NEURO-DEVELOPMENT AND PSYCHOLOGICAL ISSUES IN CONGENITAL HEART DEFECTS

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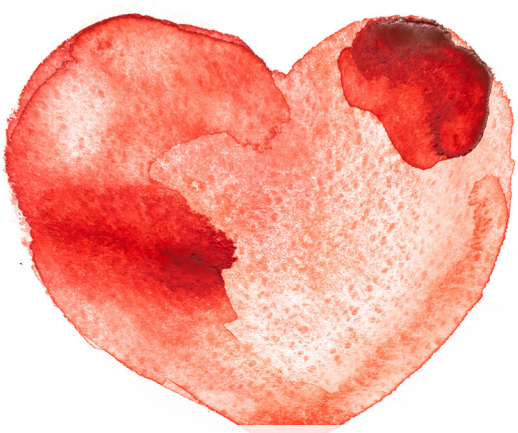


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NEURO-DEVELOPMENT AND PSYCHOLOGICAL ISSUES IN CONGENITAL HEART DEFECTS

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Editorial: Neuro-Development and Psychological Issues in Congenital Heart Defects

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Keywords: congenital heart defects, neurodevelopment, psychology, surgery, neurodevelopmental functioning, cardiac surgery

Editorial on the Research Topic

Neuro-Development and Psychological Issues in Congenital Heart Defects

The operative mortality in infants with congenital heart defects has dramatically decreased in the past few decades to less than 3% in all databases of Europe and North America. As a result, attention has been moved from the survival to the quality of life. Surviving children often experience neurodevelopmental deficits and behavioral, emotional, and social problems, which can have a profound impact on their quality of life. This Research Topic focused on recent studies conducted in this field, to predict, evaluate, and manage the neurodevelopmental and psychological outcomes after congenital heart surgery.

Moon et al. studied 180 adolescents, analyzing the relationship between parental rearing behavior, resilience, and depressive symptoms. They demonstrated that parental rearing behaviors, such as emotional warmth, rejection, punishment, control, and overprotection have a significant influence on the resilience of the adolescents. They suggested that parenting attitudes, gender, age, and severity of the defects should be taken into consideration when developing intervention programs to increase the resilience and reduce the depression in these adolescents.

In another study on children and adolescents with congenital heart defects, Meentken et al. did an extensive review of post-traumatic stress, with a particular focus on stress related to medical interventions and treatment due to their underlying congenital heart defects, particularly for invasive interventions. The authors concluded that children with congenital heart defects present with an elevated risk of developing posttraumatic stress. Therefore, early screening of psychological problems and, if indicated, referral for psychological treatment should be made early on in this group of patients.

Pike et al. evaluated memory deficits in 80 adolescents and young adults with congenital heart defects, more than a decade following their last surgery in comparison to 76 healthy controls. Long after surgery, the group with congenital heart defects demonstrated significant verbal, attention, and working memory deficits over the control group. To enhance patient memory/self-care, the authors recommend to reduce anxiety, improve self-efficacy, and use of visual patient education material.

Buratti et al. studied 184 children, adolescents, and their parents, where heart malformations were divided in mild, moderate, and severe. Irrespective of the severity of the cardiac malformation, a strong association was found between the parent's ratings of cognitive problems and the children's and adolescents' results on intelligence (Wechsler) scales, with this association present for all ages.

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Helm et al. conducted a survey into transition in Germany in 1828 patients with congenital heart defects after they had turned 18 years of age. Their survey revealed that after age 18, many young adult patients had not been transferred to certified adult congenital heart defects providers and about 1/3 were not in continuous care at a specific adult congenital heart defects clinic/heart center. These observations regarding the adult certification were particularly disappointing and indicative of a large information gap and inadequate education in the current clinical practice.

Kolaitis et al. performed an extensive literature review into parental mental health at the time of the diagnosis of congenital heart defect, following cardiac surgery, and at long-term, assessing the need for psychological care. Their review confirmed that parents of children with congenital heart defects, and especially the mothers, are at higher risk for a variety of mental health problems at all different time periods of their children's illness.

In a literature review, Hövels-Gürich identified that the factors influencing the neurodevelopment in infants undergoing cardiac surgery are not only related to the methods of cardiopulmonary bypass, procedure specific risk factors, and postoperative management but also patient specific risk factors, family and environmental factors.

Ryberg et al. investigated 228 children who underwent either surgery or interventional cardiology procedure. Their research demonstrated that socioeconomic status of the families and the severity of diagnosis had a significant influence on the full scale IQ of the children.

Kasmi et al. focused on neurodevelopment and psychiatric outcomes in a specific group of patients: those born with transposition of the great arteries. The authors conducted a detailed systematic review. They describe the results within a life-span perspective, putting particular emphasis on adolescent/young adult neuropsychological outcomes, describing potential mechanisms by which pediatric neurodevelopmental impairments can have negative influences into adulthood and also interventions to improve the clinical outcomes.

In response to an increased need for patient information congenital heart defects, Etnel et al. designed a pilot project developing an online, evidence-based information portal, with information on aortic and pulmonary valve disease, supported by both patients and physicians. If successful, this information portal will be further developed and expanded to include all common congenital heart defects, translated into other languages, and developing into a public information portal to serve patients' relatives and the general public at large.

The studies and reviews collected in this Research Topic demonstrate that the success obtained by substantially reducing the mortality in the repair of congenital heart defects has not been followed by corresponding improvement in the quality of life.

While surgery does provide patients with a better life style related to their physical health, with less cyanosis, heart failure, and better exercise tolerance, much progress is still needed to improve the neurodevelopment outcomes and psychological health of these patients. We are now beginning a new era of research and clinical efforts to prevent and reduce the negative impact of congenital heart defects. Improved psychosocial interventions that caregivers, social workers, and behavior health providers can deliver to support patients and their families are urgently needed.

AUTHOR CONTRIBUTIONS

AC and EU co-wrote this manuscript.

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ORIGINAL RESEARCH
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The Relationship between Parental Rearing Behavior, Resilience, and Depressive Symptoms in Adolescents with Congenital Heart Disease

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Objectives: Parental rearing behavior is one factor that influences the strength of resilience. In turn, resilience influences depression. However, it is unclear whether resilience has a mediating effect on the relationship between parental rearing and depression in adolescents with congenital heart disease (CHD). Therefore, the associations between parental rearing behavior and resilience and between rearing behavior and symptoms of depression were investigated with respect to age, gender and disease severity.

Subjects and methods: Patients completed a parental rearing behavior questionnaire, a resilience scale and the Children's Depression Inventory during a routine clinic visit. Structural equation modeling with maximum likelihood estimation was used to analyze the data.

Results: The median age of the 180 patients included in the study was 17.8 years, and 64% were male. Lower resilience was found to be associated with overprotection, punishment, rejection, and control. There was a strong relationship between resilience and symptoms of depression. Resilience varied according to gender, age group, and disease severity.

Conclusion: Parental rearing behaviors such as emotional warmth, rejection, punishment, control, and overprotection have a significant influence on adolescent's resilience. When developing intervention programs to increase resilience and reduce depression in adolescents with CHD, parenting attitudes, gender, age, and CHD severity should be considered.

Keywords: parental rearing behavior, resilience, depression, congenital heart disease, adolescent

INTRODUCTION

Although outcomes have continued to improve following advances in cardiac surgical and catheter intervention, the negative impact of congenital heart disease (CHD) remains. Altered body image (from operation scars), interruptions to schooling, frequent hospital admissions, physical limitations, and parental overprotection of adolescents with CHD might contribute to psychosocial problems (1–3).

Depression is a serious health problem, especially in adolescence. Approximately 27–40% adolescents and adults with CHD are affected by depression (4). Previous studies reported that adolescents with CHD have more severe problems with depression and behavioral issues than healthy adolescents (2, 5). Depression, in adolescents with CHD, was reported to be significantly associated with "resilience, parental attitude, age, cyanosis, and school performance" (2).

Resilience refers to an individual's ability to successfully adapt to life tasks in the face of social disadvantages or highly adverse circumstances (6). Individual levels of stress adaptation are determined by internal protective factors (e.g., optimism, perceptions of control, self-efficacy, and active coping) or external protective factors (e.g., social support system) (5). Thus, strengthening these protective factors is essential to facilitate adolescent healthy socio-psychological development (6–9).

In an earlier resilience study, parental rearing attitude was found to be a protective factor in adolescents (5). Also, positive associations were found between better mental health outcomes, high resilience, and supportive parenting (10, 11). Furthermore, Pereira et al. (7) and Swanson et al. (12) stated that the relationship between mental health outcomes and positive parenting rearing behavior was mediated by resilience. However, mediating effects of resilience between depression of adolescents with CHD and parental attitude were not examined.

Resilience interacts with developmental stages and changes and develops throughout the life course (12). Although Stratta et al. reported that there was a difference in resilience by gender (13), it is unclear how adolescents with CHD develop protective factors against the perceived risks by gender and age (14). Thus, a study about gender and age as moderators in the relationship between resilience and depression should provide foundational data about resilience in adolescents with CHD and intervention for their depression. In addition, because severity of disease is the major influencing factor for depression in adolescents with CHD (2, 14), it may be necessary to investigate how it affects resilience. Therefore, the aim of this study was to evaluate the mediating effect of resilience on parenting attitudes and depression, and to investigate whether gender, age, and severity of CHD affected the relationship between resilience and depression.

MATERIALS AND METHODS

Materials and Procedures

This prospective study examined adolescents with CHD from an outpatient clinic, a single tertiary center. Inclusion criteria in this study were as follows: (1) 13–18 years old; (2) had a previous diagnosis of CHD and received cardiac surgery or intervention to correct a cardiac malformation; (3) had no history of intellectual handicap syndromes or complications(s) (e.g., trisomy 21); (4) were able to understand and answer the questionnaire, and (5) both the patient and their parents consented to take part in the survey. In total, 186 patients visited the CHD clinic, at the Samsung Medical Center during research periods. We excluded six patients, five of whom provided inadequate responses to the survey, and one who was diagnosed with Marfan syndrome. Thus, 180 patients were included in the final analysis. The sample size met the requirements for structural equation modeling (15–17).

The survey was conducted after the approval of the study protocol was obtained from the Samsung Medical Center Institutional Review Board. Once the patients and their parents agreed to participate, they signed a consent form. The patients completed a battery of questionnaires while awaiting their regular checkup appointments at the outpatient clinic. Responses from all patients were collected by one cardiovascular outpatient nurse.

Instruments

Adolescents self-reported on standardized questionnaires designed to measure parental rearing behavior, resilience, depression, and general characteristics. The translation process for the parental rearing behavior and resilience instruments was based on Brislin's translation model (18). After an initial translation into Korean by a bilingual medical doctor and a qualified bilingual expert, a blinded, qualified expert verified the meaning of each sentence using backward translation. An expert monolingual reviewer and a bilingual nursing professor then evaluated and modified the translation.

Parental Rearing Behavior

An ultra-short screening version (US) of the Recalled Parental Rearing Behavior Questionnaire (19) (Fragebogen zum erinnerten elterlichen Erziehungsverhalten; FEE) (20, 21), was used to measure parental rearing behavior. The FEE-US is a shortened version of the Egna Minnen Betraffande Uppfostran (Own Memories of Child Rearing Experiences; EMBU) implemented by Petrowski et al. (19, 22) implemented by Petrowski et al. The FEE-US, utilizes scores on a four-point Likert scale (19), consists of 12 items (six items for each parent), and measures how often specific situations or circumstances were experienced by the participant (22). It has three scales: (1) paternal/maternal rejection and punishment, (2) paternal/maternal emotional warmth, and (3) paternal/maternal control and overprotection (23). The rejection and punishment scale assesses inappropriate behavior as perceived by a child, such as overly strictness and rejection (20, 22). The emotional warmth scale assesses behavior perceived positively from a respective parent, such as praise, support, and affection, without any unnecessary interference (22). Control and overprotection assess the following behaviors from a respective parent: overly thoughtful blaming, interfering, and constricting. These behaviors reflect the parents' perspectives on performance, high expectations, and effort. The FEE-US score ranges from 2 to 8 and it is calculated by adding the value of each assigned item for all three scales, and for each parent (21). The psychometric properties of the three scales of the short version were found to be satisfactory to good (21). The Cronbach's α in original version was 0.72–0.89 which indicated good reliability (24). Cronbach's α in this study was 0.89.

The Resilience Scale (RS)

Resilience was measured with a shortened version of Wagnild and Young's RS (25), or the RS-11, as implemented by Schumacher et al. (26, 27). Resilience, as conceptualized by the RS, is defined as the ability to cope with development tasks by utilizing internal

and external resources. The RS (original) was separated into two dimensions: (1) 17 items assessed personal competence and (2) 8 items assessed acceptance of self and life (25). Containment, persistence, independence, and self-value were assessed on the personal competence scale. Moreover, tolerance, flexibility, and adaptability were assessed on the acceptance of self and life scale (25). High scale values represented high resilience. Internal consistency on the original version reported by Schumacher et al. indicated very good reliability (Cronbach's $\alpha = 0.91$) (21, 26).

The RS-11 comprised items measured on a seven-point Likert scale (28), and reliability for this version correlated very highly with reliability for the original RS-25 version ($r = 0.86$) (28). Cronbach's α in this study was 0.92. The RS items were simplified into two parcels. The two groups were organized by alternately assigning the items, from highest to lowest in factor loadings of the latent variable (21).

Depression

The Korean version of the Children's Depression Inventory (CDI) was developed by Cho and Lee (29, 30) based on Kovac's modification of the Beck Depression Inventory for 8–18-year olds (31). The self-administered instrument is composed of 27 questions on patient feelings. Each item assessed depressive symptoms such as disturbed mood or apathy, in addition to school-related issues such as social rejection (31). Adolescents were asked to choose a sentence out of three, based on the severity of symptoms (no symptoms, mild symptoms, and severe symptoms) that they experienced during the past 2 weeks for each item. The score for each item ranged from 0 to 2 (2 represents the greatest symptom severity) and the total possible score ranges from 0 to 54 (a higher total score indicates a greater severity of depression). The CDI (Korean version) was found to be satisfactory with internal consistency (Cronbach's $\alpha = 0.88$) (29) and test–retest reliability (Cronbach's $\alpha = 0.82$) (29). Healthy adolescents had a mean score of 14.72 and scores between 11 and 13 represented the cutoff point for depression. In this study, Cronbach's α was 0.82.

Disease Severity

Congenital heart disease severity was measured by the Disease Severity Index (DSI). The DSI was developed to reflect the course of the illness (32, 33) and encompasses three levels of severity (low, moderate, and high). In this study, patients who received at most one cardiovascular surgery or one catheter intervention were considered low severity. The moderate severity group included patients who received more than one cardiovascular catheterization or intervention. Last, patients with persistent cyanosis were classified into the high severity group. These patients showed single-ventricle physiology or less than 92% oxygen saturation at rest (32, 33).

Statistical Analysis

The data were analyzed using SPSS (version 22.0, IBM, Chicago, IL, USA) and AMOS (version 22.0, IBM, Chicago, IL, USA) software. Descriptive statistics were used to analyze demographic data, parental rearing behavior, resilience, and depression in adolescents with CHD. Independent sample *t*-tests, analysis of variance, and Scheffe tests were performed to identify differences in the level of parental rearing behavior, resilience, and depression according to age and disease severity. Prior to examining the goodness of fit of hypothesized model, validity examination among latent variables was conducted *via* the confirmatory factor analysis (CFA). The CFA examines the construction of observed variable, in which factor loading values above 1.96 is significant (15, 17). In this study, it is confirmed that each items of parental attitude, resilience, and depression are all factor loaded with values above 2.0. A structural equation modeling approach was used in order to evaluate the mediating effect of resilience. The χ^2, degrees of freedom (df), goodness-of-fit index (GFI), normal fit index (NFI), comparative fit index (CFI), root mean square error of approximation (RMSEA), Tucker-Lewis index, and the parsimonious goodness-of-fit index were used in the goodness-of-fit tests for the model (15, 16, 34–36). Covariance matrices were used to test the model and the maximum likelihood method approach was used to estimate the model (15, 35).

