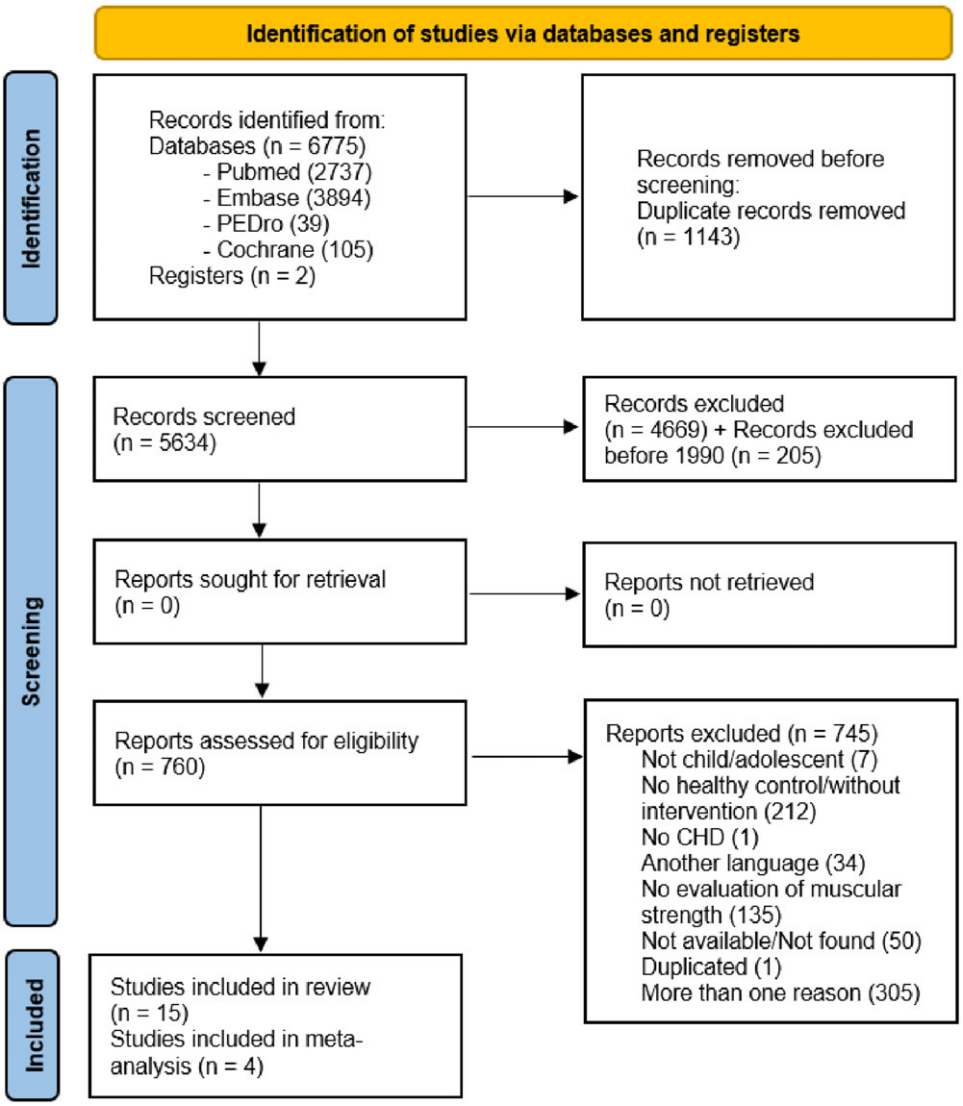

Figure 1. Prisma flow diagram of studies evaluated for systematic review.

