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A systematic review and meta-analysis of school and cognitive function domains of health-related quality of life measures for children and young adults with congenital heart disease

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Abstract

Background: Research on cognitive and school functioning domains of health-related quality of life (HRQOL) for children and adolescents with congenital heart disease (CHD) presents inconsistencies.

Objectives: To summarize and synthesize data on school and cognitive function domains of HRQOL for children and young people (CYP) with CHD.

Methods: Five electronic databases MEDLINE, Scopus, PsycINFO, EMBASE, ERI, and citations were systematically searched. We included original-research articles reporting the cognitive and school function domains of HRQOL for children and young people with CHD (child and parent reports included). Both fixed and random-effects meta-analyses were performed to estimate pooled mean test scores for cognitive and school function. A total of 34 studies met our inclusion criteria and were synthesized narratively, 17 studies were included in formal meta-analyses.

Results: Self-reported cognitive function was lower for children and young people with CHD than healthy controls (SMD −0.28 (−0.42, −0.15)). Parental reports demonstrated similar results to self-reports (SMD −0.54 (−0.91, −0.18)). School function was lower in children and young people with CHD compared with healthy controls in self-reported (SMD −0.30 (−0.48, −0.13)) and parent reported HRQOL (SMD −0.49 (0.64, −0.36)). Self-reported school function domain scores were lower for young (<8 years) (SMD −0.65 (−1.32, 0.03)) and older children (8–18 years) (SMD −0.25 (−0.47, −0.03)) with CHD than their peers. Similarly, parents reported lower school function domain scores for young (<8 years) (SMD −0.68 (−1.29, −0.07)) and older (8–18 years)

(SMD −0.46 (−068, −0.25)) children with CHD than typically developing peers.

Conclusion: Children born with CHD may experience lower cognitive and school function HRQOL scores than healthy controls (self and proxy-report). This is consistent with a subgroup meta-analysis of young (<8 years) and older (8 years old or more) children with CHD reporting lower school function scores compared to controls.

KEYWORDS

CHD, cognitive function, HRQOL, meta-analysis, school function

1 | INTRODUCTION

Congenital anomalies (CA) are structural or functional anomalies that occur during intrauterine life. Congenital heart disease (CHD) is one of the most common groups of congenital anomalies (Jenkins et al., 2007) and the total prevalence varies by region and over time (Mamasoula et al., 2022). Over the past three decades, survival rates of children born with congenital anomalies including CHD have increased due to advances in neonatal care and surgical interventions (Erikssen et al., 2015; Glinianaia et al., 2020), therefore an increasing number of these children are reaching school age. Evidence also suggests that children with CHD are at greater risk of cognitive impairments and special education needs (SEN) and are more likely to achieve poor academic results compared to their typically developing peers (Oster et al., 2017). These are thought to be caused by a poor oxygen supply during infancy, which affects brain development (McQuillen et al., 2010). However, other factors such as prolonged hospital length of stay and perioperative seizures related to CHD surgery have been shown to be associated with poor cognitive outcomes (Marino et al., 2012). Also, many milder forms of CHD (e.g., ventricular septal defect and atrial septal defect) do not need surgery and do not produce symptoms in the brain in early infancy but may be identified later in childhood. Based on previous research, testing methods take time, are not cost-effective for the entire CHD population and the prevalence of cognitive impairments has been thought to be low in other severity groups (Oster et al., 2017). However, as more evidence on health related quality of life (HRQOL) of children with CHD is being generated internationally, it is important to review cognitive and school functioning among children with CHD, especially those with mild/moderate forms, to investigate if strategies to support children with CHD in their academic life are required.

Cognitive and school functioning are important aspects of young people's HRQOL, which is defined as "an individual's or a group's perceived physical and mental health over time" (CDC, 2023). 'Cognitive function' is a broad term that refers to mental processes involved in the acquisition of knowledge, manipulation of information and reasoning. It includes the domains of perception, memory, learning, attention, decision making, language abilities and is positively correlated with school performance (Dick & Pillai, 2010). 'School function' is considered to be "a wide range of factors including school attendance, academic achievement, and social relationships" (Dick & Pillai, 2010).

In this review, we focused on the cognitive and school functioning of HRQOL of children and young people with CHD. Various validated HRQOL instruments have been used in the literature to measure HRQOL in children with chronic health conditions such as CHD, with the Pediatric Quality of Life Inventory (PedsQL) being used most frequently (Varni et al., 1999). Full details of the instruments are described in Section 2. In comparison with other instruments, the PedsQL is brief, resulting in minimal missing data and separate versions are available to allow both parent's and child's perspectives across childhood, from 2 to 18 years of age, although very young children cannot self-report. A further advantage of the PedsQL is that a large normative database of results from ethnically diverse healthy children and children with chronic diseases has been developed using the tool, which allows the evaluation of differences between specific pediatric populations (Oberhuber et al., 2020). A second measure, the KIDSCREEN, is also a reliable and valid HRQOL measure (The Kidscreen Group, 2010). The KIDSCREEN-27 proxy questionnaire which is appropriate for those aged between 8 and 18 years (using a 5-point Likert-scale) measures five HRQOL dimensions, while the KIDSCREEN-52 self-questionnaire for those aged between 8 and 18 years measures 10 dimensions.

There is a positive correlation between the PedsQL 4.0 and the KIDSCREEN-27 scales for the majority of the subscale scores, except in the case of the social factor subscale. The correlation between the PedsQL 4.0 and KIDSCREEN-52 dimensions were high for the assessments of similar constructs but low between the "school environment" (KIDSCREEN-52 HRQOL dimension) and the "school functioning" (PedsQL 4.0 HRQOL scale) as well as between the "social support" (KIDSCREEN-52 HRQOL dimension) and "peers and the social functioning" (PedsQL 4.0 HRQOL scale) domains.

There is a positive linear relationship between the PedsQL 4.0 and the KIDSCREEN-27 scales for school factor subscale, in which the rank correlation coefficient ($r = 0.34$) was statistically different from zero (Amaya-Arias et al., 2017). The KINDL is a further standardized questionnaire for evaluating children's HRQOL (Ravens-Sieberer & Bullinger, 1998). However, all constructs measured by KINDL are either not present in PedsQL or are dispersed in some of its subscales. When PedsQL 4.0 is compared to KINDL, low to moderate correlations between the two measures were found (Ferreira et al., 2014).

Research on cognitive and school functioning for children and young people with CHD presents inconsistencies. Some meta-analyses (Feldmann et al., 2021; Karsdorp et al., 2007) have used a variety of different measures with high levels of heterogeneity between the studies. Particularly, Karsdorp et al. (2007) found that children and young people with severe CHD exhibited lower cognitive function compared with less severe CHD (self-report) and may be explained by the fact that severe CHD is associated with risk factors such as acquired cognitive impairments and congenital brain anomalies. This meta-analysis (Karsdorp et al., 2007) based on 25 studies used a variety of IQ measures such as the British Ability Scale (Elliot, 1983), Wechsler Intelligence Test for Children (Wechsler, 1991), and McCarthy Scales of Children's Abilities (McCarthy, 1972). However, IQ measures are objective and test the development of different areas of cognition. For example, in the Wechsler Intelligence Test for children there are five index scores: verbal comprehension; visual spatial; fluid reasoning; working memory; and processing speed. Cognitive functioning measure based on the PedsQL 3.0 Cardiac module includes severity of perceived difficulties in writing and solving maths problems; difficulty in figuring out what to do when something bothers; maintaining attention; remembering things; and thinking quickly. Similarly, a recent meta-analysis by Feldmann et al. (2021) using IQ measures based on the following cognitive outcomes: total IQ, verbal IQ, and performance IQ (Wechsler Intelligence Scale performance) found consistent evidence for an impairment in cognitive function outcomes in school aged children with complex CHD. However, caution is needed in the interpretation of the results as the heterogeneity between the studies was large and might limit the strength of the findings.

Also, some other meta-analyses (Ladak, Hasan, Gullick, & Gallagher, 2019; Schrøder et al., 2016) have used a combination of different HRQOL questionnaires, although the meta-analyses (Ladak, Hasan, Gullick, & Gallagher, 2019) addressed this by grouping the same type of questionnaire. Therefore, a further meta-analysis using the same type of HRQOL questionnaires is needed.

This systematic review and meta-analysis of published HRQOL studies aimed to investigate if the cognitive and school functioning domains of HRQOL for children and young people with CHD differs from healthy children.

2 | METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021). A protocol for this systematic literature review was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (reference: CRD42016037846).

2.1 | Search strategy and study selection

We developed a systematic search strategy in consultation with an information specialist at the Population Health Sciences Institute, Newcastle University. We conducted comprehensive literature searches using electronic bibliographical databases. We developed search terms and subject headings for MEDLINE (Figure 1) and we translated across four other databases: Scopus, PsycINFO, EMBASE, ERIC. Combinations of keywords and search terms including: "congenital heart disease", "quality of life", "health-related quality of life" were used. The search strategy is presented in Table S1.

When relevant studies were identified and subsequently included in the review, we manually searched reference lists to identify additional references. We performed citation searching on all included studies (via Google scholar). We also checked for relevant systematic reviews registered in PROSPERO.