Additionally, latent mean analysis (LMA) was performed to examine the difference of resilience by age, gender, and severity of disease (17, 37, 38). Although the difference between groups is often examined *via* the *t*-test or multivariate analysis of variance (MANOVA), these analyses may result in incorrect outcomes as they use measured variables that contain measurement errors. LAM controls for measurement errors to overcome the limitations of the *t*-test or MANOVA and to detect group differences in greater accuracy (37). To conduct LMA, the assumptions should be satisfied by the invariance test, that is, configural invariance, metric invariance, and scala invariance (37, 38). Configural invariance examines whether identical latent variables are loaded between groups so as to confirm identical basic structures. After that, metric invariance can be examined. It is to investigate whether factor coefficients are identical by controlling the identical factor loading among groups. Once this is confirmed, the next step is to test scalar invariance (38). Scalar invariance examination stipulates that respondents with identical values of latent variables should have identical observed values regardless of involved groups (38, 39). When examining the goodness of fit of a model *via* configural invariance, metric invariance, and scala invariance, fit indices should be as follows: CFI variance less than 0.01 and RMSEA variance less than 0.015 are regarded as identical models (34, 36). This study performs LMA to find differences in resilience by gender, age, and disease severity after examining the three processes (36). In LMA, a factor mean is not directly estimated, but through the differences between the averages of latent mean of the reference group and that of comparison group after controlling for the latent mean as zero. The interpretation on the latent mean difference is based on Cohen effect size (*d*). Cohen's *d* is a value that divides a mean difference by the common SD. The reference group mean is compared with the mean of the comparison group on a standard score scale, which suggests the degrees of effectiveness. The *d* value = 0 indicates that the mean of the reference group and that of the comparison group are identical. The *d* value = 0.2 refers to a small effect size, 0.5 refers to a medium effect size, and 0.8 refers a large effect size (37).

RESULTS

Table 1 shows demographic and clinical data and **Table 2** demonstrates descriptive statistics of the study variables. The first objective was to examine the relationship between depression, resilience, and parental rearing behavior. The hypothesized model described in **Figure 1** is suitable for the data. **Table 3** shows the total structural equation model and its fit indices. All of the fit indices satisfied the recommended levels (15, 17, 36).

All path coefficients with a P-value < 0.001 in the model are significant. The three dimensions of parental rearing behavior are weakly inter-correlated, as represented in **Figure 1**. Rejection and punishment ($\beta = -0.23$, $P = < 0.001$), emotional warmth ($\beta = 0.14$, $P = 0.003$), and control and overprotection ($\beta = -0.18$, $P = 0.001$) predict a level of resilience, which predicts depression ($\beta = -0.40$, $P = < 0.001$). For the three dimensions of parental rearing behavior, the standardized indirect effects on depression are small (range: −0.05 to 0.12). According to the results, we can confirm that resilience is a mediator between depressive symptoms and parental rearing behavior.

The equivalency of the model was tested, across gender, age, and severity groups, with additional analyses (34, 40). The multigroup analyses showed that configural invariances were larger than 0.90 of CFI and smaller than 0.50 of RMSEA, across gender, age, and disease severity. Also, metric invariances and scalar invariances were smaller than 0.01 of CFI and RMSEA (34, 40), across gender, age, and disease severity, as shown in **Table 4**. Configural invariance, metric invariance, and scala invariance were all examined. Therefore, the data suggest differences in resilience by gender, age, and disease severity with the structural equation model.

Table 5 examines group differences in resilience by gender, age, and disease severity. It suggests that boys as a reference group had a significantly lower latent mean than girls as a comparison group, and the effect size was as large as 0.96. When the age group of 13–15-year olds was used as a reference group, the age group of 16–18-year olds showed a significantly lower latent mean with the effect size of 0.89. Using the group with mild disease severity as a reference, the group with severe disease severity showed a significantly lower latent mean with the large effect size 1.36.

TABLE 1 | General and clinical characteristic of the subjects (N = 180).

Variable		Category	N (%)	Mean ± SD
Age (years)				15 ± 1.4
Gender		Male	115 (64.0)	
Religion		Yes	73 (40.6)	
Family structure		Extended	18 (10.0)	
		Nuclear	150 (83.3)	
		Single parent	12 (6.7)	
Academic achievement		High	53 (59.4)	
		Middle	100 (55.6)	
		Low	27 (15.0)	
Primary CHD diagnosis	Acyanotic CHD, 72 (40)	VSD	28 (15.0)	
		ASD	22 (12.3)	
		Valvar disease (TR, MR, AR)	15 (8.3)	
		CoA	7 (3.8)	
	Cyanotic CHD, 108 (60)	TOF	47 (26.1)	
		PA with VSD	19 (10.6)	
		Tricuspid A	10 (5.6)	
		DORV	15 (8.3)	
		TGA	6 (3.3)	
		TAPVR	4 (2.2)	
		HLHS	3 (1.7)	
		Truncus A	4 (2.2)	

CHD, congenital heart disease; VSD, ventricular septal defect; ASD, atrial septal defect; TR, tricuspid regurgitation; MR, mitral regurgitation; AR, aortic regurgitation; CoA, coarctation of aorta; TOF, tetralolgy of fallot; PA, pulmonary atresia; Tricuspid A, tricuspid atresia; DORV, double outlet right ventricle; TGA, transposition of great arteries; TAPVR, total anomalous pulmonary venous return; HLHS, hypoplastic left heart syndrome; Truncus A, truncus arteriosus; SD, standard deviation.

DISCUSSION

Resilience is defined as one's ability to adapt successfully to adverse life circumstances, social disadvantages, and/or adversity (6). Many studies were conducted to understand the role of resilience in the development of depressive symptoms (7, 21). The results of this study verified that resilience has a mediating effect on parenting attitudes and depression. Moreover, an association was found between high resilience and positive parental rearing

TABLE 2 | Descriptive statistics for questionnaire of the subjects (N = 180).

Variables	All	Men	Women	P	Age		P	Disease severity			P
					13–15 years	16–18 years		Mild	Mod	Severe	
Emotional warmth (F)	4.31 (1.3)	3.85 (1.6)	4.53 (1.3)	<0.001	4.65 (1.2)	3.94 (1.3)	<0.001	4.45 (1.6)	4.19 (1.5)	3.94 (1.4)	<0.001
Emotional warmth (M)	5.21 (1.4)	5.03 (1.1)	5.50 (1.2)	0.009	5.67 (1.1)	5.04 (1.7)	<0.001	5.52 (1.4)	5.32 (1.4)	5.04 (1.2)	0.001
Control and overprotection (F)	3.13 (1.2)	3.08 (1.0)	3.15 (1.4)	0.301	3.32 (1.0)	2.89 (1.3)	0.014	3.37 (1.1)	32.7 (1.2)	3.12 (1.1)	0.011
Control and overprotection (M)	3.11 (1.3)	3.10 (1.1)	3.18 (1.5)	0.431	3.28 (1.4)	3.09 (1.1)	0.028	3.68 (1.4)	3.60 (1.3)	3.39 (1.0)	0.018
Rejection and punishment (F)	2.67 (1.1)	2.79 (1.1)	2.34 (1.0)	0.015	2.32 (1.2)	2.87 (1.2)	<0.001	2.62 (1.0)	2.75 (0.9)	2.87 (1.0)	0.022
Rejection and punishment (M)	2.87 (1.3)	2.73 (1.0)	2.92 (0.8)	0.154	2.75 (0.7)	2.97 (1.0)	0.032	2.43 (0.8)	2.5 (0.9)	2.67 (1.0)	0.021
Resilience	54.5 (10.6)	56.12 (9.2)	52.29 (10.0)	0.021	57.32 (11.0)	53.14 (9.7)	<0.001	60.42 (10.0)	58.49 (9.8)	55.51 (10.1)	<0.001
Depression	16.21 (5.6)	14.70 (6.2)	18.92 (5.9)	0.014	15.10 (6.3)	19.01 (4.9)	<0.001	13.12 (5.2)	16.32 (4.8)	18.21 (6.4)	<0.001

F, father; M, mother; mod, moderate.
All data expressed as mean (SD).

behavior (e.g., emotional warmth). In adolescents with CHD, depression may be explained by resilience and parenting attitudes, as shown in the multiple regression analysis. In addition, adolescents, who had an affectionate parent and high resilience, were found to be less depressed (2). This finding is consistent with a study in which children with chronic illnesses such as asthma had lower resilience scores and children whose parents were rigid and restrictive were more depressed (41). It is also partially consistent with the results of Pereira et al., which showed that both resilience and psychosocial functioning were predictors of depressive symptoms (7, 42).

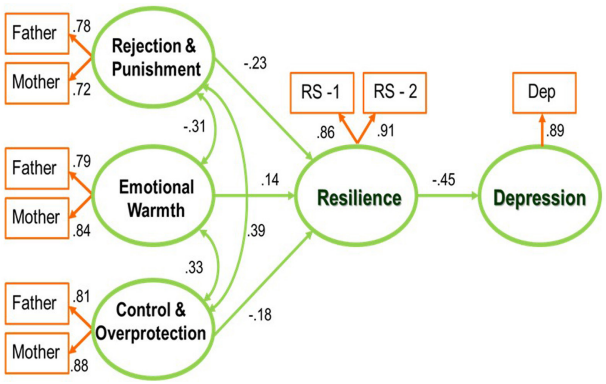

FIGURE 1 | Path diagram for the hypothetical model. All coefficients are significant with $P < 0.001$.

A previous study of adolescents and adults found a relationship between parental rearing attitude, resilience, and psychological symptoms. Depressive symptoms and resilience were both negatively associated with negative parental rearing behaviors (21), which is consistent with the findings of the present study. Therefore, improving parenting attitudes can be a way to increase resilience and lessen depression. Furthermore, the harmful effects of negative parental rearing behavior on resilience may be corrected by "positive life experiences attained from social support systems, cohesion, networking, and relationships" (7, 21).

In this study, gender- and age-specific associations between parental rearing, resilience, and depression were found. The finding that resilience and the quality of experienced parental rearing differ according to gender is consistent with the results found by Stratta et al. (13). Boys showed slightly higher levels of resilience than girls in this study. This is partly consistent with Leppert et al.'s findings for adult subjects, that women had lower levels

TABLE 3 | Test of the goodness of fit of the hypothetical model.

N	χ^2 (df)	*P*	CMIN/DF	CFI	GFI	RMSEA	TLI	NFI	PNFI
180	25.73 (2)	<0.001	12.865	0.945	0.972	0.03	0.947	0.982	0.823

df, degrees of freedom; CMIN/DF, minimum discrepancy, divided by its degree of freedom; CFI, comparative fit index; GFI, goodness-of-fit index; RMSEA, root mean square error of approximation; TLI, Tucker-Lewis index; NFI, normal fit index.

TABLE 4 | Results of invariance across gender, age, and diseases severity ($N = 180$).

	N	χ^2 (df)	*P* for $\Delta\chi^2$	CMIN/DF	CFI	ΔCFI	RMSEA	ΔRMSEA	Result
Gender									
Male	115	16.419 (2)		8.209	0.943			0.034	
Female	65	9.280 (2)		4.140	943			0.034	
Multigroup analysis									
Congfigural invariance		45.490 (4)		11.449	0.943		0.024		Accepted
Metric invariance		52.912 (6)	0.069	10.582	0.943	<0.001	0.029	0.001	Accepted
Scalar invariance		66.146 (9)	<0.001	7.349	0.959	0.012	0.028	0.001	Accepted
Age group									
13–15 years	95	13.579 (2)		6.789	0.952		0.069		
16–18 years	85	12.150 (2)		6.075	0.950		0.070		
Multigroup analysis									
Congfigural invariance		46.258 (10)		4.625	0.953		0.029	0.001	Accepted
Metric invariance		59.863 (10)	0.008	5.968	0.956	0.001	0.030	0.001	Accepted
Scalar invariance		64.891 (12)	0.002	5.407	0.951	0.004	0.031	0.001	Accepted
Disease severity									
Mild	62	8.862 (2)		4.431	0.936		0.030		
Moderate	83	11.850 (2)		5.925	0.945		0.031		
Severe	35	5.003 (2)		2.501	0.917		0.027		
Multigroup analysis									
Congfigural invariance		66.845 (14)	0.010	4.774	0.923		0.037	0.004	Accepted
Metric invariance		68.489 (16)	0.009	4.280	0.923	0.006	0.036	0.003	Accepted
Scalar invariance		89.321 (19)	0.004	4.701	0.952	0.003	0.038	0.001	Accepted

df, degrees of freedom; CFI, comparative fit index; CMIN/DF, minimum discrepancy, divided by its degree of freedom; RMSEA, root mean square error of approximation.

TABLE 5 | Differences analysis of latent mean about variables.

Latent variables		Gender		Age		Disease severity		
		Boy	Girl	13–15 years	16–18 years	Mild	Moderate	Severe
Resilience	Latent mean	0	−0.69*	0	-0.75*	0	−0.26	−1.25*
	Mean	56.12	52.29	57.32	53.14	60.42	58.49	55.51
	Cohen's *d*		0.96		0.89		0.35	1.36

*$P < 0.001$.

of resilience and worse physical symptoms than men, regardless of age (43). However, contrary to Leppert et al.'s findings, the present study found differences in the levels of resilience and depression according to age. In adolescence, parenting, resilience, and psychological symptoms may change and develop according to gender and age (11, 12). However, in adulthood, resilience as an intrapersonal resource decreases with age, while depression increases. There is also an argument that, due to reduced autonomy, protective strength of resilience decreases at this stage in life (44). Therefore, to understand resilience in adolescents with CHD, it is necessary to evaluate traits of resilience thoroughly, not only in adolescence, but also throughout the entire lifespan *via* longitudinal studies, and to apply the results to the development of interventions that increase resilience. Last, it was confirmed that the higher the severity of CHD, the lower the level of resilience. The results partially confirm the results of a previous study that suggested the CHD severity had a detrimental effect on resilience only if it was measured in poor functional status (33). Therefore, when developing an intervention program to increase resilience in adolescents with CHD and reduce depression, parenting attitudes, gender, age, and severity should be considered.

Intervention programs like "self-management training, art therapy, positive emotions, cognitive flexibilities, and social support" need to be developed in order to both prevent and decrease the risk of depressive symptoms in adolescents with CHD or any other chronic diseases (2). Moreover, these programs can help to bolster these adolescents' skills in managing stress and increase their resilience (2, 44). These educational programs could provide information to parents on their roles in the development of their child or children. The goal of the information would be to promote a better understanding of CHD and to provide parents with the appropriate child-rearing methods, problem-solving, and communication skills in fostering their adolescents' maturity (2, 14). These efforts and resources will help to develop adolescents' resilience into adulthood and also educate them that their disease is manageable.

The authors previously examined resilience and parental attitude as major determinants of depression in adolescents with CHD (2). Based on the previous study, we were curious about depression, resilience, and parental attitudes, for which we examined their relationships. To the best of our knowledge, it is the first study in adolescent with CHD. We hope to see practical interventions provided after many follow-up studies conducted with patients with CHD.

This study has several limitations. First, the study's sample is a convenient sample recruited from patients visiting a clinic for their regular checkups. Also, the results of the study may not be generalized as the sample was heterogeneous, including many patients in the moderate group of disease severity. Second, this study analyzed whether measured variables consistently represented the construct *via* CFA. Although this study used some promising screening tools, such as FEE-US and RS-11, they may not represent the full spectrum as retrospective assessment tools. Thus, we recommend replication studies with outcomes assessed by independent raters who are not family members, as observers. Additionally, DSI is a classification adopted in previous research (32, 33), which is not usual way adopted by cardiologists. Therefore, we recommend different classifications for follow-up studies as different results may come up based on various classifications.

CONCLUSION

The strength of CHD adolescents' resilience is significantly influenced by parental rearing behavior such as control, overprotection, rejection, punishment, and affection. The effect of resilience depends on gender and has varying effects according to age and disease severity. Therefore, when developing an intervention program to increase resilience of adolescents with CHD and reduce depression, parenting attitudes, gender, age, and severity should be considered.