Meta-analysis

Three cross-sectional and one cohort study were included in the meta-analysis, with a total of 1202 individuals; of these, 238 had CHD, and 964 were healthy controls. The age of participants ranged from 0 to 18 years. The characteristics of the studies are presented in Table 3. The most frequent cardiac diseases in the studies were tetralogy of Fallot, transposition of the great arteries, hypoplastic right ventricle, hypoplastic left ventricle, tricuspid atresia, pulmonary atresia, atrial septal defect, ventricular septal defect, and CoA. Only one study included patients after the Fontan procedure. In methodological analysis, the majority were classified as "fair" by the quality analysis using the Newcastle-Ottawa Scale, representing a medium risk of bias[25] (Table 4).

The lower limb muscle strength was assessed using a dynamometer in three studies (n = 616). Moalla et al.[33] assessed the isometric strength of the knee extensor muscles using maximal voluntary contraction with a gradual increase in strength lasting 2–3 seconds; Holm et al.[27] evaluated isokinetically knee flexors and extensors muscle strength by using five repetitions at an angular speed of 60° per second; and Sandberg et al.[34] evaluated the peak isometric strength of two muscle groups, namely the knee extensors through the maximum extension with the maintenance of contraction for 5 seconds and the plantar flexors of the ankle with the strongest possible flexion for 5 seconds. In the last study, values of lower limb muscle strength in knee extensors and ankle plantar flexors also were shown; however, for our meta-analysis, we only used the values of knee extensor muscular strength to allow the comparison between the other studies included in this review.

The meta-analysis of muscular strength included only two studies,[33,34] showing a reduction of −34.07 nm in patients with CHD compared with the control group (95% CI, −67.46 to −0.68; I2 47%; p for heterogeneity = 0.05) (Fig 2). Holm et al.[27] used isokinetic analysis, which may have caused the observed high heterogeneity in the results. Therefore, we removed the mentioned study from the meta-analysis, yet, yielding similar results that are a lower muscle strength."

Two studies evaluated isometric handgrip strength using manual dynamometry (n = 1093). Holm et al.[27] performed an assessment on the dominant and non-dominant hands, using one repetition for each. The study by Zaqout et al.[36] evaluated upper limb strength using a score calculated as the average of right and left handgrip strength. The meta-analysis of the handgrip muscle strength showed no significant difference between patients

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Table 1. Characteristics of the studies included in the systematic review.

STUDIES WITH ONLY CHD GROUP						
Author	**Study type**	**Total sample (n)**	**Mean age TG (SD)**	**Mean age CG (SD)**	**Objective**	**Principal Outcomes**
Longmuir et al[31]	Cross-sectional	63	9.1 (Q1 7.7, Q3 10.5)[a]	–	Examine relationships between moderate-to-vigorous physical activity (MVPA) and exercise capacity, gross motor skill, health-related fitness and evaluate parent/child perceptions of physical activity	Handgrip strength and isolated trunk strength Z scores were similar in patients with CHD and healthy controls
Moalla et al[18]	Randomised clinical trial	18	13.0 ± 1.4	12.8 ± 1.3	Investigate the effect of a whole-body physical training programme on muscular performance and on peripheral muscle oxygenation during sustained exercise and recovery in children with CHD	Individualized training programme increases muscle strength and endurance, with increased oxygenation of peripheral muscles in patients with CHD
Longmuir et al[6]	Randomised clinical trial	61	8.6 ± 2.0[b]	9.3 ± 1.3[c]	Compare the level of physical activity increment through exercise prescription and an education programme	No difference by intervention was observed for grip strength as it was considered a secondary outcome. Greater grip strength was associated with older age in child with CHD
Feltez et al[8]	Cross-sectional	48	13.3 ± 4.1	–	Evaluate the exercise capacity of children and adolescents with corrected cyanotic CHD. Secondary objectives included assessment of the respiratory muscle strength, plasma levels of BNP and heart function, as well as the possible association between these variables	Children and adolescents with cyanotic CHD, even after surgical repair, have low submaximal exercise capacity and reduced expiratory muscle strength
Klausen et al[28]	Cross-sectional	158	14.6 ± 1.3	–	Investigate the different health-related fitness (HrF) profiles that exist among girls and boys with complex CHD and how these are associated with lifestyle behaviours	There was variability in cardiorespiratory fitness among adolescents with CHD, and muscle strength was variable among the different groups
Longmuir et al[30]	Cross-sectional	64	9.0 ± 1.7	–	Evaluate the body composition, aerobic endurance, flexibility, and strength of children after Fontan relative to population data for Canadian children	Patients submitted to Fontan procedure demonstrate capacity for daily physical activity associated with a healthy lifestyle, with similar strength to previously healthy patients and good body composition
Laohachai et al[37]	Cohort	23	16 ± 2	–	Assess whether inspiratory muscle training improved inspiratory muscle strength and objective measures of exercise capacity	Respiratory muscle training improves maximal inspiratory pressure, ventilatory efficiency, and resting cardiac output in patients with CHD
McKillop et al[32]	Randomised clinical trial	36	15.28 ± 1.53	14.48 ± 1.56	Evaluate the implementation and acceptability of the adapted motivational intervention and if a new intervention has the capacity of being successful to improve physical activity, physical fitness, and quality of life in a controlled setting	Intervention participants had no improvements in the high self-efficacy or stage of change observed. Participants had comparable outcomes to peers without heart disease (except for functional capacity). There was no significant difference in change in any outcome by group
Ferrer-Sargues et al[5]	Cohort	15	14.4 ± 1.1	–	Evaluate the effect of a cardiopulmonar rehabilitation programme (including respiratory muscle training) on respiratory muscle function, functional capacity, and exercise subjective perception of children with CHD	Overall respiratory muscle strength is reduced in the CHD population. The cardiopulmonary rehabilitation programme can potentially improve respiratory muscle function and functional capacity