We undertook keyword searches in June 2022 in the following key journals: Cardiology in the Young, Birth Defects Research, Pediatric and Perinatal Epidemiology, Pediatrics, and PLOS Medicine. We also contacted an

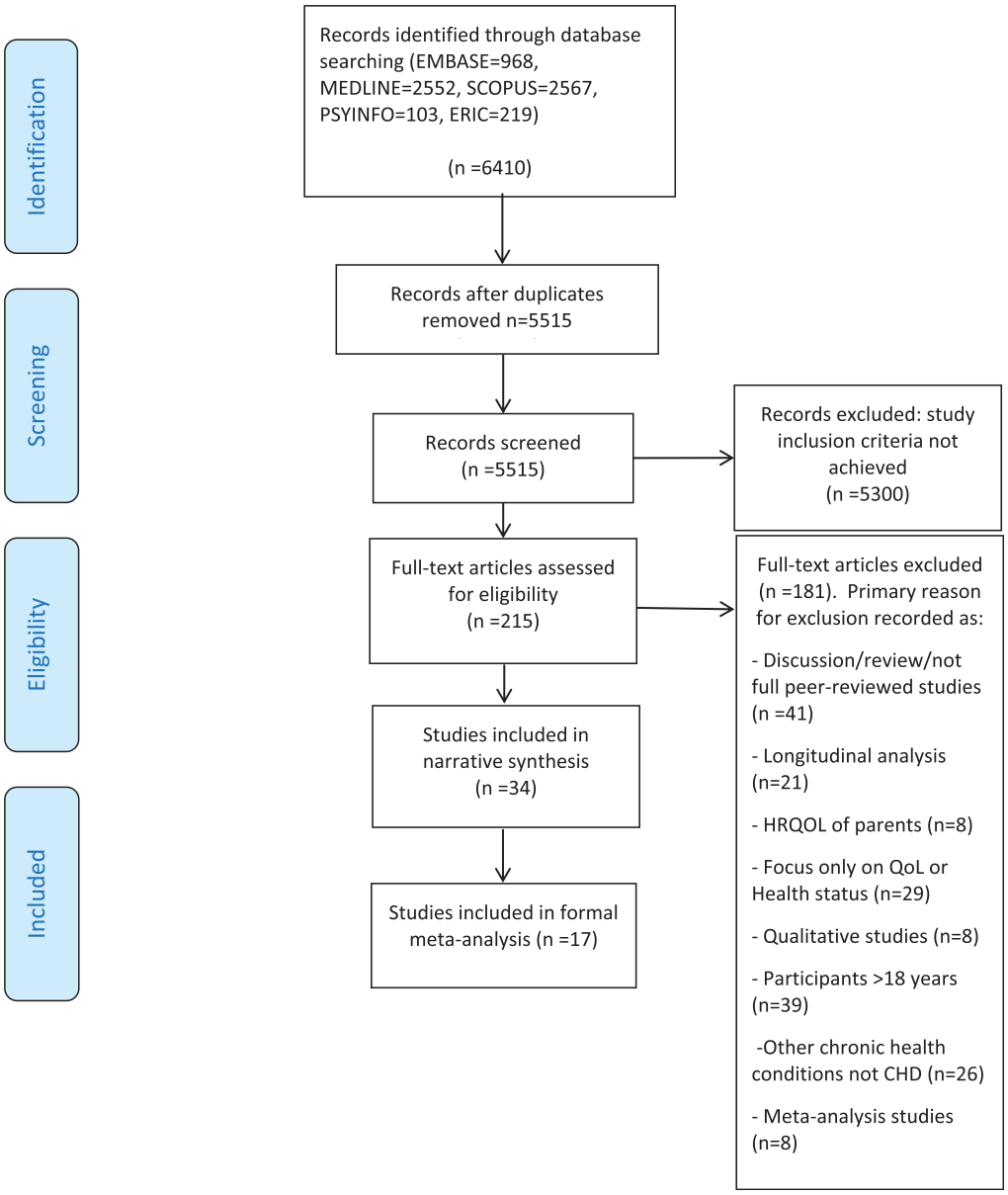


FIGURE 1 Flow diagram of results.

author of one of the included studies for additional clarification and the information received in the response was included in the review.

VM undertook all searches. After excluding duplicates, VM screened all titles and abstracts based on the inclusion criteria (see below). If the eligibility of an article was not possible to clarify from the title or abstract, we retrieved the full text for investigation. A second researcher (AMA) independently screened a random 20% sample of records using the Rayyan software for systematic reviews (Ouzzani et al., 2016) to ensure consistency in study selection. Any identified disagreements about the eligibility of the studies were discussed between the two investigators and resolved by consensus. All searches (including citation searching) were completed by August 2022.

2.2 | Eligibility criteria

Relevant studies were included after full text screening if: (1) they were original research—quantitative (prospective, cross-sectional, cohort, and case–control), peer-reviewed full studies, reporting the cognitive and school function domains of any HRQOL instrument relevant for children and young people with CHD. If a study included other CAs, then data for the relevant CHD population were extracted; (2) the study reported quantitative measurements using any validated measures of HRQOL such as the PedsQL 4.0 Generic Core Scales/PedsQL 3.0 Cardiac Module screening tool in children and young people with CHD versus healthy controls or mild/moderate versus severe CHDs (based on EUROCAT classification (EUROCAT, 2022)) (Table 1);

TABLE 1 General characteristics of HRQOL measures: validated age range, how to report, rating scale, number of items, number and titles of the domains.

Measure	Age in years	Report	Rating scale	Number of items	Number of domains	Titles of domains	Specific items
KIDSCREEN-52	8–18	Self	5-point Likert scale	52	10	Physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, parent relations and home life, social support and peers, school environment, social acceptance (bullying), and financial resources	The school environment dimension (six items) reflects adolescent's perceptions of their learning and concentration and their enjoyment of school
KIDSCREEN-27	8–18	Proxy	5-point Likert scale	27	5	Physical well-being, psychological well-being, autonomy and parent relations, social support and peers, school environment	The school environment dimension (four items) reflects children's perceptions of their attention, experience of school and relationship with teachers
PedsQL 3.0 Cardiac	2–18	Proxy or self	3- or 5-point Likert scale	27	6	Heart problems, treatment, perceived physical appearance, treatment anxiety, cognitive problems and communication	The cognitive functioning items (five items) include: problems with writing and solving maths problems, difficulty to figure out what to do when something bothers, difficulty maintaining attention and remembering things
PedsQL 4.0	2–18	Proxy or self	3- or 5-point Likert scale	23	4	Physical functioning, emotional functioning, social functioning and school functioning	The school functioning score (five items) include: paying attention in class, forgetting things, keeping up with schoolwork, missing school to go to the hospital/doctor or not feeling well
KINDL-R	4–16	Proxy or self	5-point Likert scale	24	6	Physical health, general health, family functioning, self-esteem, social functioning, school functioning	The school functioning domain include doing the schoolwork was easy, I found school interesting, I worried about my future, I worried about getting bad marks or grades
TACQOL	6–15	Proxy or self	3- and 4-point	56	7	Physical functioning, autonomy, motor functioning, cognitive	The cognitive functioning items include difficulties paying

(Continues)

TABLE 1 (Continued)

Measure	Age in years	Report	Rating scale	Number of items	Number of domains	Titles of domains	Specific items
			Likert scale			functioning, social functioning, positive emotions and negative emotions	attention or concentrating, difficulty understanding schoolwork and what others said, difficulty with arithmetic, reading, writing and learning, difficulty in saying what he/she meant

(3) they included children and adolescents (≤18 years old); (4) published between January 1946 and June 2022; (5) published in the English language as resource for translation was not available. We note studies in other languages in our reporting, but these were not included in the initial search strategy. No geographical, timescale or other restrictions were used.

Studies were excluded if they were: (1) conference abstracts, reviews, cases reports, letters to the editor, qualitative studies; (2) intervention studies or meta-analysis; (3) restricted to adults >18 years old; (4) data on participants with CHD could not be disaggregated. Articles not meeting the eligibility criteria were excluded and those meeting the inclusion criteria were selected for full-text review (Figure 1).

2.3 | Data extraction and quality appraisal

VM extracted data and assessed the quality of full-text studies selected for review. AMA extracted data for a random 20% sample. We developed and piloted a data extraction form with two included studies. The data extraction form included: information on citation, study country of origin, year of publication, aim of the study, study design characteristics, study sample [CHD vs. non-CHD/severe CHD vs. no severe CHD (as defined by authors)], sample size, HRQOL instrument, age group, child and/or whether a parent provides a response on behalf of the child (proxy response), key findings, and study outcomes (mean, *SD*).

We used the Critical Appraisal Programme (CASP) quality assessment tool (Table 2) to assess the methodological quality of the included studies as it is the most commonly used tool for quality appraisal in health-related evidence synthesis (Critical Appraisal Skills Programme, 2022). Full details for the CASP criteria are referred to in Table 2. Any discrepancies were discussed between the two researchers and agreement reached.

Studies were further grouped according to participants' age (young children (<8 years) and older children (8–18 years)) and whether child and/or parent report.

2.4 | Data synthesis and statistical analysis

We performed a narrative synthesis of the included studies. Where more than two studies (Valentine et al., 2010) reported data in the same way, a meta-analysis was performed to estimate the pooled effect estimate with a 95% confidence interval. We explored between-study heterogeneity graphically using forest plots and statistically assessed using the I^2 statistic, a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error. We considered statistical heterogeneity to be substantial when I^2 was approximately 50% (Higgins et al., 2003). If between-study heterogeneity was low as measured by I^2 (25%), we adopted a fixed-effect meta-analysis, otherwise the DerSimonian–Laird's random effects model was adopted. A negative standardized mean difference (SMD) and a lower mean score indicated lower HRQOL on the specific domain. We assessed the possibility of publication bias visually using funnel plots and formally tested for this using Egger's and Begg's tests (Egger et al., 1997; Begg & Mazumdar, 1994). We performed the analysis in Stata V.16 (StataCorp), and $p < .05$ was considered statistically significant.

TABLE 2 CASP critical appraisal of studies included in this review ($n = 34$).