ETHICS STATEMENT

All of the participants gave their written informed consent, and the protocol of the study was approved by the Institutional Review Board at Samsung Medical Center.

AUTHOR CONTRIBUTIONS

Study conceived and co-designed by J. Paper drafted by JR, who also participated in the design and coordination studies and conducted statistical analyses. JS and I-SK assisted with design and manuscript drafting. SJ and SP helped to interpret the data as well as assisted in drafting the manuscript. JY, T-GJ, and J all helped to design the study and edited the vital content. The final manuscript was read and approved by all authors.

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MINI REVIEW
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Medically Related Post-traumatic Stress in Children and Adolescents with Congenital Heart Defects

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Children and adolescents with a congenital heart defect (ConHD) frequently undergo painful or frightening medical procedures and hospitalizations. They often need multiple invasive procedures at a very young age and require regular checkups during their entire life. From other pediatric populations, it is known that these kinds of experiences can result in acute stress reactions and even in post-traumatic stress disorder (PTSD) in the long-term. PTSD and also subthreshold PTSD can lead to serious (psychosocial) impairment. However, limited information is available about PTSD in children with ConHD. Therefore, the aim of this review is to provide a summary of the current literature on post-traumatic stress (PTS) in children and adolescents with ConHD describing the prevalence of PTSD and its predictors/correlates. This review indicates that a range of 12–31% of children undergoing cardiac surgery develop PTSD. A range of 12–14% shows elevated post-traumatic stress symptoms (PTSS). These findings are comparable to those of hospitalized children without ConHD. Noteworthy, most studies used varying self-report questionnaires to measure PTSD and only one study used a semistructured interview. Although all studies point in the same direction of elevated PTSD and PTSS, systematic research is necessary to be able to draw firm conclusions. At present, as far as we know, in most clinics treating patients with ConHD, there is no regular screening for PTS in children with ConHD. In the reviewed literature, there is strong consensus that screening for PTSS and (preventive) psychological care for children and adolescents with ConHD is urgently needed.

Keywords: congenital heart defect, post-traumatic stress, PTSD, children, adolescents

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INTRODUCTION

Medical events are often experienced as stressful and frightening. Especially in young patients, this can be overwhelming. Medical procedures and treatments often cause pain, fear, a feeling of helplessness, and may give a sense of life threat (1, 2). Furthermore, such procedures can challenge the beliefs of youngsters about the world as a safe place and can give rise to uncertainty about the future. Therefore, it is normal and understandable that some kind of postoperative stress occurs after the experience of such an event. The majority of young patients and their parents

can handle this stress quite well (2, 3). However, some develop persistent traumatic stress reactions such as post-traumatic stress disorder (PTSD). This, in turn, can have a negative influence on medical adherence and consequently morbidity or even mortality and can lead to an increase in health care service use (4, 5). Furthermore, PTSD is associated with rehospitalizations, worse sleep quality, and impaired quality of life (6–8).

Children and adolescents with congenital heart defects (ConHDs) often undergo various invasive medical procedures at a very young age and some need lifelong checkups at the hospital and re-interventions (9). Therefore, children with ConHD seem to have a heightened risk for developing PTSD. Considering this and the impact that PTSD can have on medical and psychosocial functioning, research into this topic should be a priority. However, research regarding PTSD in youngsters mostly has focused on abuse, violence, accidents, and natural disasters (10). Disproportionately, few studies have looked into traumatized children and adolescents with ConHD.

This review aims to give an overview of what is known in the field of medically related post-traumatic stress (PTS) in children and adolescents with congenital heart disease and suggests future directions. To find all relevant articles, a multidatabase search was done with support from the Biomedical Information Specialist of the Medical Library of the Erasmus MC. The databases used were Embase, Medline, PsychInfo, Web of Science, Scopus, and Google Scholar. The search was limited to English language articles published from the year 2000 onward. Keywords included in the search were posttraumatic stress disorder and congenital heart disease (with a variation of corresponding terms).

OVERVIEW OF DEFINITIONS OF PTSD IN LITERATURE

In researching literature, different terms and abbreviations are used for posttraumatic stress (disorder). This variability makes it difficult to compare results across studies. In the following, all relevant terms and abbreviations are shortly discussed to highlight the differences. We suggest that future studies should use similar terms to make results more comparable across studies.

Post-traumatic Stress (PTS)

The word "trauma" is often linked to physical injury. However, it can also refer to psychological injury or pain (11). Immediately after the experience of an unpleasant or stressful event, people may express unusual physical and emotional reactions. This acute distress in response to a traumatic event is called PTS. It is considered a normal and often adaptive response (12, 13). Stress reactions enable people to react directly to threatening situations and most people can return to a normal emotional state without help from professionals after such an event (14).

Post-traumatic Stress Symptoms (PTSS)

The wide range of distressing physical and emotional reactions is sometimes also referred to as "symptoms" (15). PTSS is the term given to symptoms that can be experienced after a traumatic event. These symptoms include flashbacks, bodily sensations (e.g., sweating), avoidance of trauma-related aspects, emotional numbing, negative feelings, trouble with sleeping, anger, attention problems, hypervigilance, and others (16). As mentioned earlier, people are often confronted with some of these complaints after the experience of a traumatic event. However, the presence of some PTSS symptoms does not automatically lead to significant long-term impairment and must not be confused with a PTSD.

Post-traumatic Stress Disorder (PTSD)

Fortunately, most people do not experience long-term negative reactions after a stressful event but cope with the distress in an adaptive way. However, some develop persistent traumatic stress reactions, such as PTSD. When we speak of PTSD, a specific constellation of PTSS is present in a persistent and significantly distressing way.

In the recent fifth edition of the diagnostic and statistical manual of mental health (DSM-V), the definition of PTSD has been considerably changed as compared to the formerly used DSM-IV. Yet, most psychological diagnostic and screening instruments (used in scientific research) are based on the DSM-IV criteria (17). Therefore, both will be addressed in the following.

PTSD in the DSM-IV

According to the DSM-IV, there are 17 PTSS which are grouped into three clusters: re-experience (cluster B), avoidance (cluster C) of the traumatic event, and increased arousal (cluster D) (18). To meet the diagnostic threshold for PTSD of the DSM-IV, individuals must experience at least one symptom of cluster B, three symptoms of cluster C, and two symptoms of cluster D in reaction to a traumatic event for more than a month.

PTSD in the DSM-V

The DSM-V lists 20 symptoms and divides them into 4 clusters instead of 3. They are called intrusion (cluster B), avoidance (cluster C), negative alterations in cognition and mood (cluster D), and alterations in arousal and reactivity (cluster E) (16). Compared to the DSM-IV, the number of symptoms that must be present for a diagnosis did not change, but the distribution over the different clusters did, as the individual must experience at least one cluster B, one cluster C, two cluster D, and two cluster E symptoms for more than a month. Besides, the DSM-V introduced a PTSD subtype for children 6 years and younger. The major change for preschool children is that in order to obtain a PTSD diagnosis only one symptom in either the "avoidance" or the "negative alterations in cognition and mood cluster" is needed.

Subthreshold PTSD

Individuals can suffer from various PTSS without completely meeting all criteria for a PTSD. When this is the case, the literature speaks of "subthreshold," "partial," "subclinical," or "subsyndromal" PTSD (19). Some authors also refer to elevated PTSS (13, 20). We suggest to use the term subthreshold PTSD as it refers best to patients who do not meet full PTSD criteria, and this term is also preferred by the World Health

Organization (WHO) (21). Patients with subthreshold PTSD suffer from several PTSS but show too few symptoms to obtain a clinical diagnosis of PTSD (22). In literature, there is no strong consensus about a precise definition of subthreshold PTSD (19). Clinicians do not agree about the number of symptoms that must be experienced and to what extent all clusters must be present in order to determine the diagnosis of subthreshold PTSD. Therefore, there is a lot of variation in definition and nomenclature of this variable throughout the literature.

However, all definitions agree that even the presence of subthreshold symptoms can lead to serious impairment of everyday functioning and must not be ignored (22, 23). Unfortunately, subthreshold PTSD is not part of any official classification and is likely to be under-diagnosed. To improve the comparability of scientific findings regarding subthreshold PTSD, the WHO introduced the following definition: meeting two or three of the DSM-V criteria B–E (21). However, most screening questionnaires and diagnostic interviews used in the clinical practice and for research purposes still rely on the DSM-IV criteria, which makes it impossible to use the definition of the WHO. Therefore, updated versions of the instruments are highly needed. The three most frequently used DSM-IV definitions for subthreshold PTSD are (1) meeting criterion B plus C or D, (2) meeting two of the three criteria B, C, and D, and (3) having at least one symptom of each criterion (23). Despite the varying definitions across studies, prevalence rates were found to be most influenced by sample composition rather than definition (23).

Pediatric Medical Traumatic Stress (PMTS)

Another term, which has been developed recently, is PMTS. PMTS refers to "a set of psychological and physiological responses of children and their families to pain, injury, serious illness, medical procedures, and invasive or frightening treatment experiences" (24). PMTS is related to subthreshold PTSD in the way that it represents a concept of PTSS when not all criteria for a PTSD are met. However, PMTS is limited to the pediatric setting. The underlying theory of PMTS offers a framework for comparable psychological responses in reaction to a variety of different pediatric injuries and illnesses (13).

DIAGNOSTIC INSTRUMENTS

About seven different types of validated instruments have been used to measure PTSS in children and adolescents in the pediatric setting (17). Three of them were used in scientific research into PTSD in children and adolescents with ConHD.

(1) The Diagnostic Interview Schedule for Children (DISC) (25) is a structured diagnostic instrument to screen for more than 30 developmental psychiatric diagnoses. The child version is suited for youngsters aged 9–17 years. There is also a parallel parent version for children aged 6–17 years. Furthermore, there is an interviewer-administered computer-assisted and paper-and-pencil version and a self-administered computerized audio version. The DISC contains 24 modules that can be administered individually. One of those modules is the anxiety disorder module that, among others, addresses the DSM-IV criteria of PTSD. Yet, no DSM-V version is available. The DISC has been shown to be a reliable and valid instrument (26, 27).

(2) The University of California at Los Angeles post-traumatic Stress Disorder Reaction Index (UCLA PTSD-RI) has a child, adolescent, and parent version. It can be administered verbally (questions are read out loud) or as a self-report (completed on paper). Norms for children and adolescents between 7 and 18 years are available. It was not designed to provide a PTSD diagnosis. The psychometric properties are good, and the UCLA PTSD-RI has been used widely (28, 29). A DSM-V version has been developed recently.

(3) The Impact of Event Scale-Revised (IES-R) (30) is a self-report instrument to measure subjective distress after a traumatic event. This questionnaire has not been developed to diagnose PTSD. However, research shows that it seems to be a solid instrument for the screening of PTS (31, 32). The IES-R has not yet been updated to the DSM-V criteria.

PTS IN CHILDREN AND ADOLESCENTS WITH ConHD

In the early 1970s, Aisenberg et al. (33) for the first time raised attention to the psychological impact of cardiac catheterization and noted that especially young children showed post procedural emotional stress reactions. Despite the medical advances in pediatric cardiology and cardiac surgery over the last 30 years, a negative impact of those medical treatments on psychosocial functioning remains (34, 35). Since 2000, in total, five studies were published studying PTS in children and adolescents with a heart disease (see **Table 1** for an overview). These few studies had heterogeneous samples, as only three studies included children and adolescents diagnosed with a *congenital* heart disease. Another study included children and adolescents with a genetic heart disease, and the remaining study did not mention the exact diagnoses of the participating patients:

PTS after Cardiac Surgery

Connolly et al. (36) studied 43 children between 5 and 12 years who underwent some type of cardiac surgery. No child had a diagnosis of PTSD pre-operatively. At postoperative assessment (4–8 weeks after discharge from the hospital), 12% of the children met diagnostic criteria for PTSD measured with the anxiety disorder module of the DISC. Both, the child and the parent versions of the DISC, were administered and scored jointly. It is stated that 12% of the sample showed PTSS. Furthermore, no follow-up assessment was done.

Toren and Horesh (37) studied PTSD in adolescents who had an operation for congenital cyanotic heart disease. Thirty-one adolescents between 10 and 21 years participated, of which 29.03% scored "full PTSD likely" on the adolescent version of the UCLA PTSD-RI. Interesting fact is that PTSS were measured 13.7 years (SD = 2.48) after cardiac surgery in this study. Thus, PTSS seemed to be present in adolescents with ConHD long after surgery.

TABLE 1 | Overview of studies into PTSD and PTSS in children and adolescents with ConHD.

Reference	Sample size (*n*)	Age range (in years)	Sample population	Design	Instrument	PTSD (%)	PTSS (%)
Connolly et al. (36)	43	5–12	**Cardiac surgery**	Longitudinal follow-up study	DISC	12	12
Mintzer et al. (38)	104	12–20	Organ transplant (13 × heart)	Cross-sectional descriptive study	UCLA PTSD-RI	16	14
Toren and Horesh (37)	31	10–21	**CCHD**	Cross-sectional descriptive study	UCLA PTSD-RI	29	
Ingles et al. (40)	31	>15	ICD implant (for genetic heart disease)	Cross-sectional descriptive study	IES-R	31	50[a]
Evan et al. (39)	51	0–20	**Heart transplant**	Retrospective study	Retrospective chart review	0	34

Studies including children with congenital heart disease are given in bold.

PTSD, post-traumatic stress disorder; PTSS, post-traumatic stress symptoms; CCHD, congenital cyanotic heart disease; ICD, implantable cardioverter defibrillator; DISC, Diagnostic Interview Schedule for Children; UCLA PTSD-RI, University of California at Los Angeles Post-traumatic Stress Disorder Reaction Index; IES-R, Impact of Event Scale-Revised; ConHD, congenital heart defect.

[a]*PTSD rate in females.*

PTS after Transplantation

Mintzer et al. (38) studied 104 adolescent organ transplant recipients, of which 13 adolescents received a heart transplant. The adolescents were 12–20 years old. PTSD symptoms were measured with the adolescent version of the UCLA PTSD-RI. The authors categorized respondents as "full PTSD likely," when PTSD criteria were met, and "partial PTSD likely," when adolescents met criteria for two of the three DSM-IV symptom clusters. They found that 16.3% were "full PTSD likely" and an additional 14.4% were "partial PTSD likely." The assessment took place 7.3 years (SD = 7.3) after transplantation surgery. No difference in PTSD symptom severity was found between the organ types (liver, heart, and kidney).

Evan et al. (39) did a retrospective chart review to look for PTSS in pediatric heart transplant recipients aged 0–20 years. They reviewed 51 consecutive patients (of which 12 were known with a ConHD) and checked the medical history for any PTSS; 34% were found to have PTSS (at least 1 PTSD symptom according to the DSM-IV) up to 1 year after transplantation. Presence of PTSS was even higher around surgery: 43% were found to have PTSS in the peritransplant period. No patient was reported to have a full PTSD. It must be noted that these findings are speculative as they do not rely on prospective data from validated instruments.

PTS after ICD Implantation

Ninety patients (15 years and older, mean = 49 years, SD = 14) with a clinical diagnosis of a genetic heart disease and an ICD implant participated in the study of Ingles et al. (40). Only those who had experienced at least one ICD shock ($n = 31$) were asked to complete the IES-R. Thirty-one percent reported a score above the cutoff of 22, indicative of PTSD. Notably, 50% of the females who reported a shock showed PTSS.

Predictors and Correlates

Connolly et al. (36) found that ICU length of stay (48 h and more) was the only predictor of postoperative PTSD symptoms in children aged 5–12 years who underwent cardiac surgery. The amount of hours spent at the ICU ranged between 0 and 1008 hours in this study. Cognitive level, negative reactivity and approach/withdrawal dimensions of temperament, and family support were no predictors of postoperative PTSD symptoms.