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https://doi.org/10.1017/S1047951122003092 Published online by Cambridge University Press

Table 1. (*Continued*)

STUDIES WITH ONLY CHD GROUP						
Zaqout et al[35]	Cross-sectional	66	VSD: 10.9 ± 1.8 COA: 10.2 ± 2.1 TGA:10.4 ± 1.9 TOF: 10.5 ± 1.9	–	Determine factors associated with physical fitness in children with CHD	There were no significant differences in physical activity level by CHD type. Boys had better cardiorespiratory fitness and were more physically active, while girls had better flexibility. Higher motivation for physical activity was associated with stronger upper and lower limbs muscle strength, improved speed, and cardiorespiratory fitness
Ferrer-Sargues et al[26]	Cohort	15	14.4 ± 1.1	–	Evaluate the effect of a systematic cardiopulmonary rehabilitation programme including strength-resistance training on the peripheral muscle function of children with CHD	A substantial and statistically significant improvement was observed in the handgrip strength, biceps brachii and quadriceps femoris strength, as well as triceps surae fatigue process, with a maintenance of the results 6 months after the intervention
STUDIES WITH CONTROL GROUP						
Author	**Study type**	**Total sample (n)**	**Mean age CHD (SD)**	**Mean age HC (SD)**	**Objective**	**Principal Outcomes**
Moalla et al[33]	Cross-sectional	23	13.5 ± 1.8	12.8 ± 1.3	Evaluate if altered oxygen supply to the skeletal muscle could reduce performance in patients with CHD compared to healthy children	Patients with congenital heart disease showed reduced muscle strength and performance compared to controls
Holm et al[27]	Cohort	507	10.3 ± 1.7	10.2 ± 1.7	Explore the extent and type of motor problems in children with complex CHD compared with school-aged children with no known heart failure	The patients showed a significant reduction in muscle strength and an increase in motor problems
Zaqout et al[36]	Cross-sectional	586	10.5 ± 1.9	8.3 ± 1.5	Evaluate the physical fitness status and metabolic health of children with a surgically repaired CHD compared with healthy children	Physical fitness is similar between groups with variations regarding upper and lower limb strength between boys and girls with CHD and control group
Sandberg et al[34]	Cross-sectional	86	12.2 ± 3.9	12.3 ± 4.0	Determine the extent of difference in the isometric muscle strength of the lower limbs in children and adolescents with Fontan circulation in comparison to age- and sex-matched controls	Patients with CHD have compromised isometric knee extension strength compared to controls, with no differences in plantar flexion strength