CASP criterion[a]															
First author (year of study)	**1**	**2**	**3**	**4**	**5a**	**5b**	**6a**	**6b**	**7**	**8**	**9**	**10**	**11**	**12**	**Total score[b]**
Krol et al. (2010)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Grootenhuis et al. (2007)	2	2	2	2	2	1	2	2	2	2	2	2	2	2	27
Cohen et al. (2007)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Uzark et al. (2008)	2	2	2	1	2	2	2	2	2	2	2	2	2	2	27
Varni et al. (2007)	2	2	2	2	2	2	1	2	2	2	2	2	2	2	27
Brosig et al. (2007)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Landolt et al. (2008)	2	2	2	2	1	2	2	2	1	2	1	2	2	2	25
Berkes et al. (2010)	2	2	2	2	2	1	2	2	2	2	2	2	2	2	27
Tahirović et al. (2010)	2	2	1	2	1	2	2	2	2	2	1	2	1	2	24
Kwon et al. (2011)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Idorn et al. (2013)	2	2	2	1	2	2	2	2	2	2	2	2	2	2	27
Gracia Guerra et al. (2013)	2	2	2	2	2	2	2	2	2	1	2	2	2	2	27
Garcia Guerra et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	2	1	2	27
Eagleson et al. (2013)	2	2	1	2	2	2	2	2	2	2	2	1	2	2	26
Mueller et al. (2013)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Bertoletti et al. (2015)	2	2	2	2	2	2	2	2	2	2	1	1	1	1	24
Mellion et al. (2014)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Knowles et al. (2014)	2	2	2	2	2	1	2	2	2	2	2	2	2	2	27
Spijkerboer et al. (2006)	2	2	2	2	1	1	2	2	2	2	2	2	2	2	26
Amedro et al. (2015)	2	2	2	2	2	1	2	2	2	2	2	2	2	1	26
Ong et al. (2017)	2	2	2	2	2	1	2	2	2	2	2	2	2	2	27
Reiner et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Raj et al. (2018)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Ladak, Hasan, Gullick, and Gallagher (2019) and Ladak, Hasan, Gullick, Awais, et al. (2019)	2	2	2	2	2	2	2	1	2	2	2	2	2	2	27
Ruggiero et al. (2018)	2	2	2	2	2	1	2	2	2	2	2	2	2	2	27
Sertçelik et al. (2018)	2	2	1	2	2	2	2	2	2	2	2	2	1	2	26
Xiang et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Denniss et al. (2019)	2	2	2	2	2	1	2	2	2	1	2	2	2	2	26
Raj et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Holst et al. (2019)	2	2	2	2	2	2	2	2	2	2	2	1	2	2	27
Lee et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Saavedra et al. (2020)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	28
Abassi et al. (2020)	2	2	2	2	2	2	1	1	2	2	2	2	2	2	26
Oberhuber et al. (2020)	2	2	2	2	2	1	2	2	2	2	2	2	1	1	25

[a]CASP criterion: 1. Did the study address a clearly focused issue? 2. Was the cohort recruited in an acceptable way? 3. Was the exposure accurately measured to minimise bias? 4. Was the outcome accurately measured to minimise bias? 5a. Have the authors identified all important confounding factors? 5b. Have they taken account of the confounding factors in the design and/or analysis? 6a. Was the follow up of subjects complete enough? 6b. Was the follow up of subjects long enough? 7. What are the results of this study? 8. How precise are the results? 9. Do you believe the results? 10. Can the results be applied to the local population? 11. Do the results of this study fit with other available evidence? 12. What are the implications of this study for practice?

[b]CASP critical score: (a) criterion is completely met = 2; (b) criterion is partially met = 1; (c) criterion not applicable, not met, or not mentioned = 0; total score 28 = high quality; 16–27 = moderate quality; ≤15 = low quality.

2.5 | HRQOL instruments measuring school and cognitive functioning dimensions

From the included studies, we identified the following validated HRQOL instruments that measure HRQOL in children with CHD:

1. The PedsQL 4.0 generic module which evaluates four dimensions: physical functioning (8 items); emotional functioning (5 items); social functioning (5 items), and school functioning (5 items) for a total of 23 items using a 5-point Likert scale. Higher scores indicate better HRQOL. The PedsQL scales are composed of parallel child report and parent report formats while the content is similar across formats. Child report includes ages 5–7 years (young children), 8–12 years (children), and 13–18 years (teenagers). The parent reports include ages 2–4 (toddlers), 5–7 (young children), 8–12 (children), and 13–18 years (teenagers) as well (Varni et al., 1999). The school functioning score (paying attention in class, forgetting things, keeping up with schoolwork, missing school to go to the hospital/doctor or not feeling well) could not be calculated for the children who did not attend school.
2. The KIDSCREEN-27 proxy questionnaire (using a 5-point Likert-scale) measures five HRQOL dimensions: physical well-being (5 items); psychological well-being (7 items); autonomy and parent relations (7 items); social support and peers (4 items); and school environment (4 items) (The Kidscreen Group, 2010). The school environment dimension reflects children's perceptions of their attention, experience of school and relationship with teachers.
3. The KIDSCREEN-52 questionnaire designed for children and adolescents aged between 8 and 18 years, measures 10 dimensions: physical well-being; psychological well-being; moods and emotions; self-perception; autonomy; parent relations and home life; social support and peers; school environment; social acceptance (bullying); and financial resources. The school environment dimension (6 items) reflects adolescents' perceptions of their learning and concentration and their enjoyment of school (The Kidscreen Group, 2010). HRQOL score is calculated from each dimension and ranges from 0 to 100. Higher scores indicate better HRQOL.
4. The KINDL-R standardized questionnaire evaluating children's HRQOL (Knowles et al., 2014). The "Kiddy" version was used for parents with children between the ages of 4 and 7 years, the "Kid" version for parents and children 8–12 years of age and the "kiddo" questionnaire for adolescents 12–16 years old. The KINDL-R questionnaire contains a subjective scoring system using 24 items among six domains: physical health; general health; family functioning; self-esteem; social functioning; and school functioning (which includes the following items: doing the schoolwork was easy, I found school interesting, I worried about my future, I worried about getting bad marks or grades). Raw scores are converted to a scale of 0–100, with higher scores denoting higher HRQOL.
5. The PedsQL 3.0 Cardiac Module was developed to identify HRQOL specific to cardiac problems. It has 27 items scored using a 5-point Likert scale (Varni et al., 1999). Higher scores indicate better HRQOL. The PedsQL 3.0 focuses on the domains of heart problems (7 items); treatment (5 items); perceived physical appearance (3 items); treatment anxiety (4 items); cognitive problems (5 items); and communication (3 items). The cognitive functioning items include problems with writing and solving maths problems, difficulty to figure out what to do when something bothers, difficulty maintaining attention, and remembering things.
6. The TNO-AZL Child Quality of Life Questionnaire (TACQOL) is a generic instrument, designed to assess general aspects of HRQOL of children aged 6–15 years (Vernps et al., 1998). Higher scores represent a better HRQOL. The instrument contains seven domains of eight items each: physical functioning; autonomy; motor functioning; cognitive functioning; social functioning; positive and negative emotions. The cognitive functioning items include difficulties paying attention or concentrating, difficulty understanding schoolwork and what others said, difficulty with arithmetic, reading, writing and learning, difficulty in saying what he/she meant. A summary of the general characteristics of HRQOL measures is presented in Table 1. As school and cognitive function HRQOL are operationalized differently by each instrument, the tools are measuring different facets of the two constructs. Therefore, the challenges encountered while conducting a HRQOL meta-analysis include the diversity of HRQOL instruments. As previous meta-analysis (Ladak, Hasan, Gullick, & Gallagher, 2019; Schrøder et al., 2016) included several different HRQOL questionnaires, our systematic literature review and meta-analysis plan to address this by using the same HRQOL questionnaire within each subgroup meta-analysis.

In this analysis, we report the school and cognitive function domains of the HRQOL using the PedsQL questionnaire and for this analysis we have selected studies based on whether they include child or parent report.

TABLE 3 Characteristics of studies included in the review by year of publication.

First author name	Study country of origin	Year	Study design	Child and/or parent response	Assessment instrument	CHD subtype	Study sample	Sample size	Participant's age	Study outcomes
Krol et al. (2010)	Netherlands	2003	N/a	Child and parent	TACQOL	CHD (by severity)	Cases versus controls (child/parent proxy report)	Cases = 100 and controls = 181	8–18 years	Mean (*SD*)
Grootenhuis et al. (2007)	Netherlands	2006	N/a	Child	TACQOL	CHD	Cases versus controls	Cases = 50 and controls = 913	8–11 years	Mean (*SD*)
Cohen et al. (2007)	Israel	2007	N/a	Child	TAAQOL-CHD	CHD (by severity)	Cases versus controls	Cases = 90 and controls = 87	12–18 years	Mean (*SD*)
Uzark et al. (2008)	USA	2007	N/a	Child and parent	PedsQL 4.0	CHD (by severity)	Cases versus controls	Cases = 250 and parents = 500	2–18 years	Mean (*SD*)
Varni et al. (2007)	USA	2007	N/a	Child and parent	PedsQL 4.0 and PedsQL 3.0	CHD (by severity)	Cases versus controls and compare severity	Cases = 426 and controls = 9566	2–18 years	Mean (*SD*)
Brosig et al. (2007)	USA	2007	Cohort	Parent	PedsQL 4.0	HLHS and TGA	HLHS versus TGA	Cases = 26	3–6 years	N/a
Landolt et al. (2008)	Switzerland	2008	Cross-sectional cohort	Child and parent	TACQOL	CHD (40% cyanotic)	Cases versus controls	Cases = 110 & controls = n/a	7–16 years	Mean (*SD*)
Berkes et al. (2010)	Hungary	2009	N/a	Child and parent	PedsQL 4.0	CHD (by severity)	Cases versus controls	Cases = 373 and controls = 159	2–18 years	Mean (*SD*)/ Median
Tahirović et al. (2010)	Bosnia & Herzegovina	2010	Cross-sectional	Child and parent	PedsQL 4.0	CHD	Cases versus controls	Cases = 114 and controls = 127	2–18 years	Mean (*SD*)
Kwon et al. (2011)	USA	2011	Cohort	Child and parent	PedsQL 4.0	TOF	TOF versus Controls	Cases = 20 and controls = 386 Parent controls = 611	8–18 years	Mean (*SD*)
Idorn et al. (2013)	Denmark	2013	Cross-sectional	Child and parent	PedsQL 4.0	Patients after the Fontan procedure	Fontan patients versus controls	Cases = 93 and controls = 58	5–15 years	Median (IQR)
Garcia Guerra et al. (2013)	Canada	2013	Prospective cohort	Parent	PedsQL 4.0	Single ventricle, biventricular repairs	Single ventricle versus controls/biventricular repairs versus controls	Cases = 130 and controls = 907	4 years	Mean (*SD*)
Garcia Guerra et al. (2014)	Canada	2013	Prospective cohort	Parent	PedsQL 4.0	CHD with chromosomal anomalies	Chromo CHD versus non-chromo versus controls	Cases = 16 and controls = 16	4 years	Mean (*SD*)
Eagleson et al. (2013)	Australia	2013	Cross-sectional, single-centre	Child and parent	PedsQL 4.0 and PedsQL 3.0	HLV and TOF	HLV versus TOF	HLV = 31, TOF = 29	2–18 years	Mean (*SD*)
Mueller et al. (2013)	Germany	2013	Prospective nonrandomized	Child	KINDL-R	TOF	Cases versus controls	Cases = 168 and controls = n/a	8–16 years	Mean (*SD*)
Bertoletti et al. (2015)	Brazil	2014	Cross-sectional	Child	KIDSCREEN-27	CHD	Cases (compare severity)	Cases = 203	10–18 years	Mean (*SD*)
Mellion et al. (2014)	USA	2014	Cross-sectional	Child and parent	PedsQL 4.0	CHD (by severity category)	Cases versus controls and comparison between severity subgroups	Cases = 1138 and controls = 771	8–18 years	Mean (*SD*)
		2014			PedsQL 4.0	CHD	Cases versus controls		10–14 years	N/a