Mintzer et al. (38) found no association between any demographic (gender, ethnicity, age at interview) or illness-related (organ type, time since transplant, age at transplant) variables and PTSS severity. However, they found that illness onset (acute versus chronic) and medical complications in the past year (mild versus moderate/severe) did act as a significant predictor of PTSS when combined in the regression analysis. It is striking that adolescents with mild complications, rather than moderate/severe, had a higher chance of reporting PTSS. Furthermore, an acute onset also increased the risk for PTSS.

In the *general pediatric setting*, different factors predict the development of PTSS in children after injury (41):

- Child characteristics: prior internalizing (e.g., anxiety and depression) and externalizing (e.g., aggressive behavior) problems,
- Environmental characteristics: parental PTSS,
- Trauma-related factors: elevated heart rate immediately after injury and perceived severity of the event, and
- Cognitive processes: dysfunctional cognitive strategies/beliefs.

Remarkably, the *subjective* experience of life threat (trauma severity), rather than objective factors (mechanism, type, and severity of the injury), seems to contribute to the development of PTSS (41).

PTS IN CHILDREN AND ADOLESCENTS WITHOUT ConHD AFTER HOSPITALIZATION

Since few studies focused on PTS in children and adolescents with ConHD, other pediatric populations can serve as an important reference framework. From other pediatric populations without ConHD, it is known that the experience of an injury or illness can lead to traumatic stress reactions in children and adolescents. Hospitalization, admission to the emergency department, entering intensive care, and undergoing medical interventions all heighten the risk for psychological problems alongside the evident physical complaints (41). Research shows that even mild to moderate physical injury leads to heightened

PTSS (42). The PTSD prevalence in children undergoing admission to the pediatric intensive care unit (PICU) has been shown to be between 5 and 28% (43). Despite the overlapping medical context, it seems that PTSD prevalence rates differ between young patients with a (chronic) illness and those with an injury (2). Both illness and injury often result in invasive procedures and hospitalizations. In addition, however, children who suffer an injury were also confronted with some kind of accident that may have been a traumatic experience itself. This might explain why injured children and adolescents show higher rates of PTSD than ill children and adolescents. Furthermore, young patients rate the perceived trauma severity and/or life threat higher when injured, compared to children with an illness. However, this might also be due to differences in follow-up measurements. Across research, children who experienced an injury were followed up for a shorter time span. Nevertheless, it is recommended to disentangle the traumatic impact of illness and injury samples when studying PTSD.

CONCLUSION AND CLINICAL IMPLICATIONS

Only five studies have been found that focused on PTSD in children and adolescents with different heart diseases, of which one did not use standardized measurements. The four studies using standardized instruments to measure PTSD in children with a (congenital) heart disease found PTSD prevalence between 12 and 31% even up to many years after the traumatic experience. This is comparable to 11–21% found in adults with ConHD (44). Compared to a lifetime PTSD prevalence of 5% in the general adolescent population (13–18 years) (45), youngsters with ConHD show a clearly heightened risk for PTSD. Two of the four described articles that used standardized measurements also studied the prevalence of subthreshold PTSD and found a prevalence of 12–14% in children and adolescents with ConHD. This is comparable with the mean subthreshold PTSD prevalence of 14.7% found in a meta-analysis of Brancu et al. (23).

Methodological weaknesses of the studies described are use of small sample sizes, different time intervals in follow-up assessments, the use of different instruments, and single- versus multi-informant approaches. Moreover, it is uncertain to what extent selection bias influenced the results. Only five studies into PTSD were found regarding children with ConHD using very specific samples. This lends to limited generalizability to the overall pediatric ConHD population. However, results are comparable to outcomes in other pediatric medical populations (such as children in the PICU).

In summary, children and adolescents with ConHD have an elevated risk of developing PTSD. Given the fact that both PTSD and subthreshold PTSD lead to serious psychological and behavioral impairments and increased health-care use (23), it is astonishing that only very few studies investigated the prevalence, correlates, and impact of PTSD in children and adolescents with ConHD. Even more concerning is that no study has evaluated an evidence-based treatment in this pediatric population yet. For adults, it has been proven already that eye movement desensitization and reprocessing (EMDR) is an effective psychotherapeutic treatment to reduce (symptoms of) PTSD (46). A large randomized controlled trial into the effectiveness of EMDR for children and adolescents with ConHD is now being executed in the Erasmus MC – Sophia Children's Hospital, Rotterdam, the Netherlands. The authors of this review recommend early screening of psychosocial problems in children with ConHD, given the fact that those children have a heightened risk of developing PTSS. If indicated, referral for psychosocial treatment (trauma-focused cognitive behavioral therapy or EMDR) should be arranged.

AUTHOR CONTRIBUTIONS

This manuscript was written by MM with close collaboration and contribution of EU, WH, IB, and JL.

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Predictors of Memory Deficits in Adolescents and Young Adults with Congenital Heart Disease Compared to Healthy Controls

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Introduction: Adolescents and young adults with congenital heart disease (CHD) show a range of memory deficits, which can dramatically impact their clinical outcomes and quality of life. However, few studies have identified predictors of these memory changes. The purpose of this investigation was to identify predictors of memory deficits in adolescents and young adults with CHD after surgical palliation compared to healthy controls.

Method: One hundred fifty-six adolescents and young adults (80 CHD and 76 controls; age 14–21 years) were recruited and administered an instrument to assess memory [Wide Range Assessment of Memory and Learning Second Edition – general memory index (GMI) score] and completed questionnaires that measure anxiety, depression, sleepiness, health status, and self-efficacy. Descriptive and non-parametric statistics were used to assess group differences, and logistic regression to identify predictors of memory deficits.

Results: CHD subjects consisted of 58% males, median age 17 years, 43% Hispanic, and medians of 2 previous heart surgeries and 14 years since last surgery. Memory deficits (GMI $\leq$ 85) were identified in 50% CHD compared to 4% healthy controls (median GMI 85 vs. 104, $p < 0.001$). Of GMI subscale medians, CHD subjects had significantly worse memory performance vs. healthy controls (verbal 88 vs. 105, $p < 0.001$; attention 88 vs. 109, $p < 0.001$; working memory 86 vs. 108, $p < 0.001$). No significant differences appeared between groups for visual memory. Multiple clinical and psychosocial factors were identified which were statistically different on bivariate analyses between the subjects with and without memory deficits. By multivariate analysis, male gender,

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Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; BAI, Beck anxiety inventory; CHD, congenital heart disease; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ESS, Epworth sleepiness scale; GMI, general memory index; GSE, general self-efficacy; HLHS, hypoplastic left heart syndrome; PHQ-9, Patient Health Questionnaire Depression Module; SF-36v2, Short-Form-36 Health Survey Version 2; WRAML2, wide range of assessment memory and learning 2nd edition.

number of surgeries, anxiety, and self-efficacy emerged as independent predictors of memory deficits.

Conclusion: Adolescents and young adults with CHD, more than a decade since their last surgery, show significant verbal, attention, and working memory deficits over controls. To enhance patient memory/self-care, clinicians should explore ways to reduce anxiety, improve self-efficacy, and increase use of visual patient education material, especially in CHD males.

Keywords: memory, working memory, congenital heart disease, anxiety, self-efficacy

INTRODUCTION

Memory is an important part of cognition and is inter-related with executive function skills. Memory deficits have been reported in up to 57% of adolescents with congenital heart disease (CHD) who have undergone surgical palliation (1–5). The mechanisms contributing to memory or neurocognitive deficits are multifactorial and are likely to include factors that are related to the CHD, including cyanosis, early cardiac surgery, a wide range of genetic syndromes or gene mutations, and prenatal and other pre- and postoperative factors that can have significant adverse effects on brain development and/or injury (6–9). However, these deficits may not become apparent until school-age, when higher-level organizational skills are required and can be especially problematic in adolescents who must eventually take responsibility for their health during the transition to adulthood. Furthermore, memory deficits can significantly impact the adolescent's ability to name and follow a prescribed medication regime, adhere to preventative care and appointments, and potentially impact educational achievement, employability, and quality of life.

The improved survival of infants with complex CHD has been attributed to advancements in fetal detection, improved surgical techniques, and perioperative care (10) but many are at risk for neurodevelopmental and cognitive delays (8, 9, 11–13). Interestingly, risk factors or predictors of cognitive deficits have been more associated with innate- or patient-related factors (e.g., genetic syndrome, prematurity or weeks gestation, socioeconomic status, and maternal education) vs. intraoperative or postoperative management strategies [e.g., duration of cardiopulmonary bypass (CPB), hospital length of stay] (8, 9, 11–14). Memory deficits have emerged in some adolescent neuropsychological studies with worse memory identified in more severe or complex CHD (1–3). However, these studies lack the investigation of other potential patient or behavioral-related factors that could affect or produce transient memory loss (e.g., anxiety, depression, attentional disorders, excessive sleepiness, low self-efficacy, and perceived health status) (15–18). It remains unclear to what extent these memory deficits at a younger age persist to adolescence and young adulthood. Currently, no studies have specifically focused on predictors of memory deficits in adolescents and young adults with CHD. The identification of modifiable variables could potentially improve memory and subsequently the ability for self-care. Therefore, our specific aim of this study was to identify predictors (including clinical and behavioral factors) of memory deficit in adolescents and young adults with CHD after surgical palliation compared to age- and gender-matched healthy controls.

MATERIALS AND METHODS

Study Population and Design

This is a cross-sectional, comparative study of 156 adolescents and young adults (80 CHD and 76 Healthy) recruited *via* flyers or provider referrals from University of California Los Angeles (UCLA) and Children's Hospital Los Angeles (CHLA) pediatric cardiology clinics and non-hospital based cardiology clinics in Southern California. This study was carried out with Institutional Review Board approval from both UCLA and CHLA. We included adolescents and young adults with CHD between the age of 14 and 21 years, who have undergone surgical palliation requiring CPB. CHD participants were excluded, if they had isolated coarctation of the aorta or patent ductus arteriosus (not requiring CPB), previous head injury (e.g., concussion, stroke) severe developmental delay precluding active study participation and self-reporting (e.g., cerebral palsy, severe hypoxic-injury, or genetic syndrome associated with cognitive delays). If eligible, either a same day or future appointment was made to participate in the study.

Healthy controls were recruited from local high schools and community flyer. This control group was recruited instead of using normative data to capture the high prevalence of Hispanic ethnicity in the City of Los Angeles. Participants were screened by self-report and excluded for any chronic medical or psychiatric conditions or any previous head injury. If eligible, controls were matched to a CHD participant for age (±2 years) and gender, and an appointment was made to participate in the study either at their home, public library, or research office.

Procedure

After parental permission and assent were obtained from participants under age 18, and informed consent was obtained from participants aged 18 and over, all study procedures were performed with the adolescent and test administrator in a private room. The test administrators were two trained graduate research assistants who met qualifications for administration with interrater agreement of 98% for the Wide Range of Assessment Memory and Learning second edition (WRAML2).

The WRAML2 core and optional subtests were completed on all subjects (approximately 1 h) followed by self-administered questionnaires (approximately 15–20 min). Demographic and clinical data were obtained from a limited medical record review which included age, gender, ethnicity, type of CHD, number and type of surgical procedures, first surgery performed <30 days of life, cyanosis at birth, presence of genetic syndrome, attention deficit disorder (ADD) and/or hyperactivity (ADHD), and use of remedial educational services.

Memory

Memory was measured using the WRAML2. This administered test is a highly reliable and valid measure of memory and learning abilities in subjects from age 5 to 90 years (19). The broad age range of the WRAML2 was important in instrument selection because of the need to cover adolescents and young adults compared to using two different measures (i.e., child and adult). The WRAML2 is a comprehensive test that measures an overview of memory function which consists of verbal and visual memory, attention/concentration, working memory, and memory recognition. The core battery consists of six subtests [story memory, verbal learning, design memory, picture memory, finger window (short-term memory of a visual sequential pattern), numbers/letters (digit-span format using both numbers and letters)] that when combined yield a general memory index (GMI) score (mean 100, SD ± 15) (19). Additional optional subtests performed were working memory and memory recognition yielding the general memory recognition index (GMR) score (mean 100, SD ± 15). The GMI measures immediate recall and the GMR measures delayed recall. The WRAML2 or GMI has been used in previous cognitive studies in children with and without CHD (20–22). The alpha reliabilities for the core subtests range from 0.85 to 0.94 (GMI 0.93) (19).

Perceived Health Status

Perceived health status was measured using the Short-Form-36 Health Survey Version 2 (SF-36v2). The SF-36 was originally developed to measure perceived health status. However, many researchers incorrectly use the terms *health-related quality of life* or *quality of life* in reference to what the SF-36 measures (23). This self-reported questionnaire consisting of 36 Likert questions with 8 health concepts that assess perceived health status in: (1) physical function, (2) the physical function limitation as result of physical injury, (3) the role due to emotional problems, (4) energy and vitality, (5) mental health, (6) social function, (7) physical pain, and (8) general health (24). Two summary scores are calculated from the eight domain scores which include a physical component summary (PCS) and mental component summary (MCS). Summary scores range from 0 to 100 with higher scores indicating better health status (24). The SF-36 has been used in other studies in CHD (18, 25–27). Correlations between the SF-36 and other health status measures ranged from 0.51 to 0.82 in mental health, and 0.52 to 0.85 in physical health (24).

Anxiety

Anxiety levels were measured using the Beck anxiety inventory (BAI) (28). The self-reported BAI is a 21-item questionnaire that measures the severity of common anxiety symptoms. Responses are rated on a 4-point (0–3) Likert-type scale (0 = "not at all bothered" to 3 = "severely bothered") with a scores ranging from 0 to 63. Higher scores indicate greater anxiety severity (0–21 as low anxiety to 36–63 as severe anxiety). The BAI has been used in previous studies in CHD with a Cronbach's alpha of 0.93 (29).

Depression

Depressive symptoms were measured using the Patient Health Questionnaire Depression Module (PHQ-9). The self-reported PHQ-9 is a 9-items questionnaire, responses are rated on a 4-point (0–3) Likert-type scale (0 = "not at all bothered" to 3 = "bothered nearly every day"), with scores ranging from 0 to 27. Higher scores indicate greater depression severity (0–4 = no depression to greater than 20 = severe depression) (30). The PHQ-9 is a widely used measure of depression severity in the CHD population with a Cronbach's alpha range of 0.86–0.89 (18, 31).

Sleepiness

Excessive sleepiness was assessed using the Epworth sleepiness scale (ESS) (32). The self-reported ESS is a 9-item questionnaire, responses are rated on a 4-point (0–3) Likert scale (0 = "no chance of falling asleep" to 3 = "high chance of falling asleep"), with scores ranging from 0 to 24. Higher scores on the ESS indicate more excessive sleepiness (≥10 is considered positive). The ESS is a widely used instrument with established reliability and validity with a Cronbach's alpha of 0.86 (32).

Self-Efficacy

Self-efficacy was measured using the general self-efficacy (GSE) scale. The GSE is a 10-item questionnaire used to assess the belief in one's own ability to cope with difficult demands in life (33). The self-reported responses are rated on how true the statement is for the person on a 4-point Likert-type scale (1 = "not at all true" to 4 = "exactly true") with scores ranging from 10 to 40. Higher scores indicate greater self-efficacy with a Cronbach's alpha range from 0.76 to 0.90 (33).

Statistical Analysis

Characteristics of the sample are presented as means with SD or medians with range for continuous variables. Subjects were classified into two groups (CHD and Healthy). Variables were examined for normality and outliers. The continuous data had non-normal distributions (per Shapiro–Wilks tests of normality), and groups were compared using non-parametric statistics consisting of the Mann–Whitney *U* test for all continuous variables and Chi-squared for all categorical variables. Spearman's rho correlation coefficients between all predictor and the outcome variable GMI were examined. Only predictors with significant correlations ($p < 0.05$) to the outcome variable GMI were entered into the multivariable analysis. The stepwise logistic regression model was performed for the binary variable of GMI ≤85 and >85 (1 SD below the expected population mean 100). The software identified the sequence of entry of covariates into the statistical model. All analyses were conducted using the Statistical Package for the Social Sciences version 23.0 (IBM; Somers, NY, USA).