HC: healthy control; TG: training group; CG: control group; VSD: ventricular septal defect; COA: coarctation of aorta; TGA: transposition of the great arteries; TOF: tetralogy of fallot; BNP: B-type natriuretic peptide
[a]Values in interquartile range.
[b]Activity group (AG).
[c]Education group (EG).

with CHD and healthy peers, with the value of 0.08 nm (95% CI, −6.39 to 6.55; I2 98%; p for heterogeneity <0.00001) (Fig 3).

Discussion

This systematic review and meta-analysis aimed to evaluate the peripheral and respiratory muscle strength of children and adolescents with CHD. The meta-analysis showed a significant reduction in isometric muscular strength in patients with CHD compared to controls and no differences in handgrip muscle strength.

The evaluation of the peripheral muscle strength included different muscle groups, obtaining data related to the strength of lower and upper limbs. Regarding lower limb strength, most of the articles used isokinetic dynamometry as an evaluation method. The studies of Moalla et al.[33] and Sandberg et al.[34] showed reduced values of this variable in comparison with healthy controls in the meta-analysis. On the other hand, Brassard et al.[39] did not find any difference in the muscular strength of children and adolescents submitted to Fontan procedure and their healthy pairs.

Upper limb strength was assessed through isometric handgrip dynamometry in most articles. Zaqout et al.[36] showed a reduction of this variable in boys compared to healthy controls. Other studies, such as those by Longmuir et al.[30,31] showed that upper limb strength does not differ in patients with CHD when compared with values predicted for healthy children. It was possible to perform a meta-analysis of two articles that assessed upper limb muscle strength[27,36] however, we did not find any difference between patients with CHD and healthy controls. However, the high heterogeneity ($I^2 = 98\%$) was a problem, and therefore, this result cannot be extrapolated. We hypothesised that methodological

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Table 2. Characteristics of the studies included in the systematic review without healthy controls.

PERIPHERAL MUSCLE STRENGTH							
Author	Study type	Total sample (n)	Mean age CHD (SD)	Mean age CG[a] (SD)	Outcomes and Evaluation methods	Muscle strength CHD	Muscle strength CG[a]
Longmuir et al[31]	Cross- sectional	63	9.1 (Q1 7.7, Q3 10.5)[a]	–	Grip and trunk strength were assessed as maximum right/left hand (Smedlays dynamometer)	0.19 (Q1 – 0.56, Q3 0.94)[b]	–
Moalla et al[18]	RCT	18	13.0 ± 1.4	12.8 ± 1.3	Isometric strength and endurance of the knee extensors muscles were measured on an isokinetic dynamometer (Cybex Norm II). Muscle strength corresponded to maximal voluntary contraction (MVC)	101.6 ± 14.0	–
Longmuir et al[6]	RCT	61	8.6 ± 2.0[c]	9.3 ± 1.3[d]	Grip strength was evaluated by the total right and left handgrip force	28.3 ± 7.6[c]	23.7 ± 7.9[d]
Klausen et al[28]	Cross- sectional	158	Girls: 14.6 ± 1.3 Boys: 14.6 ± 1.2	x	Muscle strength was measured as handgrip strength by a North Coast Hydraulic Dynamometer (PROcare, Roskilde, Denmark)	Girls: 26.1 ± 4.7 Boys: 30.3 ± 9.4	–
Longmuiret al[30]	Cross- sectional	*64*	9.0 ± 1.7	x	Maximal grip strength was evaluated with Smedlays dynamometer for the right and left hands	26 ± 8	–
McKillop et al[32]	RCT	36	15.28 ± 1.53	14.48 ± 1.56	Grip strength	66.20 ± 19.84 (lb) 30.02 ± 8.99 (kg)	27.10 ± 5.60
Zaqout et al[35]	Cross- sectional	66	VSD: 10.9 ± 1.8 COA: 10.2 ± 2.1 TGA:10.4 ± 1.9 TOF: 10.5 ± 1.9	x	Handgrip strength was evaluated using a Dynamometer (TKK 5101 Grip D Takei). The score was calculated as the average of the right and left handgrip strength	VSD: 17.3 ± 4.4 COA: 15.8 ± 6.3 TGA: 16.0 ± 6.6 TOF: 14.7 ± 6.0	–