(Continues)

TABLE 3 (Continued)

First author name	Study country of origin	Year	Study design	Child and/or parent response	Assessment instrument	CHD subtype	Study sample	Sample size	Participant's age	Study outcomes
Knowles et al. (2014)	United Kingdom		Retrospective cohort	Child and parent				Cases = 477 and control = 464		
Spijkerboer et al. (2006)	Netherlands	2015	N/a	Child and parent	TACQOL	CHD (4 diagnostic group)	Cases versus controls	Cases = 113 and controls = 2330	8–15 years	Mean (*SD*)
Amedro et al. (2015)	France	2015	Cross-sectional	Child and parent	KIDSCREEN-52 and 27	CHD (by severity)	Cases versus controls	Cases = 282 and controls = 180	8–18 years	Mean (*SD*)
Ong et al. (2017)	Malaysia	2017	Cross-sectional	Child and parent	PedsQL 4.0	CHD	CHD versus siblings	Cases = 179 and siblings = 172	2–18 years	Mean (*SD*)
Reiner et al. (2019)	Germany	2018	Cross-sectional	Child	KINDL-R	CHD (by severity, left heart obstruction, isolated shunts, TGA, right heart obstruction, UVH, other heart defects)	CHD versus controls	Cases = 514 and controls = 734	7–17 years	Mean (*SD*)
Raj et al. (2018)	India	2018	Cross-sectional	Parent	PedsQL 4.0 and PedsQL Infant Scales	CHD (acyanotic and cyanotic)	CHD versus controls (acyanotic subgroups vs. cyanotic subgroups)	Cases = 499 and controls = 628	1–24 months	Mean (*SD*)
Ladak, Hasan, Gullick, Awais, et al. (2019)	Australia	2018	Cross-sectional	Parent	PedsQL 4.0 and PedsQL 3.0	CHD (by severity)	Patients with CHD and age-matched healthy siblings	Cases = 129 and siblings =129	5–18 years	Mean (*SD*)
Ruggiero et al. (2018)	USA	2018	Correlational design	Parent	PedsQL 4.0 and PedsQL 3.0	CHD	CHD (Comparison between age group)	Parents of children = 71	5–12 years	Mean (*SD*)
Sertçelik et al. (2018)	Turkey	2018	N/a (acyanotic = 40, cyanotic = 40)	Parent 6–16 years	KINDL-R N/a	CHD	CHD (acyanotic versus cyanotic)	Children = 80		
Xiang et al. (2019)	China	2019	Cross-sectional	Parent	PedsQL 4.0 & PedsQL 3.0	CHD	Comparison between specific cases	Cases = 2037	2–12 years	Mean (*SD*)
Denniss et al. (2019)	Australia	2019	Cross-sectional	Mothers	PedsQL 4.0 and PedsQL Infant Scales	Single ventricle CHD or CHD requiring neonatal BR	Cases versus controls	Cases = 87 and controls = n/a	1–2 years & 2–5 years	Mean (*SD*)
Raj et al. (2019)	India	2019	Cross-sectional	Child and parent	PedsQL 4.0	CHD	Cases versus controls	Cases = 308 and controls = 719	8–18 years	Median (IQR)
Holst et al. (2019)	Denmark	2019	Cross-sectional	Child and parent	PedsQL 4.0	VSD, TGA and TOF	Cases versus controls (comparison between subtypes)	Cases = 161 and controls = 33	10–16 years	Median (IQR)
Lee et al. (2020)	Canada	2019	Cross-sectional, single-centre	Parent		CHD or an innocent heart murmur		Cases = 112 and controls = 28	1–3 years	Mean (*SD*)

TABLE 3 (Continued)

First author name	Study country of origin	Year	Study design	Child and/or parent response	Assessment instrument	CHD subtype	Study sample	Sample size	Participant's age	Study outcomes
					PedsQL 4.0 and PedsQL 3.0		Cases versus controls (comparison between treatment group)			
Saavedra et al. (2020)	Argentina	2019	Cross-sectional observational	Parent	PedsQL 4.0	CHD	Cases versus controls	Cases = 31 and controls = 62	2–4 years	Median (IQR)
Abassi et al. (2020)	France	2020	Prospective cross-sectional	Child and parent	PedsQL 4.0	CHD (Ross severity class)	Cases versus controls	Cases = 124 and controls = 125	5–7 years	N/a
Oberhuber et al. (2020)	Austria	2020	Prospective	Child and parent	PedsQL 4.0	HLHS	HLHS versus controls	Cases = 41 and controls = 44	6–16 years	Mean (*SD*)

Note: Fontan procedure: a type of open-heart surgery, biventricular repairs: address a small right or left ventricle that is not large enough or strong enough to function normally, Cyanotic: any heart defect present at birth that reduces the amount of oxygen delivered to your body, Acyanotic: a heart defect that affects the normal flow of bl.
Abbreviations: HLHS, hypoplastic left heart syndrome; TGA, transposition of the great arteries; HLV, hypoplastic left ventricle; UVH, univentricular heart; VSD, ventricular septal defect.

Studies were also synthesized according to different age groups.

3 | RESULTS

The searches resulted in 5515 articles which were screened. Of these, 215 studies were selected (see Figure 1 for details) and reviewed for inclusion criteria. Following detailed review, 181 of these were excluded. The reasons for exclusion are given in Figure 1. A total of 34 studies published between 2003 and 2022 were included in the review.