RESULTS

Sample Characteristics

Demographic characteristics of the CHD and healthy control groups are summarized in **Table 1**. No statistically significant differences in age, gender, ethnicity, and education emerged between groups. However, ethnicity showed a trend toward significance ($p = 0.06$) with 41 and 39% Hispanic ethnicity in the CHD and control group, respectively. Public insurance was higher in the CHD group (68%) compared to controls (10%) and the incidence of having ADD or ADHD (21%) compared to controls (4%). Use of remedial education services was identified in 24% of the CHD group only. Clinical characteristics of the CHD group are summarized in **Table 2**. Fifty percent of the sample had complex CHD, first surgery <30 days of age (58%), median of 2 previous surgeries, median 14 years from last surgery, taking 1–2 medication (48%), and New York Heart Association class I (64%).

Memory, Anxiety, Depression, Sleep, Self-Efficacy, and Health Status Scores between Groups

Comparison of memory, anxiety, depression, sleepiness, self-efficacy, and health status between CHD and healthy controls is summarized in **Table 3**. In the CHD group, 50% scored 1 SD below the normal for GMI and 8% were 2 SD below the normative of 100 compared to 4 and 0% in the controls, respectively. Furthermore, GMI scores 1 SD below the normal were greater in males [$n = 26$ (62%)] vs. females [$n = 9$ (32%)]. Median GMI scores between CHD and healthy controls were 85 vs. 108, $p < 0.001$, respectively. All subgroups of the GMI and GRI showed statistically significant differences between CHD and controls except for visual memory.

TABLE 1 | Demographic characteristics between the congenital heart disease and control groups.

Variable	CHD ($n = 80$)	Healthy ($n = 76$)	p-Value
Age (median)	17 (14–21)	18 (14–21)	0.700
Gender %			1
Male	42 (58%)	42 (58%)	
Female	38 (42%)	34 (42%)	
Ethnicity %			0.066
White	35 (44%)	36 (47%)	
Hispanic	33 (41%)	30 (39%)	
Other	12 (15%)	10 (14%)	
Education %			0.410
9th–11th grade	49 (61%)	47 (62%)	
High school graduate	18 (22%)	15 (20%)	
1–4 years of college	13 (13%)	14 (18%)	
Insurance[a]			<0.001*
Private	16 (20%)	38 (50%)	
Public	54 (68%)	8 (10%)	
Unknown/self pay	10 (12%)	30 (40%)	
ADHD/ADD %	17 (21%)	3 (4%)	<0.001*
Remedial education %	19 (24%)	0 (0%)	<0.001*

ADHD, attention deficit hyperactivity disorder; ADD, attention deficit disorder; CHD, congenital heart disease; CPB, cardiopulmonary bypass; N/A, not applicable.
[a]Insurance was self-reported in healthy controls.
**Statistically significant ($p < 0.05$).*

The CHD group had 68 and 50% with greater than or equal to mild anxiety and depression symptoms, respectively, compared to 32 and 25% of the healthy controls. Median anxiety and depression scores between CHD and healthy controls were statistically significant (15 vs. 6; $p = < 0.001$ and 6 vs. 2; $p = 0.002$), respectively. Males had more anxiety and depressive symptoms compared to females.

Median sleepiness scores were statistically significant in the CHD group compared to the healthy controls (10 vs. 8; $p = 0.016$), respectively. Excessive sleepiness (abnormal ≥10) was identified in 32% of the CHD group compared to 27% of healthy controls with no gender differences identified.

Median self-efficacy scores were lower in the CHD group compared to healthy controls (28 vs. 34; $p = 0.006$), respectively. Low self-efficacy (scores <30) was identified in 51% of the CHD group compared to 19% in the healthy control group. Lower self-efficacy was associated with worse anxiety, depression, sleepiness, and perceived health status. Males had lower self-efficacy than females in the CHD group.

TABLE 2 | Clinical characteristics of the congenital heart disease group.

Clinical variables	$n = 80$ (%)
Defect severity[a]	
Simple	4 (5%)
• Isolated atrial septal defect (ASD)	2
• Isolated ventricular septal defect (VSD)	2
Moderate	36 (45%)
• Tetralogy of Fallot with or without pulmonary atresia (PA)	14
• Aortic stenosis	11
• Coarctation of the aorta (COA) with VSD and/or ASD	5
• Mitral stenosis/regurgitation	2
• Ebstein anomaly	2
• Partial atrioventricular canal (AVC)	1
• ALCAPA	1
Great complexity	40 (50%)
• Transposition of the great arteries (d-TGA)	14
• Congenitally corrected TGA (s/p double switch)	2
• Truncus arteriosus	1
• PA with intact ventricular septum (IVS)	1
• Single ventricle (s/p modified Fontan procedure) ($n = 22$)	
○ HLHS, DORV, unbalanced AVC (single right)	12
○ TA, DILV, unbalanced AVC (single left)	10
First surgery <30 days of age	46 (58%)
# Surgeries with CPB (median)	2 (1–5)
Years since last surgery (median)	14 (1–20)
Genetic syndrome %	2 (4%)
# Medications	
None	15 (19%)
1–2	38 (47%)
3–4	20 (25%)
≥5	7 (9%)
Pacemaker	10 (11%)
Cyanosis at birth	48 (60%)
Current oxygen saturation <90%	9 (12%)
NYHA classification	
I	51 (64%)
II–III	29 (36%)

[a]Based on Bethesda conference classification.
HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; TA, tricuspid atresia; DILV, double inlet left ventricle; ALCAPA, anomalous left coronary artery to pulmonary artery; NYHA, New York Heart Association.

TABLE 3 | Comparison of memory, anxiety, depression, sleepiness, self-efficacy, and health status between congenital heart disease and healthy control groups.

Variables	CHD ($n = 80$)	Healthy ($n = 80$)	p-Value
	Median (range)		
WRAML2			
General memory index	85 (49–112)	108 (85–123)	<0.001*
Visual memory	100 (79–115)	100 (79–127)	0.162
Verbal memory	88 (69–120)	105 (80–135)	<0.001*
Attention/concentration	88 (37–117)	109 (65–134)	<0.001*
General recognition index	93 (57–122)	112 (87–128)	<0.001*
Working memory	86 (55–122)	108 (86–139)	<0.001*
Visual memory recognition	93 (62–122)	105 (82–122)	<0.001*
Verbal memory recognition	93 (58–128)	109 (84–128)	<0.001*
Anxiety (BAI)	15 (3–52)	6 (0–34)	<0.001*
Depression (PHQ-9)	6 (0–24)	2 (0–17)	0.002*
Sleepiness (ESS)	10 (0–18)	8 (0–13)	0.016*
Self-efficacy (GSE)	29 (14–40)	34 (22–40)	0.006*
Perceived health status (SF-36v2)			
Subscales			
Physical function	75 (5–100)	100 (15–100)	<0.001*
Role function physical	71 (0–100)	100 (50–100)	<0.001*
Bodily pain	84 (0–100)	84 (41–100)	0.221
General health	68 (10–100)	82 (37–100)	<0.001*
Energy/fatigue	62 (6–100)	63 (18–100)	0.625
Social function	87 (0–100)	100 (25–100)	<0.001*
Emotional function	83 (16–100)	91 (16–100)	0.005*
Mental health	70 (20–100)	80 (35–100)	0.109
Component summary scores			
Physical	49 (27–66)	58 (28–63)	<0.001*
Mental	47 (13–62)	51 (19–64)	0.259

BAI, Beck anxiety inventory; CHD, congenital heart disease; ESS, Epworth sleepiness scale; GSE, general self-efficacy; PHQ-9, Patient Health Questionnaire Depression Module; SF-36v2, Short-Form-36 Health Survey Version 2; WRAML2, Wide Range Assessment of Memory and Learning, Second Edition.
**Statistically significant ($p < 0.05$).*

Perceived health status is summarized in two component scores (physical and mental). Median scores in physical were statistically significant in the CHD group compared to healthy controls (49 vs. 58; $p < 0.001$) with no difference identified in the mental component scores. In the eight subscales, all were statistically significant except for bodily pain, energy/fatigue, and mental health.

Predictors of Memory Deficits

The list of covariates associated with GMI included in the multivariate model for the total cohort is summarized in **Table 4**. Gender, number of surgeries, pacemaker, cyanosis at birth, first surgery <30 days of life, number of medications, defect severity, self-efficacy, sleepiness, anxiety, depression, and physical and mental health status were all entered in the stepwise logistic regression if the variables were significant on the bivariate analyses for memory deficits. The final multivariate logistic regression model for GMI is presented in **Table 5**. Male gender, number of surgeries, anxiety, and self-efficacy were independent predictors which explain approximately 45–64% of the variance for memory deficits using Cox and Snell R^2 or −2 log likelihood, respectively.

TABLE 4 | List of covariates associated with GMI included in the multivariate model.

Variables	r	p-Value
Gender	0.18	0.029*
Number of surgeries	−0.60	<0.001**
Pacemaker	−0.29	0.020*
Defect severity	−0.31	0.009**
Infant surgery <30 days	−0.53	<0.001**
Cyanotic at birth	−0.36	0.003*
Number of medications	−0.57	<0.001**
Self-efficacy	0.46	<0.001**
Sleepiness	−0.37	<0.001**
Anxiety	−0.44	<0.001**
Depression	−0.31	<0.001**
Physical health status (SF-36)	0.41	<0.001**
Mental health status (SF-36)	0.18	0.030*

r = Spearman's rho correlation coefficient.
**Correlation is significant at 0.05 level (2-tailed).*
***Correlation is significant at 0.01 level (2-tailed).*

DISCUSSION

Significant memory deficits in immediate and delayed tasks were identified in a high proportion of adolescents and young adults with moderate to complex CHD who had undergone surgical palliation at least 10 years previously compared to age- and gender-matched to age- and gender-matched controls. This finding suggests that memory deficits detected at a younger age (13, 34, 35) persists into adolescence and young adulthood. Unintentional or selective "forgetting" is a common behavioral trait seen in adolescence when the information processed is viewed as a low priority or unimportant (36), but in CHD, there could be a behavioral or biologic substrate. Our findings are consistent with three studies by Bellinger et al. (1–3) on young adolescents with complex CHD (D-transposition of the great arteries, tetralogy of Fallot, and single ventricle defects) in which memory was evaluated as part of a neuropsychological assessment and structural brain imaging was performed. In these studies, brain imaging identified focal or multifocal white matter abnormalities but the exact location(s) of injury were not specified in areas affecting memory (1–3). Most covariates in these studies, associated with the GMI scores, were related to the number of surgical or catheterization complications, history of postoperative seizures, and few patient-related factors, such as male gender, birth weight, or gestational age (1–3). Our study similarly identified male gender and number of surgical procedures with additional behavioral-related factors (anxiety and self-efficacy) also emerging as independent predictors of memory deficits. The CHD group was noted to have a higher incidence of ADD/ADHD than the healthy controls. Attentional disorders are more common in males than females and have an increased prevalence in the CHD population (37, 38). Although the incidence of ADD/ADHD was lower in our CHD group compared to other reports (37, 38), this may be the reason why the diagnosis did not emerge as a covariate associated with memory deficits. However, ADD/ADHD is often un-diagnosed and can co-exist with other mood disorders (anxiety/depression) that impact one's self-efficacy or perceived ability to accomplish the task at hand. Male gender continues to be a

TABLE 5 | Final multivariate logistic regression model for general memory index (<85 and ≥85).

Predictor variables	*B*	SE	*p*	Exp (*B*)	CI (95%) for Exp (*B*)	Model summary
Gender (male)	−1.948	0.781	0.013	0.143	0.031–0.659	Cox and Snell R^2 = 0.45 or
Number of surgeries	−1.596	0.327	0.000	0.203	0.107–0.385	−2 log likelihood = 64
Anxiety	0.079	0.041	0.050	1.082	0.999–1.172	
Self-efficacy	0.326	0.086	0.000	1.385	1.171–1.639	

risk factor for memory deficits into adolescence and young adulthood with males having worse anxiety and depressive symptom scores than females in our study. This non-modifiable predictor warrants awareness related to gender differences and the need for early assessment, referral, and to engage males in targeted interventions to improve memory deficits.

The multivariate analysis emphasized the importance of patient-related factors compared to clinical or disease specific variables. However, the size and significance of the beta coefficient for the variable number of surgeries suggest that surgery may have a greater impact on memory. The number of surgeries has been reported in other studies to be predictive of abnormal developmental outcomes in younger children (39) or for internalizing (anxiety/depression) and externalizing (attentional disorders) behavior problem in CHD (40). Utens and colleagues (40) also found the number of surgeries to be predictive of behavioral problems and suggested that the number of surgeries, procedures, or hospitalizations could potentially reflect the "experiential" aspect of living with CHD. However, the number of surgeries may also be a surrogate for greater CHD complexity. With advancement in cardiac interventional procedures, such as percutaneous valve replacements, the potential to modify or reduce the total number of surgeries required throughout the lifespan is a realistic possibility for some CHD subgroups (e.g., tetralogy of Fallot) and reduce the risk for procedural focused anxiety.

Our data confirmed that a significant number of adolescents and young adults with CHD had mild to moderate anxiety symptoms compared to controls. Anxiety and depression have been documented previously in adolescents and adults with CHD (41, 42) and can affect cognitive abilities both independently or simultaneously. Ong and colleagues (43) discovered that heart-focused anxiety was associated with parental overprotection and severity of CHD, which may promote feelings of dependency, low self-efficacy, and in turn could potentially compromise cognitive and academic performance. In addition, a positive sense of self, particularly self-efficacy has been associated with better self-care, health status, quality of life, and academic performance (31, 44–46). Anxiety and self-efficacy are modifiable aspects related to psychosocial adjustment in adolescents and young adults living with CHD. Our study findings in the multivariate analysis show anxiety and self-efficacy to have less of an impact on memory deficits compared to other variables (i.e., number or surgeries). Although optimistic, it is unclear the extent that memory deficits will improve with the fostering of psychosocial adjustment.

An interesting discovery in our study was worse verbal compared to visual subtests of the GMI in the CHD group. This finding is consistent with other studies in younger CHD populations in which different verbal memory tasks (e.g., narrative recall, memory of names) were worse than a comparative CHD or control group (34, 35, 45). Some authors suggest this may not be related to memory but to poor attention and alertness and deficiencies in language skills or lower processing speeds needed for verbal memory or executive functioning tasks (34, 35). A study in school age children with hypoplastic left heart syndrome (HLHS) identified deficits in both verbal and visual long-term memory (35). However, visual short-term memory was impaired in children who underwent deep hypothermic circulatory arrest (DHCA) during surgical palliation compared to continued antegrade cerebral perfusion suggesting the impact of DHCA on central nervous system structures involved with visual memory processes. Conversely, Bellinger and colleagues (3) identified better verbal than visual memory for both immediate and delayed trials in adolescents with tetralogy of Fallot without a genetic/phenotypic diagnosis. This finding may be associated with a higher number of complications and surgeries as well as brain image abnormalities in almost half of the study sample which may involve regions related to visual impairment/memory. Our study cohort had significant deficits in attention/concentration which could partially explain worse verbal compared to visual memory. Nonetheless, this finding warrants the use of more visual educational material (e.g., handouts, apps, website material) than verbal training to maintain attention and improved learning/self-care as part of CHD transition/educational programs.

Clinical Implications for This Study

Our findings are important for providers, patients, and parents to be awareness of potential risk factors associated with memory deficits in adolescents and young adults living with CHD. Unfortunately, certain variables such as male gender and number of surgeries are non-modifiable while anxiety and self-efficacy are amenable to change. More research has suggested that family and maternal factors (i.e., mental health, education, socioeconomic status) may play a more significant role than disease or surgical variables related to behavioral/psychosocial outcomes. However, there are very few reported intervention studies to support psychosocial adjustment in children with CHD and their families (47, 48). Interventions focused on maternal well-being and optimizing parenting skills that focus on self-efficacy and reducing anxiety or worries can be helpful in early childhood development. Other intrinsic or patient factors not included in this study (i.e., hypoxic–ischemic brain injury) that can contribute to memory deficits may benefit from future pharmacological strategies to protect or promote neurogenesis [i.e., thiamine or green tea extract supplementation (49–51) and statins (52)]. Nonetheless, special focus on males with CHD to encourage participation in future interventions is warranted.