Table 2. (*Continued*)

Ferrer-Sargues et al[26]	Cohort	15	14.4 ± 1.1	x	Handgrip strength was evaluated in both hands using a Jamar Plus+® device (Patterson Medical, Sammons Preston, Bolingbrook, IL, USA). The quadriceps femoris strength was evaluated on legs using a dynamometry Lafayette Manual Muscle Tester device (Lafayette, IN, USA)	Dom Handgrip: 24 ± 8.6 N-Dom Handgrip: 21.9 ± 7.9 Dom Quadriceps-femoris: 160.5 ± 40.8 N-Dom Quadriceps-femoris: 152.8 ± 48.3	–		
RESPIRATORY MUSCLE STRENGTH									
Author	Study type	Total sample (n)	Mean age TG (SD)	Mean age CG (SD)	Outcomes and Evaluation methods	MIP (cmH2O)	MIP Predicted (%)	MEP (cmH2O)	MEP Predicted (%)
Feltez et al[8]	Cross- sectional	48	13.3 ± 4.1	x	Respiratory muscle strength was assessed using a digital manovacuometer (Globalmed MVD300), with maximum expiratory pressure and maximum inspiratory pressure	58.2 ± 22.3	111.4 ± 40.0	63.2 ± 23.3	63.0 ± 21.5
Laohachai et al[37]	Cohort	23	16 ± 2	x	Inspiratory and expiratory muscle strength, measured as maximum inspiratory pressure and maximal expiratory pressure at the mouth, were assessed using a MicroRPM respiratory pressure meter (Carefusion). The maximum value of these 3 readings was recorded	69 ± 22	–	67 ± 23	–

(*Continued*)

Table 2. (*Continued*)

RESPIRATORY MUSCLE STRENGTH									
Author	Study type	Total sample (n)	Mean age TG (SD)	Mean age CG (SD)	Outcomes and Evaluation methods	MIP (cmH2O)	MIP Predicted (%)	MEP (cmH2O)	MEP Predicted (%)
Ferrer-Sargues et al[5]	Cohort	15	14.4 ± 1.1	x	Maximum static inspiratory pressure and maximum static expiratory pressure was assessed by a Manovacuometer. Three acceptable and reproducible measurements were made and the highest value was registered	94.3 ± 30.1	81.4 ± 0.2	119.3 ± 32.3	87.3 ± 0.2

CHD: congenital heart disease; HC: healthy control; TG: training group; CG: control group; RCT: randomised clinical trial; VSD: ventricular septal defect; COA: coarctation of aorta; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; BNP: B-type natriuretic peptide.
[a]Values in interquartile range.
[b]Values in Z score.
[c]Activity group (AG).
[d]Education group (EG); isokinetic strength was expressed in newton (n) and newton meters (Nm); handgrip strength was expressed in kilograms (Kg); Dom: dominant; N-Dom: non-dominant.

Table 3. Characteristics of the studies included in the meta-analysis.