3.1 | Characteristics of studies included

An overview of the included studies is presented in Table 3. Studies were carried out in Europe ($N = 14$) (Abassi et al., 2020; Amedro et al., 2015; Berkes et al., 2010; Grootenhuis et al., 2007; Holst et al., 2019; Idorn et al., 2013; Knowles et al., 2014; Krol et al., 2010; Landolt et al., 2008; Mueller et al., 2013; Oberhuber et al., 2020; Reiner et al., 2019; Spijkerboer et al., 2006; Tahirović et al., 2010), North and South America ($N = 11$) (Bertoletti et al., 2015; Brosig et al., 2007; Garcia Guerra et al., 2013, 2014; Kwon et al., 2011; Lee et al., 2020; Mellion et al., 2014; Ruggiero et al., 2018; Saavedra et al., 2020; Uzark et al., 2008; Varni et al., 2007), Asia ($N = 6$) (Cohen et al., 2007; Ong et al., 2017; Raj et al., 2018, 2019; Sertçelik et al., 2018; Xiang et al., 2019), and Australia ($N = 3$) (Denniss et al., 2019; Eagleson et al., 2013; Ladak, Hasan, Gullick, Awais, et al., 2019). Eighteen studies adopted a cross-sectional design (Abassi et al., 2020; Amedro et al., 2015; Bertoletti et al., 2015; Denniss et al., 2019; Eagleson et al., 2013; Holst et al., 2019; Idorn et al., 2013; Ladak, Hasan, Gullick, Awais, et al., 2019; Landolt et al., 2008; Lee et al., 2020; Mellion et al., 2014; Ong et al., 2017; Raj et al., 2018, 2019; Reiner et al., 2019; Saavedra et al., 2020; Tahirović et al., 2010; Xiang et al., 2019) eight (Brosig et al., 2007; Garcia Guerra et al., 2013, 2014; Knowles et al., 2014; Kwon et al., 2011; Mueller et al., 2013; Oberhuber et al., 2020; Ruggiero et al., 2018) used a cohort design and the design was not clearly specified for the remaining eight studies (Berkes et al., 2010; Cohen et al., 2007; Grootenhuis et al., 2007; Krol et al., 2010; Sertçelik et al., 2018; Spijkerboer et al., 2006; Uzark et al., 2008; Varni et al., 2007). Five studies elicited children's ratings of their HRQOL (Bertoletti et al., 2015; Cohen et al., 2007; Grootenhuis et al., 2007; Mueller et al., 2013; Reiner et al., 2019), 11 studies obtained parents' report (Brosig et al., 2007; Denniss et al., 2019; Garcia Guerra et al., 2013, 2014; Ladak, Hasan, Gullick, Awais, et al., 2019; Lee et al., 2020; Raj et al., 2018; Ruggiero et al., 2018; Saavedra et al., 2020; Sertçelik et al., 2018; Xiang et al., 2019) and 18 studies reported both child and parent report (Abassi et al., 2020; Amedro et al., 2015; Berkes et al., 2010; Eagleson et al., 2013; Holst et al., 2019; Idorn et al., 2013; Knowles et al., 2014; Krol et al., 2010; Kwon et al., 2011; Landolt et al., 2008; Mellion et al., 2014; Oberhuber et al., 2020; Ong et al., 2017; Raj et al., 2019; Spijkerboer et al., 2006; Tahirović et al., 2010; Uzark et al., 2008; Varni et al., 2007). Seven studies (Brosig et al., 2007; Eagleson et al., 2013; Garcia Guerra et al., 2013; Holst et al., 2019; Kwon et al., 2011; Mueller et al., 2013; Oberhuber et al., 2020) reported specific CHD subtypes of multiple severities including single ventricle (Garcia Guerra et al., 2013), ToF (Eagleson et al., 2013; Holst et al., 2019; Kwon et al., 2011; Mueller et al., 2013), HLHS (Brosig et al., 2007; Oberhuber et al., 2020), TGA (Brosig et al., 2007; Holst et al., 2019), ventricular septal defect (VSD) (Holst et al., 2019), and hypoplastic left ventricle (HLV) (Eagleson et al., 2013). Seven studies reported results for the cognitive function domain of HRQOL (Grootenhuis et al., 2007; Krol et al., 2010; Ladak, Hasan, Gullick, Awais, et al., 2019; Landolt et al., 2008; Lee et al., 2020; Raj et al., 2018; Spijkerboer et al., 2006) and 23 studies reported results for the school function HRQOL domain (Abassi et al., 2020; Amedro et al., 2015; Berkes et al., 2010; Bertoletti et al., 2015; Cohen et al., 2007; Denniss et al., 2019; Eagleson et al., 2013; Garcia Guerra et al., 2013, 2014; Holst et al., 2019; Knowles et al., 2014; Kwon et al., 2011; Mellion et al., 2014; Mueller et al., 2013; Oberhuber et al., 2020; Ong et al., 2017; Raj et al., 2019; Ruggiero et al., 2018; Saavedra et al., 2020; Sertçelik et al., 2018; Tahirović et al., 2010; Uzark et al., 2008; Varni et al., 2007). Two studies reported both cognitive and school function HRQOL scores (Eagleson et al., 2013; Xiang et al., 2019) while another two studies focused on the general HRQOL (Brosig et al., 2007; Reiner et al., 2019), which we did not include in the formal meta-analysis.

The majority of the studies employed the PedsQL 4.0 Generic Core Scales or PedsQL3.0 Cardiac assessment tools ($N = 13$ studies) (Berkes et al., 2010; Denniss et al., 2019; Eagleson et al., 2013; Garcia Guerra et al., 2013, 2014; Kwon et al., 2011; Ladak, Hasan, Gullick, Awais, et al., 2019; Lee et al., 2020; Mellion et al., 2014; Oberhuber et al., 2020; Tahirović et al., 2010; Uzark et al., 2008; Varni et al., 2007), four studies used the TACQOL (Grootenhuis et al., 2007; Krol et al., 2010;

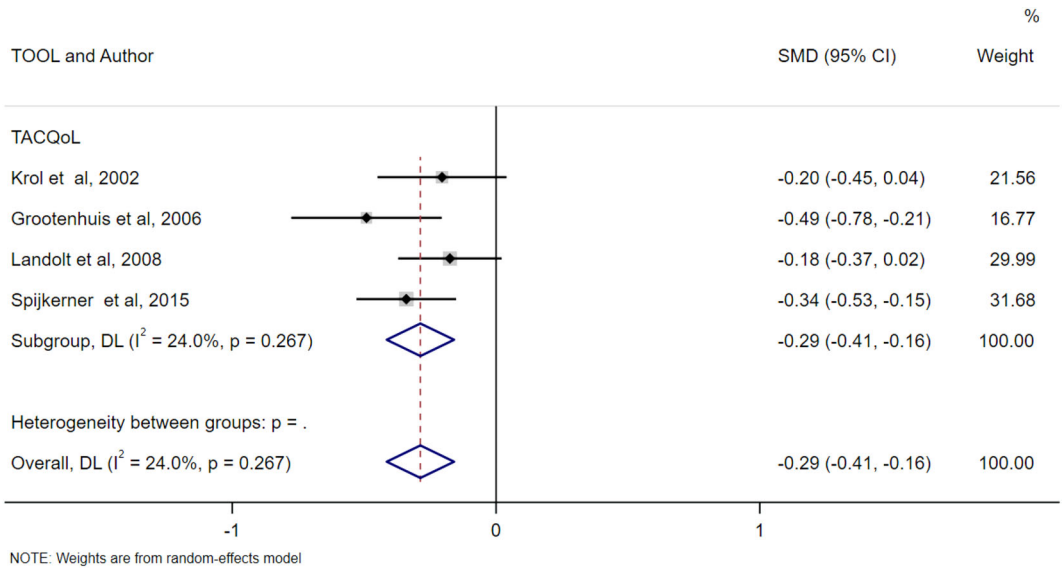


FIGURE 2 Cognitive function domain of HRQOL—child-report. CHD, cases versus controls.

Landolt et al., 2008; Spijkerboer et al., 2006), two studies used the KIDSCREEN-27 (Amedro et al., 2015; Bertoletti et al., 2015) and one study the KINDL-R measure (Mueller et al., 2013). As the number of studies that used KIDSCREEN-27 ($N = 2$) and KINDL-R ($N = 1$) were small, we chose to exclude those three studies from the meta-analysis and the formal meta-analysis finally included 17 studies; 13 using PedsQL 4.0/PedsQL 3.0 and four involving the TACQOL. Overall, the studies were found to be of good quality, using the CASP quality assessment tool (Table 2) (Critical Appraisal Skills Programme, 2022).

3.2 | Cognitive function domain of HRQOL

Nine studies (Eagleson et al., 2013; Grootenhuis et al., 2007; Krol et al., 2010; Ladak, Hasan, Gullick, Awais, et al., 2019; Landolt et al., 2008; Lee et al., 2020; Raj et al., 2018; Spijkerboer et al., 2006; Xiang et al., 2019) reported the cognitive functioning domain of HRQOL. Seven of them, using various children's age ranges, were included in a meta-analysis (Eagleson et al., 2013; Grootenhuis et al., 2007; Krol et al., 2010; Ladak, Hasan, Gullick, Awais, et al., 2019; Landolt et al., 2008; Lee et al., 2020; Spijkerboer et al., 2006); one study (Raj et al., 2018) was excluded as it focused only on infants and another one (Xiang et al., 2019) compared PedsQL scores by socioeconomic status tertiles. Four studies (Grootenhuis et al., 2007; Krol et al., 2010; Landolt et al., 2008; Spijkerboer et al., 2006) used the TACQOL to investigate the cognitive function domain of HRQOL of children with CHD versus healthy controls (child report), and three studies (Krol et al., 2010; Landolt et al., 2008; Spijkerboer et al., 2006) focused on parental reports. The cognitive function HRQOL was worse for CHD children compared with healthy controls in both child (SMD −0.28 (−0.42, −0.15)) (Figure 2) and parental (SMD −0.54 (−0.91, −0.18)) reports (Figure 3).

3.3 | School function domain of HRQOL

Twenty-three studies (Abassi et al., 2020; Amedro et al., 2015; Berkes et al., 2010; Bertoletti et al., 2015; Cohen et al., 2007; Denniss et al., 2019; Eagleson et al., 2013; Garcia Guerra et al., 2013, 2014; Holst et al., 2019; Knowles et al., 2014; Kwon et al., 2011; Mellion et al., 2014; Mueller et al., 2013; Oberhuber et al., 2020; Ong et al., 2017; Raj et al., 2019; Ruggiero et al., 2018; Saavedra et al., 2020; Sertçelik et al., 2018; Tahirović et al., 2010; Uzark et al., 2008; Varni et al., 2007) reported the school functioning domain of HRQOL. The remainder were excluded from meta-analysis: seven studies (Abassi et al., 2020; Garcia Guerra et al., 2013; Holst et al., 2019; Knowles et al., 2014; Raj et al., 2019; Saavedra et al., 2020; Sertçelik et al., 2018) did not provide the mean estimate; three studies did not use the per protocol comparison group (Cohen et al., 2007; Ong et al., 2017; Ruggiero et al., 2018), two studies used the KIDSCREEN-27 (Amedro et al., 2015; Bertoletti et al., 2015), and one study the KINDL-R measure (Mueller et al., 2013).The remaining 10 studies used the

PedsQL 4.0 instrument and were included in the formal meta-analysis (Berkes et al., 2010; Denniss et al., 2019; Garcia Guerra et al., 2013, 2014; Kwon et al., 2011; Mellion et al., 2014; Oberhuber et al., 2020; Tahirović et al., 2010; Uzark et al., 2008; Varni et al., 2007). These studies showed that school function domain scores of the HRQOL tool were worse for children with CHD compared with healthy controls (SMD −0.30 (−0.48, −0.13)) based on self-report (Figure 4). Parental reports demonstrated similar results to the child reports. Specifically, the school function HRQOL was worse when compared with healthy controls (SMD −0.49 (0.64, −0.36)) (Figure 5) with no statistically significant heterogeneity. However, we should be cautious in interpreting the above results because of the possibility of publication bias that was observed in funnel plots (Figures 6 and 7) and formally based on Egger's test: p-value = .08 for child and p-value = .05 for parent report respectively.