Our study should be interpreted in light of some limitations. Although the logistic regression model explained almost half of the variance, other factors not accounted for in this study are making a contribution to memory deficits. Other studies have identified the contribution of maternal factors and socioeconomic status to impact cognitive and neurodevelopmental outcomes (38) which were not measured in this study. However, we did find that the CHD group had a higher prevalence of public vs. private insurance compared to controls. Parents suspicious of a memory problem in their child might have been more motivated to participate, whereas parents of children who perform well at school or parents not wanting to potentially find another problem with their child may have decline disproportionately to participate. Our sample was heterogeneous with the majority of CHD diagnoses classified as moderate to severe and cannot be generalized to simple/less complex forms of CHD. The sample size prohibited further group comparison related to defect severity. The numbers of participants with genetic syndromes or ADD/ADHD in both groups may be higher as testing was not performed and only identified *via* medical chart review in CHD participants or parental self-report in healthy controls. Primary care chart reviews were not performed on healthy controls as this would be difficult or almost impossible due to inconsistent medical follow-up during adolescents creating potential sample bias. Generalizability of our findings can be challenging given the high proportion of Hispanic participants which is quite different from other cardiac centers. Furthermore, most CHD participants had their last surgical procedure over a decade ago and did not have the advantages in improved surgical technique and medical management of the current era. Neuroimaging was not performed for this study, so the incidence of congenital or acquired brain injury is unknown. However, neuroimaging is currently being performed by our research team in the single ventricle participants in relation to brain structures that affect memory, and we are hopeful that this will provide clarification on the relationships between brain structure and cognitive status in these subjects.

CONCLUSION

A combination of fixed and modifiable factors influenced memory deficits in adolescents and young adults with moderate to complex CHD after surgical palliation. In this cohort of adolescents and young adults, more patient-related (self-efficacy, anxiety, male gender) rather than clinical factors (number of surgeries) were predictors of memory deficits. Deficits emerged in verbal memory, attention/concentration, working memory, and memory recognition compared to healthy control. However, visual memory appeared to be less affected. Therefore, to potentially enhance adolescent CHD self-care, clinicians should explore the development of clinical interventions targeted to reduce anxiety, improve self-efficacy, and increase use of visual patient education material in transition educational programs in the CHD population.

AUTHOR CONTRIBUTIONS

NP: study concept/design, data analysis, interpretation, and drafting of the original manuscript. WE and DF: acquisition of data. MW, MP, NH, AL, and RK: analysis and interpretation of the data and critical revisions of the manuscript. All the authors approved the final version of the manuscript.

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Do Self- and Proxy Reports of Cognitive Problems Reflect Intellectual Functioning in Children and Adolescents with Congenital Heart Defects?

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Aim: Children with congenital heart defects (CHD) who suffer from cognitive impairments and school difficulties need to be identified as early as possible in order to set appropriate interventions in place that may enhance the school situation and quality of life for these children. Identifying children and adolescents at risk for cognitive difficulties requires specific screening tools. This study assessed such a tool – Pediatric Quality of Life Inventory Cardiac Module subscale: Cognitive Problems – to investigate whether proxy reported and self-reported cognitive problems were associated with measured intellectual functioning in children and adolescents with CHD treated with surgery or by catheter interventions.

Method: The sample consisted of 184 children/adolescents aged 3, 5, 9, and 15 years. The severity of the CHD diagnoses was categorized into three groups (mild, moderate, or severe) for all age groups. For all the age groups, we collected proxy ratings of cognitive problems, and for the 5-, 9-, and 15-year-olds, we also collected self-reported cognitive problems. Intellectual functioning was measured with the Wechsler intelligence scales. The control variables were socioeconomic status and severity of diagnosis.

Results: A strong association was found between the parent's ratings of cognitive problems and the children's and adolescents' results on the Wechsler scales. This association was present for all ages, including the 3-year-olds. As for the self-reports, an association was only found between the 15-year-olds self-report of cognitive problems and their results on the Wechsler scales.

Conclusion: To identify children with cognitive problems as early as at the age of 3 years, parent-rated Pediatrics Quality of Life subscale: Cognitive Problems can be used as a screening tool. For 15-year-olds, the self-report ratings can be used as a screening tool. We also suggest a cutoff score of 80 for both the 15-year olds as well as the proxy reports. If the score falls below 80 the child should be formally evaluated using standardized cognitive test.

Keywords: intellectual functioning, neurodevelopment, congenital heart defects, cardiac treatment by surgery or by catheter interventions, quality of life, self-report, proxy reports

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INTRODUCTION

A large number of studies show that children with congenital heart defects (CHD) have higher incidence of cognitive impairments and poor academic results compared to healthy controls (1, 2). Low intellectual functioning can adversely influence many aspects of an individual's life (3). Cognitive impairments affect not only school functioning and education (4) but also emotion regulation (5) and health (4); however, cognitive impairments affect many other aspects of daily functioning and life expectancies. Because cognitive impairments are overrepresented in children and adolescents with CHD, it is important to have reliable screening tools to identify children and adolescents in need of more extensive evaluations (3). One such possible measure is the Cognitive Problems Scale from the Pediatric Quality of Life Inventory Cardiac Module. In the current study, the aim was to evaluate whether the Cognitive Problems scale could be used as a screening tool. We investigated the association between self- as well as proxy reports on the Cognitive Problems Scale for children and adolescents with CHD for four different age groups (3-, 5-, 9-, and 15-year-olds) with their actual cognitive performance on standardized cognitive test, i.e., the Wechsler Scales of Intelligence (Swedish versions). Standardized measures of cognitive functioning, such as the Wechsler Scales of Intelligence, are time-consuming and require the person administrating the test and interpreting the test results to be a psychologist; access to a reliable and swift screening tool not requiring a psychologist would help identify the children who need to undergo standardized testing.

Intellectual Functioning in Children with CHD

Over the last 10 years, two large meta-analyses have shown that children suffering from CHD show lower intellectual functioning than healthy controls (1, 2). However, the result is not entirely consistent since some studies show no relationship between CHD and low intellectual functioning (6, 7). This inconsistency might be explained by the fact that earlier studies investigated different levels of severity of the cardiac diagnoses. Some studies have shown a negative association between the severity of the cardiac diagnosis and intellectual functioning (8, 9), and type of cardiac diagnosis is related to certain types of cognitive difficulties (10).

An earlier study by Limbers et al. (3) investigated factors affecting self- and parental proxy reports of cognitive problems in children with CHD. There was an association between the severity of diagnosis and parental socioeconomic status (SES) with the proxy reports of cognitive problems, a finding that suggests that children from families with low SES and children with severe diagnosis should be targeted for further evaluation.

The Association between Perceived Cognitive Problems and Actual Cognitive Functioning

Few studies have investigated the association between self- and proxy reports of cognitive ability and actual intellectual functioning as measured by standardized cognitive test batteries for children with CHD. Two studies show that there exist association between self- and proxy report of executive functioning in children with CHD (11) as well as in children with systemic lupus erythematosus (12) and the executive functioning abilities of these patients. A study by Miatton et al. (13) investigated the association between parental proxy reports and estimated full scale IQ (FSIQ) for children between 6 and 12 years with CHD: the more cognitive problems the parents reported the lower the children's FSIQ.

Our study adds to Miatton et al.'s (13) study by also investigating the children's own reports (self-reports) as well as their parents' reports (proxy reports). Furthermore, we include younger children (3- and 5-year-olds). Investigating self- and proxy reports for younger children has important implications for when it is valid to start using screening tools to detect children who need to undergo further evaluation. In addition, the earlier these children are identified, the earlier interventions can be implemented in (pre)school and daily lives.

MATERIALS AND METHODS

Participants

Participants were tested over a 7-year period (2008–2015). The recruitment of the sample is illustrated in **Figure 1**, for more information about the recruitment of the participants, see Ref. (9). In the beginning, only children with severe CHD were recruited from the whole region of Västra Götaland. Later, children with milder CHD (a larger population) were recruited to obtain comparision groups of comparable sizes. The medical records of children living in the Västra Götaland Region (VGR) showed that 1,133 children were treated with surgery or catheter interventions for CHD at Queen Silvia Children's Hospital in Gothenburg, Sweden during the data collection period. Of these 1,133 children, 144 children with chromosomal defects and disabilities known to influence intellectual functioning were excluded. All eligible children with severe CHD ($N = 99$) and 432 (of 890) children with milder CHD were invited. The invited families were required to speak, read, and write Swedish and to provide a signed consent. In total, 237 children and their families (44.6%) agreed to participate in the study. Participation rate was higher in the severe group than in the milder groups. All children met with a clinical psychologist at their local hospital for a psychological evaluation. Of these 237 children and their families, 228 completed testing with Wechsler Scales. Of these 228 children, self-reports and proxy ratings on the Cognitive Problems Subscale were available for 184 children.

Therefore, the target population of the current study consists of 184 children with CHD and their parents (for more demographic information about the sample, please, see **Table 1**). The children that were tested belonged to four different ages: 3-year-olds ($n = 56$); 5-year-olds ($n = 34$); 9-year-olds ($n = 53$); and 15-year-olds ($n = 41$). The ages for data gathering were chosen according to the follow-up program for children with severe CHD at The Queen Silvia Children's Hospital in Gothenburg. The aim was to have a wide range of ages so the study includes cognitive testing for two preschool ages (3- and 5-year-olds) and two school ages

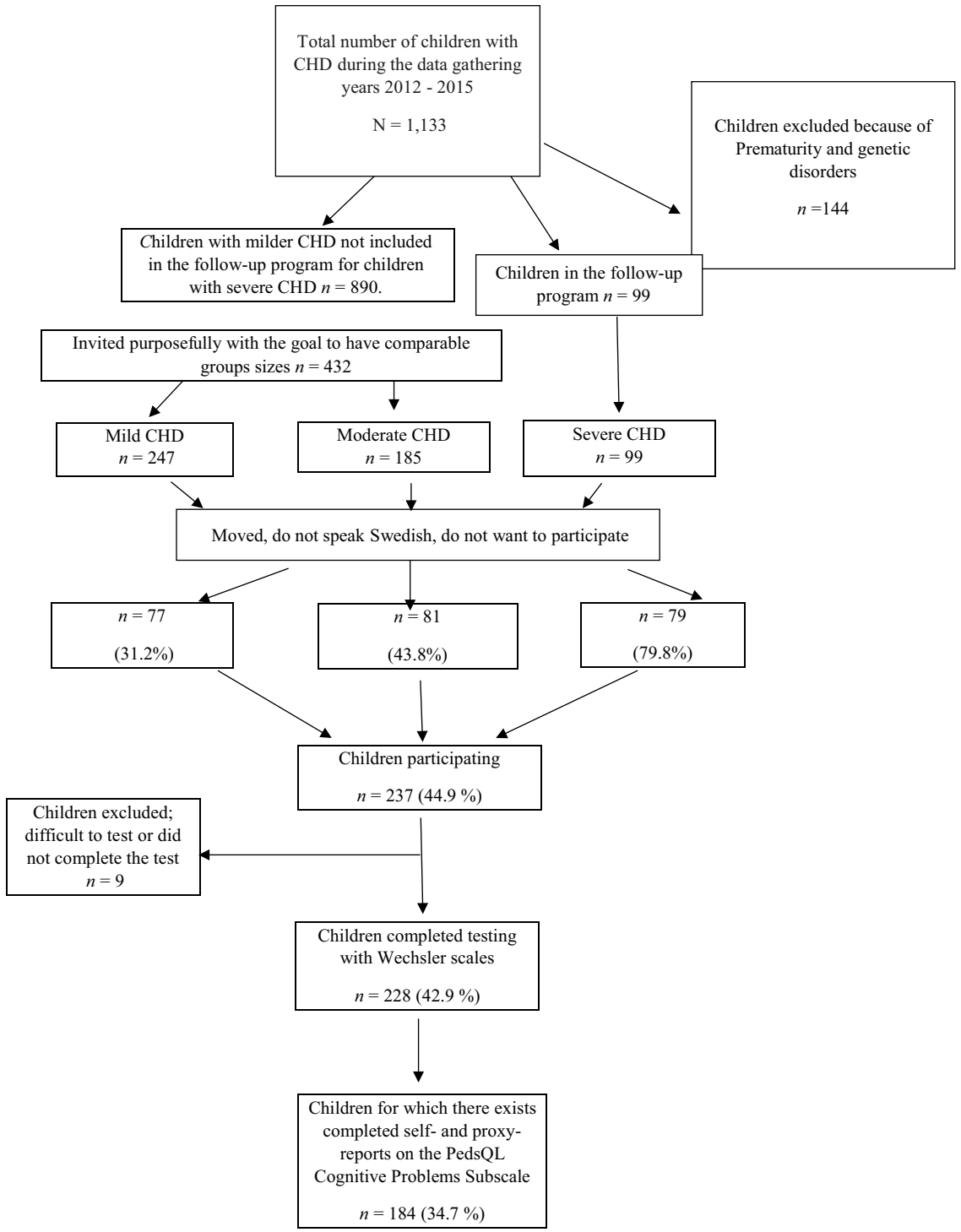

FIGURE 1 | **Patients treated with surgery or by catheter interventions for CHD**.

(9- and 15-year-olds). When the youth reach the age of 18, they are transferred to the grown ups with congenital heart (GUCH) defects program. The parents of the children and adolescents had a mean age of 40.4 years (SD = 7.1) and a median income of 25,000–29,000 SEK, which indicated that the parents' belonged to a middle class setting. Of these parents, 65% stated that they were married, 26% stated that there were co-living with a partner (not-married), and 10% stated that they were single. Approval from the ethics committee in Gothenburg, Sweden was obtained on September 20, 2011 (ref. no. 391–11).

TABLE 1 | Descriptive statistic of the participants for each age group.

	Age group			
Variable	**3-year-olds (*n* = 56)**	**5-year-olds (*n* = 34)**	**9-year-olds (*n* = 53)**	**15-year-olds (*n* = 41)**
Mean age at testing	**3 years and 1 month**	**5 years and 3 months**	**9 years and 1 month**	**15 years and 0 month**
Gender, *n* (%)				
Male	31 (55)	11 (32)	29 (55)	17 (41)
Female	25 (45)	23 (68)	24 (45)	24 (59)
FSIQ[a], mean (SD)	106.6 (12.9)	101.6 (13.4)	98.8 (13.3)	98.6 (14.9)
Hollingshead SES, mean (SD)	45.4 (11.5)	44.6 (11.2)	43.6 (12.6)	42.0 (13.9)
Self-reports Peds. Cog[b] mean (SD) α	–	80.7 (25.6) 0.81	72.5 (23.4) 0.86	67.4 (24.1) 0.85
Proxy reports Peds. Cog mean (SD) α	83.0 (15.2) 0.79	82.4 (17.2) 0.87	69.8 (23.8) 0.91	67.7 (26.0) 0.93
Severity of diagnosis, *n*				
Mild	18	11	17	15
Moderate	19	14	23	16
Severe	19	9	13	10

[a]*For the 3- and 5-year-olds, WPPSI-III was used, and for the 9- and 15-year-olds, WISC-IV was used.*
[b]*The age appropriate Pediatric Quality of Life Heart module Cognitive Subscale was used.*

Measures

Intellectual Cognitive Functioning

Full scale IQ was measured with Wechsler Preschool and Primary Scale of Intelligence–third edition (WPPSI-III) for the 3- and 5-year-olds (14) and with the Wechsler intelligence Scale for children–fourth edition (WISC-IV) for the 9- and 15-year-olds (15). The test is constructed to have a mean score of 100 (SD 15) in the general population and according to the normal distribution curve, 68% of children in a population should have IQ scores between 85 and 115, 28% should have IQ scores between 70 and 84 or 116 and 130, and only 4% should have extreme IQ scores, between 55 and 69 or 131 and 145.