Author	Study type	CHD subtype	CHD (n)	CG (n)	Mean age of CHD (SD)	Mean age of CG (SD)	Male/ Female CHD	Male/ Female CG	Outcomes and Evaluation methods	Muscle strength CHD	Muscle strength CG
Moalla et al[33]	Cross-sectional	TGA: 4 PA: 2 TOF: 2 ASD: 1	9	14	13.5 ± 1.8	12.8 ± 1.3	6/3	9/5	Isokinetic dynamometer (Dynamometer Cybex Norm II) – Measure of isometric strength of the knee extensors through MVC (Gradual increase in force lasting 2–3s)	101.0 ± 6.2[a]	125.5 ± 7.4 [a]
Holm et al[27]	Cohort	TOF: 29 TGA: 32 HRV/HLV:18 TA: 3 Others: 38	120	387	10.3 ± 1.7	10.2 ± 1.7	74/46	188/199	Isokinetic dynamometer (Dynamometer Cybex 6000) – Measure of isokinetic strength of the knee extensors and flexors through five repetitions at an angular velocity of 60° per second.	14.8 ± 4.83 [a]	18.0 ± 5,22 [a]
									Grip strength (Dynamometer Jamar) – Measure of grip strength of the dominant and non-dominant hands with 1 repetition for each hand.	219 ± 106.3 [b]	278.8 ± 112.6[b]
Zaqout et al[36]	Cross-sectional	VSD: 19 COA: 10 TOF: 22 TGA: 15	66	520	10.5 ± 1.9	8.3 ± 1.5			Grip strength (Dynamometer TKK 5101 Grip D (Tokio) – Measure of the upper limb through the average of right and left handgrip strength.	16.0 ± 5.9 [b]	12.6 ± 3.0 [b]
Sandberg et al[34]	Cross-sectional	Fontan	43	43	12.2 ± 3.9	12.3 ± 4	24/19	24/19	Isokinetic dynamometer (Dynamometer Anyload VETEK 0-5000 n) – Measure of isometric muscle strength of the knee extensors through the maximum contraction for 5 seconds.	221.8 ± 100.7 [a]	286.2 ± 160.7 [a]

CG: control group; TGA: transposition of the great arteries; PA: pulmonary atresia; TOF: tetralogy of Fallot; ASD: atrial septal defect; VSD: ventricular septal defect; COA: coarctation of aorta; HRV: hypoplastic right ventricle; HLV: hypoplastic left ventricle; TA: tricuspid atresia; MVC: maximal voluntary contraction

[a]Nm: newton meters

[b]N: newton.

Table 4. Evaluation of methodologic quality of studies and risk of bias with Newcastle-Ottawa Scale.

NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE				
COHORT STUDIES				
	Selection	Comparability	Outcome	Total Stars
Holm et al, 2007[27]	**	*	***	6
Ferrer-Sargues et al, 2020[5]	***	*	***	7
Ferrer-Sargues et al, 2021[26]	***	*	***	7
CROSS-SECTIONAL STUDIES				
	Selection	Comparability	Outcome	Total Stars
Moalla et al, 2006[33]	**	*	**	5 fair
Zaqout et al, 2017[36]	***	*	**	6
Sandberg et al, 2020[34]	***	*	**	6
Longmuir et al, 2011[31]	*	*	**	4
Moalla et al, 2012[18]	*	*	**	4
Feltez et al, 2015[8]	*	*	**	4
Klausen et al, 2015[28]	**	*	**	5
Longmuir et al, 2015[30]	*	*	**	4
Zaqout et al, 2021[35]	**	*	**	5
Laohachai et al, 2017 [37]	***	*	**	6
Longmuir et al, 2013[a] [6]	*	*	**	4
McKillop et al, 2018[a] [32]	*	*	**	4

[a]Randomised clinical trial studies with baseline data used for evaluation.