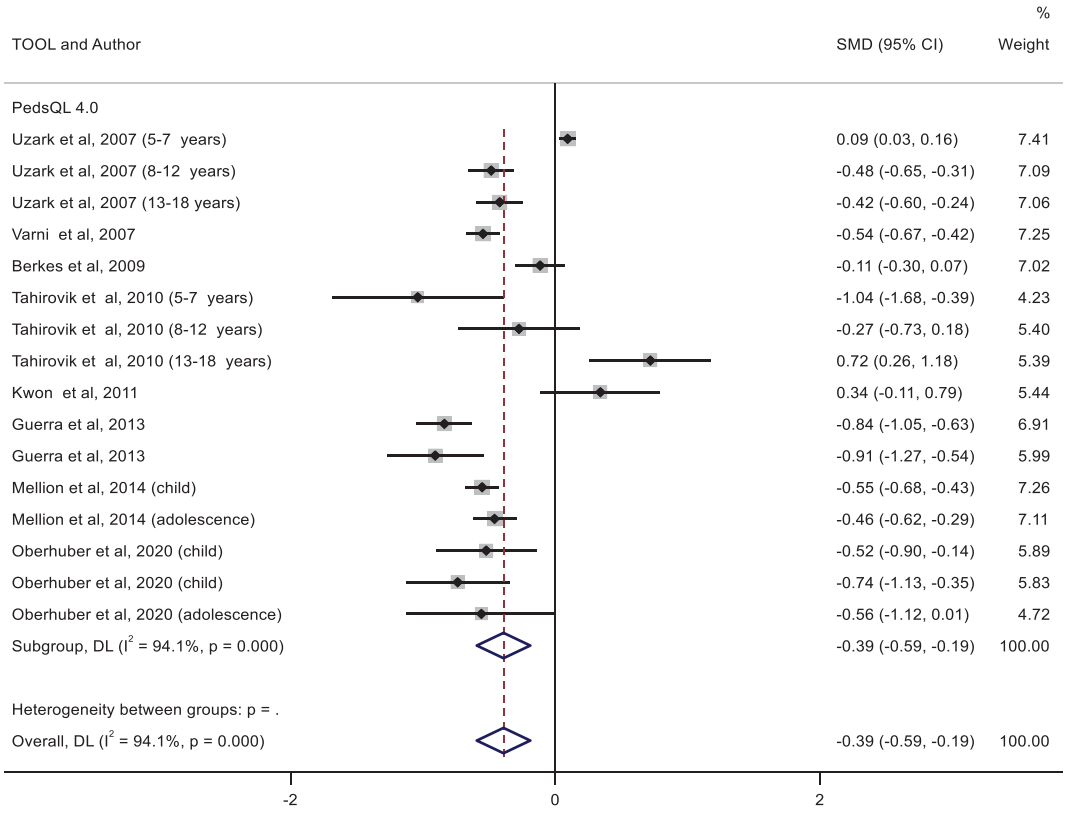


FIGURE 4 School function domain of HRQOL—child-report. CHD, cases versus controls. *In Guerra et al. study separate populations within the same study have been consider.

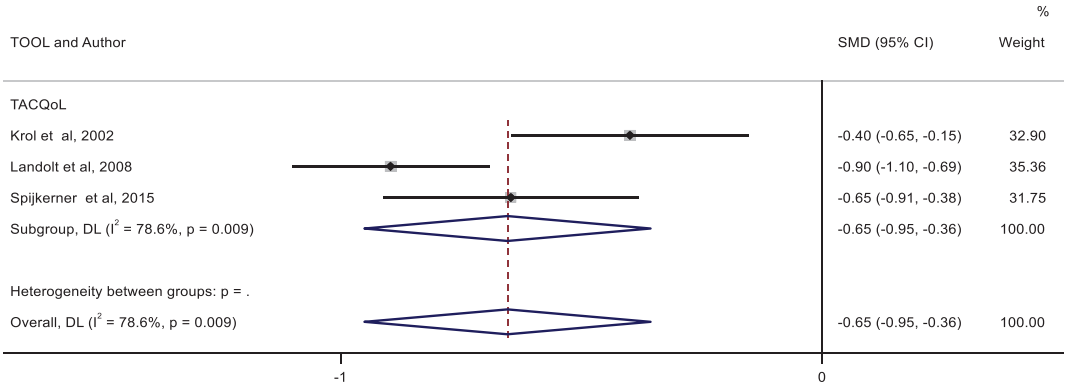


FIGURE 3 Cognitive function domain of HRQOL—parent-report. CHD, cases versus controls.

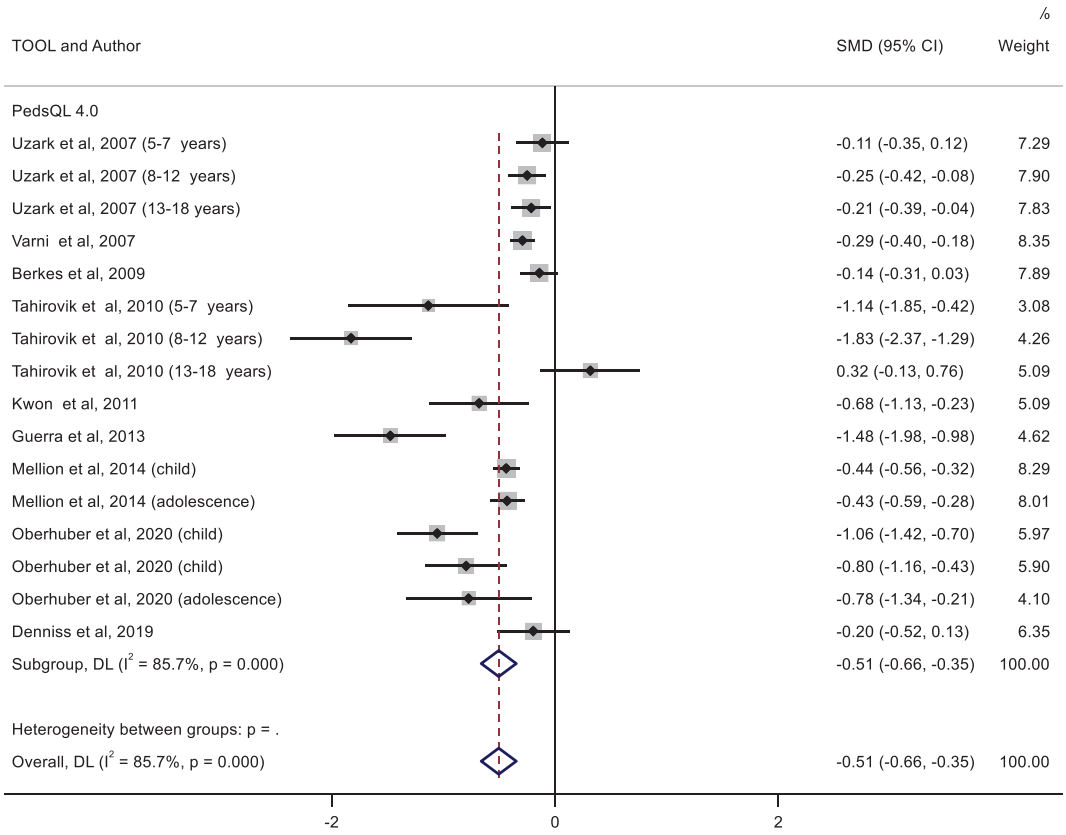
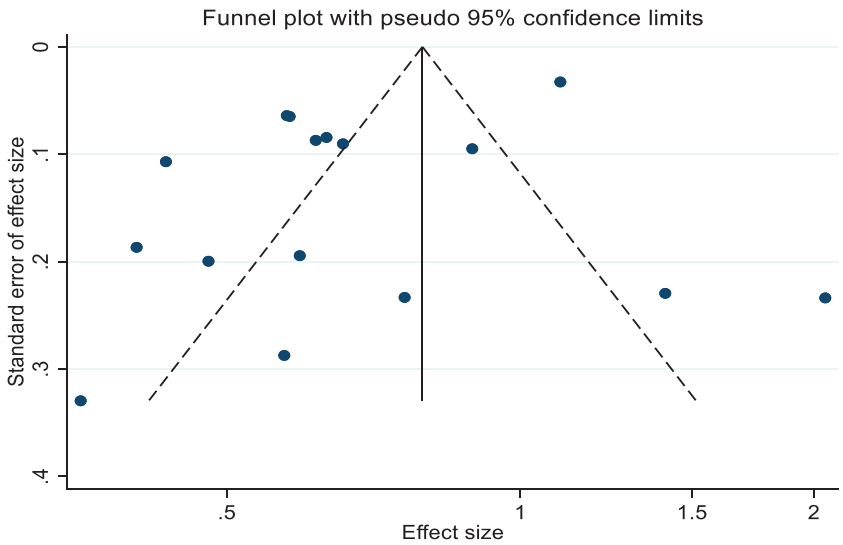


FIGURE 5 School function domain of HRQOL—parent-report. CHD, cases versus controls.

FIGURE 6 School function domain of HRQOL—child-report. CHD, cases versus controls.