Self- and Proxy Reports of Cognitive Problems

To measure perceived cognitive problems, the subscale Cognitive Problems from the PedsQL Cardiac Module 3.0 was used. There is a self-report version as well as a parental-report version of the scale. The Cognitive Problem subcale consists of only five items (the exception is the parental report version for the 2–4 year-olds which consist of 3 items). The questionnaire has been extensively validated and reliability tested internationally (16), including on a Swedish sample (17). Cronbach alpha values for child self-report in the Swedish sample was 0.50, which is surprising since we in the current study noted an alpha value above 0.80 for all three age groups as can be seen in **Table 1**. For the parent proxy report, the alpha value was 0.89 in the study by Sand et al. (17). In our study, the alpha value for the parent proxy reports ranged from 0.79 to 0.93 for all age groups. The self-report versions have formats appropriate for children from the age of 5 through 18. Although wording and content is highly similar between the different age groups, the tests for the different age groups are designed to be age appropriate in both language and content.

Self-reports were gathered from the 5-, 9-, or 15-year-olds, but not for 3-year-olds as they are too young for self-reports. Due to the variability of the 5- and 9-year-olds' reading skills, the questions were read out loud by the test leader for these two age groups. The 5-year-olds indicated their answer by pointing on a scale with different "smiley faces," and the 9-year-olds pointed out their answers using a five-point Likert scale ranging from 0 (never a problem) to 4 (almost always a problem). The 15-year-olds as well as the parents completed the form by reading it themselves and rating their answers on a five-point Likert scale ranging from 0 (never a problem) to 4 (almost always a problem). Both parents were asked to complete the form separately and were specifically told not to discuss their answers with each other. For the majority of the patients (72%), we had the rating for both parents on the PedsQL Cognitive Problems subscale so we used the mean value of these two values in our analyses. The intra-class correlation for the two parental measures was 0.86. For 22% of the patients we only had the mother's ratings, and for 5% of the patients we only had father's rating, and for 1% we only had ratings from one parent who had not provided gender information in the form, so for all these patients we just used this one value.

When calculating the final scores, the items are reversed and linearly transformed according to following formula provided with the PedsQL: 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0. Thus, the higher the score, the lesser the perceived cognitive problems and *vice versa*.

Demographic Variables

Demographic variables included the gender of the patient as well as the parents' SES. The parents' SES was calculated using Hollingshead Four Factor Index of Social Status (18, 19). The index uses a composite score between 3 and 66 determined by the parents' education and occupation. For the majority of the patients (72%), we had information to calculate SES for both parents so we used the mean value of these two values in our analyses. According to the manual, when the score is present for both the parents, the mean of these two values should be used (18). For 22% of the patients we only had information about the mother's SES, and for 5% of the patients we only had information about the father's SES, and for 1% we had information from only one parent who had not provided gender information in the form, so for all these patients we just used this one value. We found that the parents had a mean SES of 44.0 (SD = 12.3), which is comparable with previous studies that have shown an average SES of 37.0 (SD = 11.7) in the Swedish population (20).

Severity of the Cardiac Diagnosis

The participants had various forms of cardiac diagnoses. These diagnoses were categorized into three diagnosis groups reflecting the severity of the diagnosis and the risk for further complications. The first group consisted of patients with *mild* severity diagnoses such as atrial septal defect, ventricular septal defect, persistent ductus arteriosus, isolated coarctation of the aorta, and pulmonary stenosis. The second group consisted of *moderate* severity diagnoses such as transposition of the great arteries, tetralogy of Fallot, complete AV-defect, total anomalous pulmonary venous drainage, and aortic stenosis. The third group consisted of *severe* diagnoses such as univentricular heart lesions, pulmonary atresia with VSD and major aortopulmonary collaterals, and patients who have undergone heart transplantation. As can be seen in **Table 1**, the distribution of children belonging to the three different cardiac diagnosis groups were fairly even. This does however not represent the distribution in the populations since severe cardiac diagnosis are more scarcely occurring than mild forms.

Statistical Analysis

Statistical analyses were conducted using the IBM SPSS Statistics v. 22 software. Descriptive data of the different variables were calculated, and ANOVAs were calculated to further investigate differences between groups on the descriptive measures. For the ANOVAs, the effect size eta-square is reported: 0.01 is a small effect, 0.06 is a medium effect, and 0.14 is a large effect (21). The relevant variables all met the normality assumption, and homogeneity assumptions were also checked. When the homogeneity assumptions were not met, the Games–Howell *post hoc* test was used instead of the Bonferonni correction. Correlations were conducted for the different predictors and the outcome variable. Finally, multiple linear regression analyses were conducted to investigate the unique contribution of the different predictors in the model. In the final regression analyses, SES, severity of diagnoses, and self-ratings as well as proxy ratings were entered as predictors with FSIQ as the dependent variable. Gender was not included since no association was found between this variable and the dependent variable for any of the age groups. Hierarchical regressions were computed since they allow for evaluation of variance accounted for by the different blocks of predictors. Due to the nature of the data as well as the desire to clarify the results, hierarchical regression was calculated separately for each age group. In the first step of the hierarchical regression, the control variable SES was entered. In the next step, the dummy coded variables moderate and severe diagnoses (mild diagnosis was the reference group) were entered. In the final step, the self-reports (for the 5-, 9-, and 15-year-olds) and proxy reports were entered. The different steps in the regression were evaluated using R^2 change, and the final model was evaluated by comparing the adjusted R^2.

RESULTS

Descriptive Statistics

Table 1 shows the means and SDs for the variables measured. All the age groups displayed an FSIQ close to 100. However, the two preschool ages had a slightly higher FSIQ. A one-way ANOVA showed that there was a significant difference in the level of FSIQ between the four age groups [$F(3, 180) = 3.94$, $p = 0.009$, $\eta^2 = 0.06$]. This effect was of a medium size, and Bonferroni comparisons showed that the preschool children's FSIQ was significantly higher than the school children's FSIQ ($p < 0.05$).

The SES displayed in the four age groups is above 40, indicating that the sample on average is a middle class sample. No significant differences were found between the age groups on SES scores.

For the self-reports of cognitive problems no significant differences were found between the three age-groups that made such self-reports. For the proxy report, however, there was a significant difference between the different age groups [$F(3, 180) = 6.85$, $p < 0.001$, $\eta^2 = 0.10$]. This effect was of a medium size, and the Games–Howell *post hoc* comparison showed that the parents of the preschool children reported significantly less cognitive problems than the parents of the school children ($p < 0.05$).

Intra-Class Correlations between Self-Report and Proxy Report

To measure the consistency between the self- and the proxy reports, intra-class correlations were calculated using a two-way random model (ICC) for each age group (except the 3-year-olds for which no self-report exists).

For the 5-year-olds, we found no significant ICC between the self- and proxy report. For the 9-year-olds, however, we found a significant ICC of 0.74 ($p < 0.001$) between the self- and proxy report. In addition, for the 15-year-olds we found a significant ICC of 0.68 ($p < 0.001$). This result suggests that the 9- and 15-year-olds' view of their cognitive problems are consistent with how their parents view their cognitive problems.

Correlations between the Predictors and FSIQ

Correlations were calculated for the predictors and FSIQ for each age group (**Table 2**). Since severity of diagnosis was entered as an ordinal variable, where a higher value indicates a more severe diagnosis, Spearman's rank correlation was used. Because there was no significant correlation between gender and FSIQ for any of the age groups (**Table 2**), this predictor was excluded from the regression analysis. As for the SES, there was a positive relation between this variable and the FSIQ for all but the 5-year-olds. For the 3-year-olds, there was a negative relation between severity of diagnosis and FSIQ, a result that indicated that the severity

TABLE 2 | Spearman's rank correlations between the predictors and the FSIQ for all age groups.

	FSIQ			
	3-year-olds	5-year-olds	9-year-olds	15-year-olds
Gender	−0.101	−0.087	−0.172	0.145
SES	0.308*	0.238	0.338*	0.440**
Severity of diagnosis	−0.335*	−0.298	−0.183	0.075
Self-report	–	−0.156	0.266	0.456**
Proxy report	0.460**	0.368*	0.599**	0.524**

*$p < 0.05$.
**$p < 0.01$.

of diagnosis was associated with poorer intellectual functioning. No such relationship, however, was found for the older children. When it comes to the association between self-report and FSIQ, there was only a significant positive relationship for the 15-year-olds, indicating that the less perceived cognitive problems, the better their intellectual functioning. For the proxy report, we found a positive correlation for all age groups, indicating that the less cognitive problems the parent's perceived, the higher the intellectual functioning in the children.

Regression Analyses

To test the unique contribution and to further investigate the variance accounted for by self- and proxy reports on the dependent variable, hierarchical regression analyses were conducted separately for all age groups. SES predicted a significant amount of the variance in three of the four regression analyses (7, 13, and 20%, respectively) (**Table 3**). Severity of diagnosis, however, was only significantly associated with intellectual functioning for the 3-year-olds, where children with a more severe diagnosis had a significantly lower FSIQ than children with a mild diagnosis. When controlling for SES and severity of diagnosis, there still existed an association between the proxy ratings and the FSIQ for the 3-, 9-, and 15-year-olds. For the 3-year-olds, this association accounted for 13% or of the variance, and for the 9-year-olds, it accounted for 22% of the variance. For the 15-year-olds, the self- and proxy reports of cognitive problems explained 27% of the variance in the dependent variable.

Analyses Investigating a Possible Cutoff Score for the Cognitive Problem Subscale

In order to investigate which cutoff score would be appropriate when using PedsQL Cognitive Problem subscale, the children were divided into two groups. Since children achieving an FSIQ score of below 85 very often experience learning difficulties and in order to have an inclusive cutoff score criteria, children scoring below 90 in FSIQ were compared to children achieving a score of 90 and above on the FSIQ.

As can be seen in **Table 4**, children having a FSIQ score above 90 and thus is very unlikely of experiencing learning difficulties should have a mean value of 73.7 on the self-reports at the age of 15. For the proxy reports, these value ranges from 75.5 to 85.3 for the children with an FSIQ above 90 depending on age group. Thus, a possible inclusive cutoff score for both the 15-year-olds' self-reports and the proxy reports for all age groups is 80. Thus, if the score falls below 80 on the Cognitive Problem subscale, the child should be formally evaluated.

To further investigate what a cutoff score of 80 on PedsQL Cognitive Problems subscale would mean when used as a screening tool, odds ratios were calculated for both the self-report of the 15-year-olds and the for the proxy reports for all age groups.

TABLE 3 | Hierarchical multiple regression analyses predicting intellectual functioning for four different age groups of patients with CHD.

	3-year-olds		5-year-olds		9-year-olds		15-year-olds	
Predictor	**ΔR^2**	**β**	**ΔR^2**	**β**	**ΔR^2**	**β**	**ΔR^2**	**β**
Step 1	0.072*		0.066		0.128**		0.201**	
SES		0.269*		0.256		0.358**		0.448**
Step 2	0.085		0.115		0.017		0.009	
Moderate diagnosis (dummy)		–0.058		–0.020		–0.134		0.073
Severe diagnosis (dummy)		–0.336*		–0.370		–0.128		–0.037
Step 3	0.131**		0.104		0.215**		0.267***	
Self-report		–		0.007		–0.152		0.170
Proxy report		0.398**		0.356		0.616***		0.443**
Total R^2	0.288***		0.156		0.360***		0.477***	

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

TABLE 4 | Mean values and SDs for self- and proxy reports on the PedsQL Cognitive Problem Subscale for children with a FSIQ below and above 90.

	FSIQ							
	<90			>90				
	M	**SD**	***n***	**M**	**SD**	***n***	***z*-Value**	***p*-Value**
Self-reports								
15-year-olds	48.0	20.2	10	73.7	22.0	31	2.9	0.003
Proxy reports								
3-year-olds	67.3	18.1	7	85.3	13.5	49	2.5	0.012
5-year-olds	74.0	25.3	5	83.8	15.6	29	0.8	n.s.
9-year-olds	55.4	16.4	15	75.5	24.0	38	3.1	0.002
15-year-olds	41.5	22.2	10	76.1	21.2	31	3.5	<0.001

Mann–Whitney U tests were conducted to compare the self-reports and proxy reports of the children with an FSIQ of below 90 with those above 90.

The odds ratio of a 15-year-old having an FSIQ below 90 and reporting a score of below 80 on the PedsQL Cognitive Problem subscale self-report is 22.4 times more likely than the 15-year-old reporting a value above 80. Concerning the proxy reports, it is 9.4 times more likely that a child with an FSIQ below 90 would receive a proxy rating score below 80 on the Cognitive Problem subscale than above 80. Thus, the diagnostic value of using 80 can be considered fairly adequate.

DISCUSSION

This study aimed to evaluate whether the PedsQL Cognitive Problems subscale from the cardiac module could be used as a screening tool for identifying children with CHD who need to undergo more extensive cognitive assessments. This evaluation was done by investigating the association between children with CHD self-reports of their cognitive problems as well as their parents' reports (proxy reports) of their children's cognitive problems and their children's actual FSIQ (measured using the Wechsler Intelligence Scales).

When looking at the children's self-report, there was a strong association between the 15-year-olds' reports of cognitive problems and their FSIQ. These results are in line with previous empirical results and metacognitive theory (22). This type of self-evaluation demands that the child has developed certain metacognitive skills. In this particular case, the children needed to have a metacognitive component referred to as *cognitive knowledge*, i.e., knowledge about themselves as learners and the factors that affect their cognition (23). The metacognitive ability of cognitive knowledge can be evident in children as young as six, but often these skills consolidate in adolescence (24). Therefore, it is not surprising that we only found an association for the 15-year-olds, since this group is the only group where the majority of the children should have fully developed this type of metacognitive ability. However, it is likely that some of the 9-year-olds had this cognitive knowledge regarding themselves although this did not affect the results on a group level. This assumption is supported by the correlation of 0.27, albeit not significant, between the 9-year-olds self-report and their FSIQ.

Regarding the proxy reports, our results showed a moderate to strong correlation between the parental rating of cognitive problems and the FSIQ for all age groups. This result agrees with the results of Miatton et al. (13), but our study adds to their results by showing that this correlation also exists for children as young as 3 and 5. This result suggests that parents have a good understanding of their very young children's cognitive problems (i.e., as early as 3-year-olds). However, when controlling for other factors in the regression, the association between the proxy reports and the FSIQ was not significant for the 5-year-olds. This inconsistency could be a power issue due to the low number of participants ($n = 34$) in this particular age group compared to the other groups. This is evident when considering the high beta value of the proxy report predictor for the 5-year-olds compared with the other age groups.

This study lends support to the idea that both the self-report and the proxy reports of PedsQL Subscale Cognitive Problems can be used as a screening tool for identifying children who need to undergo further cognitive evaluation. Regarding the self-reports, the children need to be 15 years old for the screening tool to be valid. A suggested cutoff value for both the self- and the proxy reports is that a value below 80 on the PedsQL Cognitive Problem subscale should warrant a more formal evaluation with standardized tests.

Using the PedsQL Subscale Cognitive Problems as a screening tool is both economically sound and time-saving alternative compared to more standardized cognitive testing procedures. In addition, not all clinics have the trained staff to perform more standardized evaluations, so this type of screening tool can help these clinics identify patients who need further evaluations. Using a screening tool also enhances the possibility of testing more children from an early age. This early detection means that appropriate resources and interventions can be set in place as early as possible for children with CHD, which in turn leads to better development for the child. Cognitive abilities not only affect learning but also affect many daily functions such as emotion regulation (5) as well as health (4).

Earlier studies have shown that it is mainly children with severe cardiac diagnosis (8) who suffer from cognitive impairments, so performing extensive testing on children with milder forms of cardiac diagnosis could prove to be an insufficient and costly procedure. In these circumstances, it is highly beneficial to use the Cognitive Problems Subscale to screen children in the mild groups in order to identify those few who may experience cognitive problems and need to undergo more extensive evaluations.