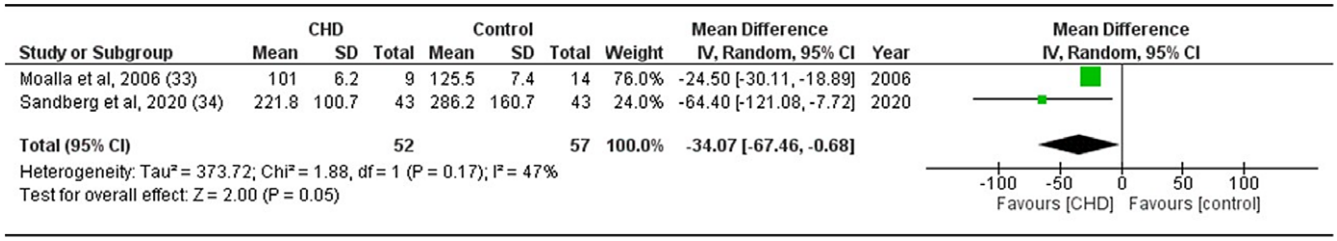

Figure 2. Meta-analysis of isometric muscle strength in children and adolescents with CHD and controls.

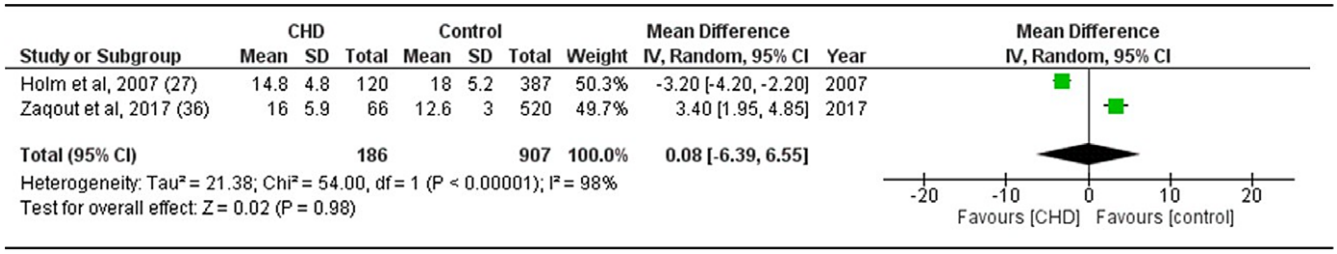

Figure 3. Meta-analysis of handgrip strength in children and adolescents with CHD and controls.

differences could explain the results in different ways. Holm et al.[27] analysed one repetition for each in dominant and non-dominant hands without explaining which value was chosen. Zaqout et al.[36] analysed a score between the right and left handgrip average. Another explanation could be that these patients perform more activities with their upper limbs and that this variable would not be appropriate to represent a global force in this population. Therefore, future studies need to be performed to highlight the behaviour of the handgrip muscle.

Turquetto et al.[40] evaluated patients aged 12 and 30 years with a 5-year follow-up after Fontan surgery and observed that handgrip strength was reduced in cardiac patients, along with variables related to exercise capacity. Moreover, Rego et al.[41] estimated handgrip muscle strength in hospitalised children with cardiac

https://doi.org/10.1017/S1047951122003092 Published online by Cambridge University Press

disease before surgery and revealed a reduction in 96.6% of cases. Compared with our study, this difference in results can be explained by the fact that most of the studies included in our meta-analysis were conducted on patients after surgery.

The reduction in peripheral muscle strength can be multifactorial and related to negative prognostic factors that significantly impact motor development and performance of physical activities, as well as in relation to psychosocial factors. Brandlistuen et al.[38] concluded that children with severe CHD significantly increased the odds of gross and fine motor and social impairment, per example.

Four articles in this review showed that muscular strength was similar to reference values in literature.[6,30–32] We found some studies in the literature using these values from healthy populations for the evaluation of muscle strength. This can be seen in the survey by Fricke et al.[42] which evaluated adolescents and young adults with CHD, showing reduced handgrip strength compared to the predicted values. The reference values and predictive equations for isokinetic strength and handgrip strength in a healthy paediatric population were described by Wiggin et al.[43] and McQuiddy et al.[44] However, there have been few studies that make comparisons between patients with CHD and healthy controls, which is an essential method of assessment to establish a more reliable standard for different populations. In this way, more studies with this methodology are required.