3.4 | School and cognitive function domains of HRQOL for young (<8 years) and older (8–18 years) children and young people with CHD

Eight studies (Berkes et al., 2010; Denniss et al., 2019; Garcia Guerra et al., 2013; Kwon et al., 2011; Mellion et al., 2014; Oberhuber et al., 2020; Tahirović et al., 2010; Uzark et al., 2008) investigated the school function HRQOL of children with CHD versus healthy controls across age subgroup categories. All studies used the PedsQL 4.0 assessment tool. We performed a subgroup meta-analysis for the school function HRQOL of the young children (<8 years) (Garcia Guerra et al., 2013;

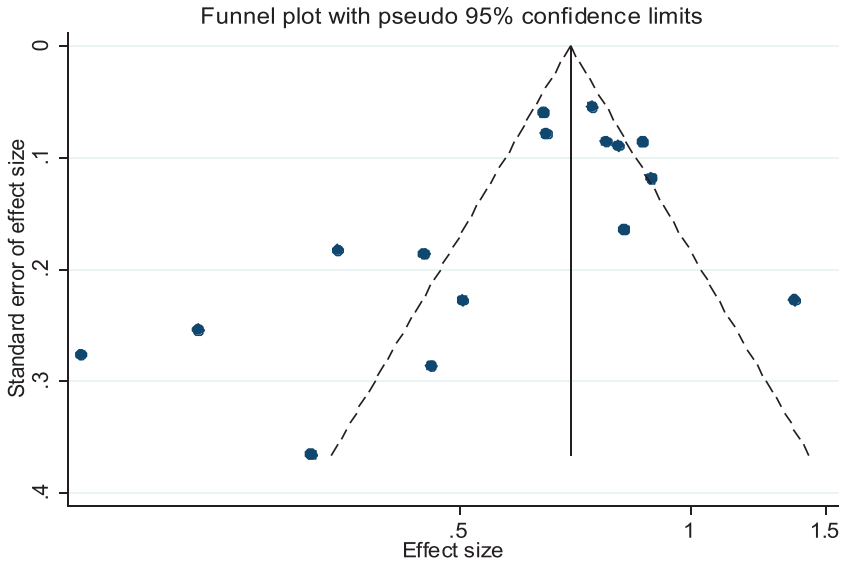


FIGURE 7 School function domain of HRQOL—parent-report. CHD, cases versus controls.

Tahirović et al., 2010; Uzark et al., 2008) and older children (8–18 years) (Kwon et al., 2011; Mellion et al., 2014; Tahirović et al., 2010; Uzark et al., 2008) versus healthy controls based on child reports. The school function domain scores of the PedsQL 4.0 tool were worse in reports from children with CHD compared with healthy controls both for young (SMD −0.65 (−1.32, 0.03)) (Figure 8) and older (SMD −0.25 (−0.47, −0.03)) children (Figure 9).

Parental reports of school function HRQOL demonstrated similar results to the child self-reports for young (Denniss et al., 2019; Garcia Guerra et al., 2013; Tahirović et al., 2010; Uzark et al., 2008) and older (Kwon et al., 2011; Mellion et al., 2014; Oberhuber et al., 2020; Tahirović et al., 2010; Uzark et al., 2008) children. Scores of the PedsQL 4.0 tool were worse in parent reports for children with CHD compared with parent reports for healthy controls (SMD −0.68 (−1.29, −0.07)) (Figure 10) and older (SMD −0.46 (−068, −0.25)) children (Figure 11). Finally, one study (Berkes et al., 2010) that was not included in the subgroup meta-analyses (as no mean estimate was provided), compared a sample of CHD patients with healthy controls across four age groups (toddler 2–4 years, young children 5–7 years, children 8–12 years, and teenagers 13–18 years). This study found no significant differences in the parental report of toddlers (2–4 years), for children (8–12 years), and teenagers (13–18 years) (child and parents reports). However, significant differences between CHD cases versus controls for school functioning HRQOL scores in young children (5–7 years) were observed (child and parents reports).

Four studies (Denniss et al., 2019; Grootenhuis et al., 2007; Raj et al., 2018; Spijkerboer et al., 2006) investigated the cognitive function HRQOL of children with CHD versus healthy controls across age subgroup categories. Two studies used the PedsQL 3.0 assessment tool (Denniss et al., 2019; Raj et al., 2018) and found that young children (<8 years) with CHD had lower cognitive function HRQOL than healthy controls. Specifically, Raj et al. (2018), found that infants and toddlers with uncorrected CHD had significantly lower cognitive functioning HRQOL compared to controls; while Denniss et al. (2019), reported lower cognitive function HRQOL scores in young children (1–5 years) with complex CHD. Furthermore, two other studies that used the TACQOL assessment tool (Grootenhuis et al., 2007; Spijkerboer et al., 2006) investigated the cognitive function HRQOL of older CHD children (8–18 years) versus controls and conflicting results were observed. Spijkerboer et al. (2006) found that CHD children aged 8–15 had significant lower mean scores on cognitive function HRQOL than reference peers while Grootenhuis et al. (2007) did not report any difference in cognitive function HRQOL scores between CHD children aged 8 and 11 years versus controls.

4 | DISCUSSION

The main findings of this systematic review and meta-analysis was that children and young people with CHD report worse cognitive and school functioning HRQOL compared to healthy controls (self and proxy-report). This was consistent with a subgroup meta-analysis of young (<8 years) and older (8 years old or more) children with CHD reporting lower school function scores compared to controls.

Previous studies have focused on the cognitive and/or school functioning of children and young people with

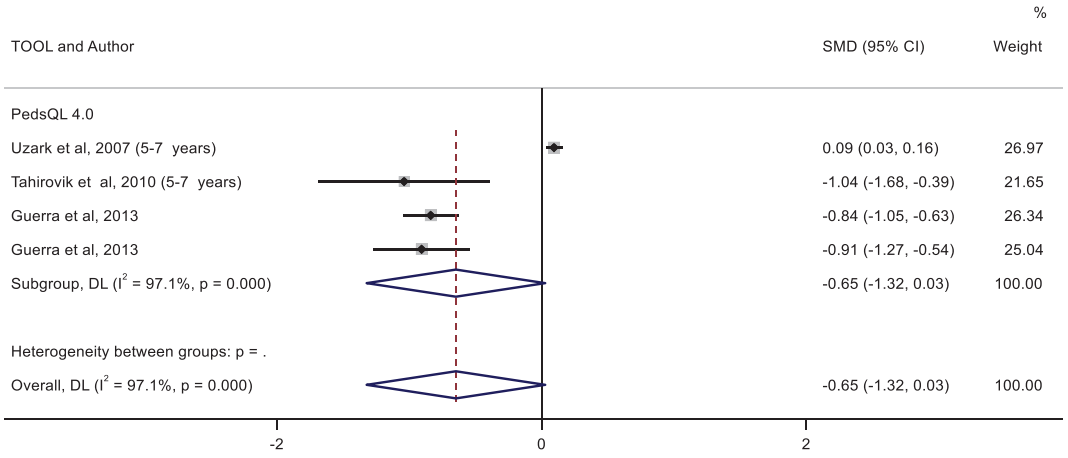


FIGURE 8 School function domain HRQOL—child-report in young children with CHD (<8 years old), cases versus controls.

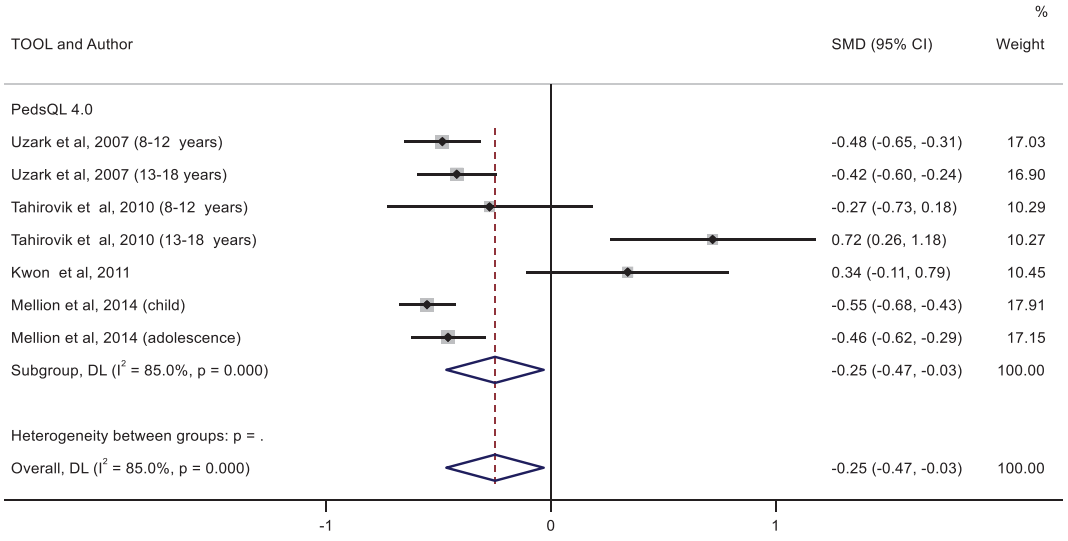


FIGURE 9 School function domain HRQOL—child-report in children with CHD (8–18 years old), cases versus controls.

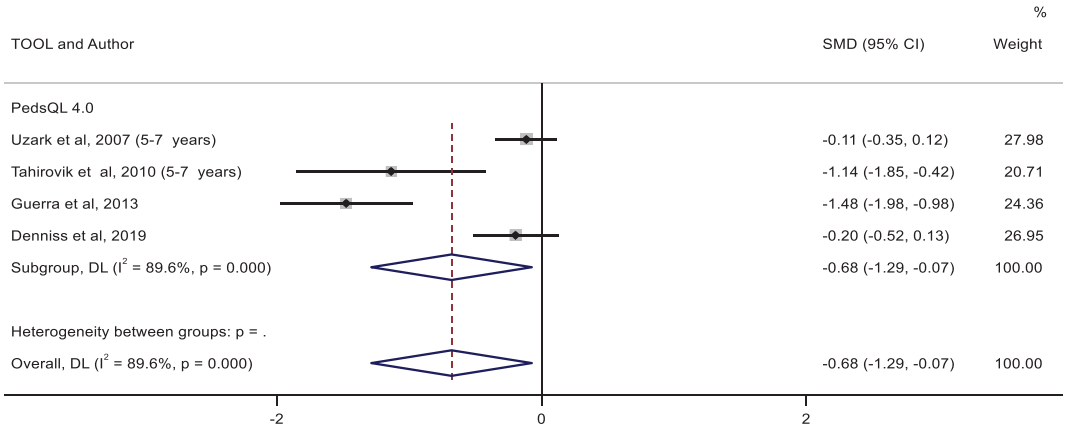


FIGURE 10 School function domain of HRQOL—parent-report in young children with CHD (<8 years old), cases versus controls.

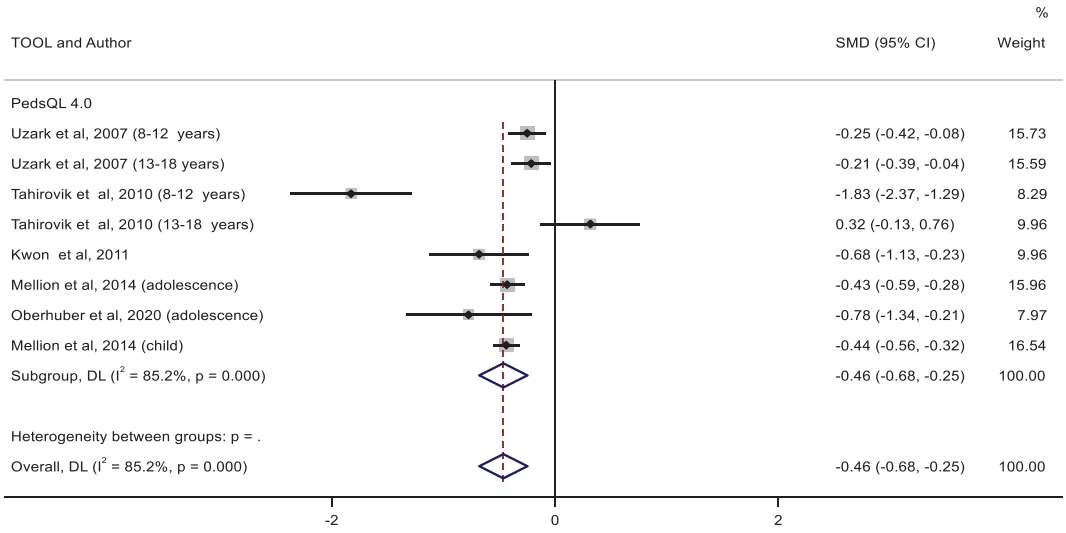


FIGURE 11 School function domain of HRQOL—parent-report in children with CHD (8–18 years old), cases versus controls.

CHD compared to healthy controls. However, there are inconsistencies in their conclusions with some studies indicating worse cognitive and/or school function scores (based on different assessment tools) (Feldmann et al., 2021; Karsdorp et al., 2007; Ladak, Hasan, Gullick, & Gallagher, 2019) whereas another study found no difference (Schrøder et al., 2016). Our findings support previous studies (Feldmann et al., 2021; Karsdorp et al., 2007; Ladak, Hasan, Gullick, & Gallagher, 2019) but contrast with other meta-analysis (Schrøder et al., 2016) which found no difference. Possible explanations for inconsistencies include methodological differences such as age ranges at assessment, age at surgical repair, different assessment instruments, diagnostic groups, sample size, and the use of parent report instead of child report (Lin et al., 2013).

Specifically, a meta-analysis by Ladak, Hasan, Gullick, and Gallagher (2019) on postoperative cases using a variety of different HRQOL instruments and a subgroup meta-analysis by instrument (including the PedsQL and TACQOL) found that cases with CHD reported better HRQOL scores in school function (based on a variety of HRQOL instruments) compared to parental perception. Those results contrast with our meta-analysis as we saw agreement between case and parental perception scores. Additionally, the results of Schrøder et al. (2016) were contradictory to our analysis (and previous meta-analyses), by indicating that the overall HRQOL in adolescents and young adults with CHD is not reduced compared with controls (Schrøder et al., 2016). However, the total number of studies included in this meta-analysis ($N = 6$) (Schrøder et al., 2016) was relatively small compared to our meta-analysis, $N = 7$ for cognitive and $N = 10$ for school function. Also, Schrøder et al. (2016) combined different HRQOL instruments together compared to our meta-analysis where we used the same instruments: TACQOL and PedsQL 4.0 respectively.

Identifying children and adolescents at risk for cognitive difficulties would require specific screening tools and performing testing on children with milder forms of CHD could be costly and inefficient. Cognitive screening could be done as part of long-term follow up of children with CHD within health services, given that cognitive differences are seen in children and young people with all severities of CHD. Based on Buratti et al. (2016), the cognitive domain in the PedsQL Cardiac module could be used as a screening tool, with a cut-off score of 80 for identifying children who need to undergo further cognitive evaluation. Use of the PedsQL as a screening tool would take less time and be more economical than standardized cognitive testing procedures and increase the possibility of testing more children from an early age (Buratti et al., 2016). Thus, it could be beneficial to use the PedsQL to clinically screen children with milder forms of CHD in order to identify those who might experience cognitive impairments.

Most of the published HRQOL studies included cohorts that were predominantly composed of teenagers or young adults with CHD and few HRQOL studies included young children with CHD (Kwon et al., 2011; Oberhuber et al., 2020). In our subgroup meta-analysis, four studies from different countries and with different school starting ages, investigated the school function domain of the HRQOL for young (<8 years) children with CHD compared to controls (child and parent report) and found worse school function domain scores in CHD children.

The reason why impairment appears to be focused also on the young children might be that this is the time

of starting to go to nursery or primary school. This is when pupils with a chronic condition are faced with the stigmatization of being different, or the period when the parents realize that their child's development is different (Miller et al., 2015).

Regarding the school function domain of HRQOL in children of 8 years old or older, our subgroup meta-analysis ($N = 5$) (child and parent report) found lower quality of life compared to controls. However, a study by Berkes et al. (2010) did not find any significant difference between children with CHD and controls aged 8 years or older (child report), although the total PedsQL HRQOL score were significantly lower in children 8–12 years of age (parent report). The discordance between the children's and parents' answers has already been demonstrated previously in the literature (Hong et al., 2007; Tong et al., 1998; Werner et al., 2014). Additionally, a subgroup meta-analysis was not feasible for an investigation of the cognitive function score between young or older children with CHD versus controls due to the small number of studies. However, one study reported a lower cognitive function score in young children with CHD than in controls (Denniss et al., 2019) while another study (Raj et al., 2018) found no significant difference in cognitive function between young children with CHD and controls (proxy report). This may be because of the difficulties in identifying cognitive responses during this early phase of life (Raj et al., 2018).

Regarding older children, conflicting results were also observed with one study (Spijkerboer et al., 2006) reporting lower cognitive function score compared to controls while the other (Grootenhuis et al., 2007) did not report any difference. It is worth noting that the sample size of this study (Grootenhuis et al., 2007) was relatively small ($N = 50$ cases) compared to the previous study ($N = 113$) (Spijkerboer et al., 2006).

While self-report should be considered the gold standard for measuring perceived HRQOL domains, generally the picture is complete when both self and proxy views are integrated. However, there may be cases where the child is too young, or too cognitively impaired, to complete a HRQOL instrument and thus proxy report alone may be needed.

Some studies demonstrated differences between self and proxy reports, with parents reporting their children to have more problems than the self-reported responses (Derridj et al., 2022; Idorn et al., 2013). This may be explained by parents appearing to have the tendency to be overly concerned about their child's disorder (Idorn et al., 2013). However, in our meta-analysis this did not appear to be the case as there was agreement between self and proxy-reports.

The major strengths of our systematic review include a comprehensive search strategy using multiple sources with advice from an information scientist. We manually searched the reference lists and citations of included papers to identify relevant papers. We used an established quality assessment tool as part of the critical appraisal process and powerful meta-analysis techniques in order to determine accurate estimates.

However, some limitations must also be considered. The studies in this meta-analysis were mostly conducted in countries classified as high income by the World Bank (The World Bank's Classification of Countries by Income, 2022). Therefore, these outcomes reported from high income countries may not necessarily be applied to low/middle countries. Previous research also noted inter-country variations in HRQOL with the USA and countries from Europe having increased scores compared with Asian countries (Luo et al., 2017). However, the small number of included studies from Asia in our analysis precluded further exploration. In the subgroup meta-analysis, the small number of studies and a high level of heterogeneity could limit the strength of the findings emerging from this systematic review.

Exploration of possible publication bias is generally discouraged in meta-analyses that include fewer than 10 studies (Van Aert et al., 2019) and therefore, we were unable to assess this for the cognitive function domain which might have added uncertainty to our final outcomes.

A further possible limitation is that the CHD subtype analysis was rarely feasible due to the small number of studies suitable for inclusion in meta-analysis.

"Furthermore, a subgroup analysis comparing various severities of CHD was not appropriate due to varying classifications of CHD used in the studies included in this meta-analysis. It is also worth noting that the classification of CHDs should be undertaken not based on a simple diagnosis but evaluating the disease course, functional status, and stage of intervention as well as information regarding the use of cardiopulmonary bypass and associated hypoxia during surgery.

In conclusion, children and young people with CHD may experience worse cognitive and school function HRQOL scores compared to controls (both self and proxy-report). Regarding the school function domain of HRQOL in young (<8 years) and 8 years old or older children our subgroup meta-analysis found also lower quality of life compared to controls. Also this meta-analysis differs from those undertaken in previous studies as the same assessment tools are considered within each meta-analysis.

HRQOL is a complex phenomenon in which many parameters are involved and requires multi-directional

analysis. A major problem of most studies in HRQOL in CHD patients is their inclusion of heterogeneous groups of patients. However, the assessment of specific domains of HRQOL and the need of cognitive screening as part of long-term follow up for children with CHD within health services are important as they provide valuable information for defining risk groups and the planning of new health and educational policies.

AUTHOR CONTRIBUTIONS

Chrysovalanto Mamasoula, Judith Rankin and Lindsay Pennington, Adenike Motunrayo Adesanya conceptualized and designed the study and contributed to drafting the manuscript. Chrysovalanto Mamasoula conducted the analysis and drafted the initial manuscript. All authors contributed to data interpretation, reviewed the manuscript and approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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