The articles included in our review showed different types of CHD and patients undergoing Fontan surgery. To date, little evidence has been found evaluating muscle strength in various types of CHDs, which makes it difficult to extrapolate the data obtained in this study to the entire cardiac population. Only one article stratified the patients according to the type of heart disease without presenting significant differences regarding the levels of physical activity, muscle strength, and exercise capacity.[35] The study conducted by Banks et al. (45) showed similar results, indicating that the degree of complexity or the type of CHD does not influence muscle strength. The majority of the studies included in this systematic review did not stratify data by sex or age. Only one study by Klausen et al.[28] showed separate peripheral muscle strength results for boys and girls. This may suggest that patients with CHD, regardless of sex or age, already present a global deficit in relation to muscle strength, differently from what is expected for the healthy population, where boys tend to have greater muscle strength. A study by Fredriksen et al.[46] showed similar results, in which there was no difference regarding the levels of physical activity, age, and sex in patients with CHD and their healthy controls.

The articles that evaluated respiratory muscle strength[5,8,37] used manovacuometry to measure isometric maximum inspiratory pressure and maximal expiratory pressure. Two studies observed a reduction in maximum inspiratory pressure and maximal expiratory pressure[5] and only one in the maximal expiratory pressure.[8] The studies by Laohachai et al.[37] and Ferrer-Sargues et al.[5] evaluated the respiratory muscle strength associated with rehabilitation programmes, the first one through a home-based inspiratory muscle training programme where an increase in muscle strength was associated with an increase in ventilatory efficiency and cardiac output at rest. The second one observed an increase in maximum inspiratory pressure compared to predicted values and after a 3-month cardiopulmonary rehabilitation, but no significant difference was found in maximal expiratory pressure values. These findings may be due to the choice of training protocol, in which the workload should be between 30 and 70% of baseline maximum inspiratory pressure.

The study by Feltez et al.[8] was the only one that did not propose a rehabilitation or muscle training programme. A reduction in maximal expiratory pressure was associated with lower exercise capacity but without correlation with the 6-minute walk test and ventricular ejection fraction values. Turquetto et al.[47] found a significant reduction only in maximum inspiratory pressure, both in males (63% of predicted values) and females (71% of predicted values). Greutmann et al.[17] showed similar results, with a reduction of maximum inspiratory pressure in the CHD group, as well as a significant correlation between maximum inspiratory pressure and peak VO_2; however, the population was adults with CHD. The reduction in respiratory muscle strength and the correlation with exercise capacity may indicate that patients with CHD usually remain with cardiopulmonary alterations that influence the practice of physical activity and muscular performance.

We observed that two articles that evaluated the respiratory muscle strength included in this review found a reduction of this variable, as well as an association with rehabilitation or muscle training programmes. The pilot study by Wu et al.[48] corroborates these findings, showing that in adult Fontan patients, there is a trend toward a higher peak of maximal oxygen consumption (VO_2) and improved ventilatory efficiency after 12 weeks of inspiratory training. Therefore, periodic evaluation and implementation of rehabilitation programmes could promote the reversal of cardiorespiratory limitations. However, more studies are needed to confirm these results, especially in paediatric patients.

Additionally, the articles in this systematic review did not speculate about body mass index, stature, and body size. Until today, these associations do not entirely explain differences between children with CHD and healthy peers.[49] Although this could be interpreted as a limitation of our systematic review, we did not find evidence in the methodological analysis of the included original papers.

In conclusion, this systematic review showed reduced peripheral and respiratory muscular strength in children and adolescents with CHD. Our meta-analysis showed that children and adolescents with CHD had lower isometric muscle strength evaluated by an isokinetic dynamometer. We did not find any difference in handgrip muscle strength. In addition, a lower respiratory muscular strength was found in qualitative analysis, yet no meta-analysis was possible to perform. Further research with higher methodological quality and a larger sample size is still necessary to clarify peripheral and handgrip muscle strength and the possible relation with exercise capacity.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflicts of interest. None.

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