A limitation of the study is that measured IQ in younger children is slightly unstable and does not necessarily reflect the intellectual functioning the child will have as an adolescent (14, 15). According to leading researchers within the field, IQ becomes stable around early adolescence (25). Although we should expect a higher variability in FSIQ in children below the age of 8, our study still found moderate association between the younger age groups and proxy reports, suggesting that a valid relationship between these measurements and the parents' ratings of their children's ability. Another limitation is also that the distribution of the children with different cardiac diagnosis severity was slightly biased. Although the number of children from the different diagnosis groups was fairly equal (**Table 1**), in real life there are more children with mild forms of CHD than children with severe cardiac diagnosis. In our study, 80% of those suffering from a severe diagnosis who were contacted about the study agreed to participate in the study. However, only 44% of the children with a moderate cardiac diagnosis and 31% with mild cardiac diagnosis agreed to participate in the study. However, because cognitive impairments are more prevalent among the children with more severe cardiac diagnoses, it is fortunate that this group is the most well represented. Although there exists a distribution bias in this study, this bias is unlikely to significantly impact the results.

In recent years, many studies have investigated the intellectual functioning of children with CHD (1, 2). This study adds to the literature by also looking at how children themselves and their parents rate their experienced cognitive problems, and how these subjective ratings are associated with the more objective measures of intellectual functioning. In addition, this study found that the screening tool PedsQL Cognitive Problems subscale was

useful for identifying children and adolescents who need further cognitive interventions. Future studies should focus on trying to explain why we see an overrepresentation of children with cognitive impairments among the children with more severe diagnoses.

AUTHOR CONTRIBUTIONS

SB has made substantial contribution to the analysis and interpretation of the data for the work. She has been the main responsible person for the manuscript, drafted the work, and has also revised it critically for important intellectual content. CR has made substantial contributions to the conception and design of the work, the acquisition of the data, and interpretation of the work. She has also revised it critically for important intellectual content. MB has made substantial contributions to the conception and design of the work and interpretation of the work. She has also revised it critically for important intellectual content. JS has made substantial contributions to the conception and design of the work and interpretation of the work. He also made the classification of the severity of the cardiac diagnosis. He has also revised it critically for important intellectual content. All the authors (SB, CR, MB, and JS) have made a final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Transition in Patients with Congenital Heart Disease in Germany: Results of a Nationwide Patient Survey

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Background: A growing number of adults with congenital heart disease (ACHD) pose a particular challenge for health care systems across the world. Upon turning into 18 years, under the German national health care system, ACHD patients are required to switch from a pediatric to an adult cardiologist or an ACHD-certified provider. To date, reliable data investigating the treatment situation of ACHD patients in Germany are not available.

Materials and methods: An online survey was conducted in collaboration with patient organizations to address the life situation and the conditions of health care provision for ACHD patients in Germany. ACHD patients were recruited from the database of the National Register for Congenital Heart Defects (NRCHD) and informed about the survey *via* email, websites, and social networks. A total of 1,828 ACHD patients (1,051 females) participated in this study. The mean age was 31.7 ± 11.7 years. Participants were surveyed about treating physicians and the institution mainly involved in the treatment of their CHD. In addition, participants were asked questions to assess the level of trust toward their treating physician and their familiarity with the term "ACHD-certified provider."

Results: Among the surveyed patients, 25.4% stated that they attended a specific ACHD clinic at a heart center regularly, 32.7% were treated in a private practice setting by a pediatric cardiologist, 32.4% in a private practice (adult) cardiology setting, and 9.5% were treated by an "other physician." Only 24.4% of the male and 29.7% of the female ACHD patients were familiar with the term "ACHD-certified provider."

Conclusion: The transfer from pediatric cardiology to ACHD care requires further attention as many adult patients have not transferred to certified ACHD providers. The question of whether ACHD patients in Germany are offered consistent and adequate care

should also be investigated in more detail. The answers regarding the ACHD certification are particularly disappointing and indicative of a large information gap and inadequate education in clinical practice.

Keywords: transition, congenital heart disease, online survey, adult with congenital heart disease, treatment, lost to follow-up, National Register for Congenital Heart Defects

INTRODUCTION

About 6,000 children are born with congenital heart disease (CHD) in Germany each year (1). The number of adults with CHD (ACHD) is growing constantly (2, 3). Due to major advances of diagnosis and treatment, more than 90% of all children born with CHD reach adulthood today in western countries (2–6). The growing number of ACHD patients is a particular challenge for health care systems worldwide (7, 8). With increasing age, the medical needs of these patients are changing and motivate the need for a specific transition program (9). In this context, the term "transition" refers to the transitory stage from child-oriented care to a type of medical care that meets the requirements of adult patients (10).

Throughout their lives, patients with CHD have special medical and emotional needs. Thus, a successful transition from pediatric to adult centered care is particularly important (11, 12).

In 2010, the European Society of Cardiology (ESC) published practical guidelines for the management of ACHD (13). These guidelines, however, do not give specific recommendations regarding organization of ACHD care or further training for physicians (7, 13). It is accepted that ACHD patients have special needs requiring their treating physicians to have special expertise and training in the field of CHD in order to offer adequate care (4, 13–22). In Germany, certified heart centers and certified cardiologists/pediatric cardiologists in private practice, offering care tailored specifically to ACHD patients (23, 24) hold a certificate for "ACHD specialization." The process for awarding "ACHD certification" has been standardized as a result of a cooperation within a joint task force that includes the German associations of cardiology, pediatric cardiology, and cardiothoracic/vascular surgery, as well as professional associations and patient organizations (23, 24).

Until their 18th year of life, patients are usually treated by pediatric cardiologists in private practice, heart centers, or university hospitals. According to the regulations of the German Medical Association, child and adolescent medicine, which includes pediatric cardiology, is responsible for treating infants, toddlers, children, and adolescents (25). The 19th year of life usually marks the end of adolescence (Youth Courts Law, par. 1, Social Act 8, par. 7 sections 1 and 2) (26, 27). As of this age, patients usually cannot be treated by a pediatrician any more.

Representative data regarding the question of who mainly treats ACHD patients in Germany for their CHD are not available. The present study aims to shed light on the treatment situation of ACHD patients in Germany and specifically answer the question of whether transition is successful or not. The answers to these questions are highly relevant not only in terms of adequate health care provision and policy but also for optimizing support for CHD patients and their relatives throughout their lives.

MATERIALS AND METHODS

The National Register for Congenital Heart Defects (NRCHD) conducted an online survey in collaboration with the two patient organizations "Bundesverband Herzkranke Kinder e. V." (BVHK) and "Bundesvereinigung Jugendliche und Erwachsene mit angeborenem Herzfehler" (BV JEMAH). The survey's primary objective was to collect information on the general life situation and the conditions of health care of ACHD patients in Germany.

With 51,134 members (as of October 2016), the NRCHD is Europe's largest register of CHD. It is representative of the German cohort of patients with CHD (28). For patient recruitment, the register's database was searched for patients who were 18 years or older at the time of the survey and for whom an email address was available. Respective individuals were invited to take part in the survey *via* email. In addition, the NRCHD, BVHK, and BV JEMAH informed ACHD patients about the survey *via* websites and social media channels.

Questions asked included:

- Which kind of physician mainly treats you for your heart disease?
- Do you attend regular follow-up examinations at a heart center/university hospital?
- Is the physician who mainly treats you for your heart disease ACHD-certified?
- Would you rather be treated by a pediatric cardiologist or an adult cardiologist?

Furthermore, four rating questions were asked using a six-tier scale for analysis:

- Do you understand the explanations given by your physician concerning your heart defect?
- Do you feel well-informed about your heart defect by your treating physician?
- How well do you rate your knowledge regarding your heart defect?
- How much do you trust your treating physician?

The six-tier scales were divided into three categories:

- 1−2 = low/negative rating
- 3−4 = medium/neutral rating
- 5−6 = high/positive rating.

For compiling the online questionnaire, the software EFS survey was used (29).

The respondents' statements regarding their own CHD diagnosis were assigned to four groups according to Bethesda criteria (14).

The NRCHD has extensive experience in data collection *via* online surveys. The established data infrastructure of the NRCHD

allows for storing data within the framework of an own data protection concept, which is registered with the Berlin Official for Data Protection and Freedom of Information (No. 531.390). General approval by the Ethics Committee Charité Berlin is available for all research conducted within the scope of the NRCHD. Registration to the NRCHD is voluntary. Participation is based on a broad consent. Patients agree that the NRCHD obtains and stores medical data from their attending physicians, for use in ongoing and future research studies until withdrawal. By consenting to this, patients have the option of taking part in studies and of regularly receiving information on the current state of research studies in the field of CHD *via* the patient website "www.herzregister.de." The above Ethics Committee has approved the NRCHD ethical concept in 1999 and 2011. Participation in the NRCHD is promoted by patients' and parents' associations through their websites and in print.

Statistical Analysis

The chi-square test was used for group comparisons including nominal data; data that were at least ordinally scaled were analyzed by using the Mann–Whitney *U* test or, in the case of more than two comparison groups, the Kruskal–Wallis test. Alpha error adjustment in multiple comparisons (30) was not performed as this was mainly an explorative and descriptive study and to avoid overlooking potential influencing factors.

SPSS (version 22) was used for all statistical analyses (31).

RESULTS

A total of 1,828 individuals participated. The mean age was 31.7 years (± 11.7 years) and 57.5% of patients were female (**Table 1**).

Underlying Heart Defect

At the beginning of the survey, the participants were asked to provide information regarding their CHD. Based on this information, patients were assigned to four diagnostic groups: simple CHD ($n = 398$), moderate CHD ($n = 606$), complex CHD ($n = 699$), and non-classifiable CHD ($n = 125$) (**Table 1**).

Who Treats ACHD in Germany?

Overall, 58.1% of those surveyed were treated mainly at specific ACHD clinics at a heart center or by a pediatric cardiologist in private practice. Significant gender differences ($p < 0.05$) were found: women were more often treated at specific ACHD clinics at heart centers. Significant differences ($p < 0.001$) were also found between groups of CHD severity: In 70.5% of all cases, patients with complex CHD and in 43.5% of all cases, patients with simple CHD were treated mainly at a specific ACHD clinic at a heart center or by a pediatric cardiologist in private practice. More detailed information can be found in **Table 2**.

Regular Follow-up at a Specialized ACHD Clinic at a Heart Center

The majority of respondents (53.8%) stated that they attend a specific ACHD clinic at a heart center for a follow-up examination at least once a year (**Table 2**). Significant gender differences were not detected. However, significant differences ($p < 0.001$) according to CHD severity were found: While 71.1% of patients with complex CHD attended a specialized ACHD clinic at a heart center at least annually, only 24.1% of patients with simple CHD did so (**Table 2**).

ACHD Certification of the Mainly Treating Physician

The majority of respondents (66.1%) stated that they did not know if the physician mainly treating them for their CHD was ACHD-certified. Significant gender differences ($p < 0.05$) were found: 29.7% of the female participants possessed knowledge about the ACHD certification status of their mainly treating physician compared to 25.4% of the male participants. Also in this case, patients with complex CHD were best informed regarding the their physician's ACHD certification status, with 39.9% possessing knowledge, compared to participants with less complex disease (**Table 2**).

Patient Preferences for Particular Physicians

Overall, 28.5% of those surveyed stated a preference for being treated by a pediatric cardiologist in private practice. Out of these, only 55.7% are actually treated mainly by a pediatric cardiologist in private practice. Thirty percent would prefer a treatment by an adult cardiologist in private practice (see **Table 2**), while 58.3% of these are actually treated in this setting. Furthermore, 7.9% of those surveyed stated not to know the difference between pediatric cardiology and adult cardiology, while 33.5% did to not care who mainly treats them (**Table 2**).

Significant gender differences ($p < 0.05$) were found. Female participants rather preferred treatment by a pediatric cardiologist

TABLE 1 | Sample composition (*N* = 1,828).

	% (*N*)	Age	Full-time employment	High education level	In a relationship
Total	100 (1,828)	31.7 ± 11.7	37.3% (681)	32.4% (592)	61.7% (1.128)
Male	42.5 (777)	32.7 ± 12.6	49.3% (383)	36.7% (285)	56.9% (442)
Female	57.5 (1,051)	31 ± 11	28.4% (298)	29.3% (307)	65.3% (686)
Simple congenital heart disease (CHD)	21.8 (398)	33.4 ± 14.2	40.2% (160)	34.2% (136)	67.3% (268)
Moderate CHD	33.2 (606)	31.1 ± 10.7	41.4% (251)	37.8% (229)	62.9% (381)
Complex CHD	38.2 (699)	32.2 ± 11.1	33.2% (232)	28.4% (199)	58.5% (409)
Unclassified CHD	6.8 (125)	26.7 ± 10	30.4% (38)	22.4% (27)	56% (70)

N, sample size.

TABLE 2 | Descriptive statistics (subjective patient statements).

Which kind of physician mainly treats you for your heart disease?

	Total (N = 1,828)	Male (n = 777)	Female (n = 1,051)	Simple CHD (n = 398)A	Moderate CHD (n = 606)B	Complex CHD (n = 699)C	Others/unclassified CHD (n = 125)D
Adults with congenital heart disease (ACHD) clinic at a heart center	25.4% (*n* = 465)	23.3% (*n* = 181)	27% (*n* = 284)	19.1% (*n* = 76)	23,1% (*n* = 140)	33,2% (*n* = 232)	13.6% (*n* = 17)
Pediatric cardiologist in private practice	32.7% (*n* = 598)	33.1% (*n* = 257)	32.4% (*n* = 341)	24.4% (*n* = 97)	34% (*n* = 206)	37,3% (*n* = 261)	27.2% (*n* = 34)
Adult cardiologist in private practice	32.4% (*n* = 592)	32.3% (*n* = 251)	32.4% (*n* = 341)	38.4% (*n* = 153)	36,8% (*n* = 223)	23,2% (*n* = 162)	43.2% (*n* = 54)
Another physician	9.5% (*n* = 173)	11.3% (*n* = 88)	8.1% (*n* = 85)	18.1% (*n* = 72)	6,1% (*n* = 37)	6,3% (*n* = 44)	16% (*n* = 20)
Group differences		***$p < 0.05$		**$p < 0.001$ (A vs. B: ***$p < 0.001$; A vs. C: ***$p < 0.001$; B vs. C: ***$p < 0.001$; B vs. D: ***$p < 0.001$; C vs. D: ***$p < 0.001$)			

Do you attend regular follow-up examinations at a heart center/university hospital?

	Total (N = 1,828)	Male (n = 777)	Female (n = 1,051)	Simple CHD (n = 398)A	Moderate CHD (n = 606)B	Complex CHD (n = 699)C	Others/unclassified CHD (n = 125)D
At least once a year	53.8% (*n* = 984)	56.8% (*n* = 441)	51.7% (*n* = 543)	24.1% (*n* = 96)	54.1% (*n* = 328)	71.1% (*n* = 497)	50.4% (*n* = 63)
At least every 2 years	14% (*n* = 256)	12.7% (*n* = 99)	14.9% (*n* = 157)	16.8% (*n* = 67)	16.3% (*n* = 99)	10.3% (*n* = 72)	14.4% (*n* = 18)
At least every 3 years	6.4% (*n* = 117)	5.4% (*n* = 42)	7.1% (*n* = 75)	12.3% (*n* = 49)	6.9% (*n* = 42)	2.7% (*n* = 19)	5.6% (*n* = 7)
Less than every 3 years	20.1% (*n* = 368)	20.2% (*n* = 157)	20.1% (*n* = 211)	36.4% (*n* = 145)	18.2% (*n* = 110)	12.9% (*n* = 90)	18.4% (*n* = 23)
Never visited an ACHD-center	5.6% (*n* = 103)	4.9% (*n* = 38)	6.2% (*n* = 65)	10.3% (*n* = 41)	4.5% (*n* = 27)	3% (*n* = 21)	11.2% (*n* = 14)
Group differences		***$p = 0.60$		**$p < 0.001$ (A vs. B: ***$p < 0.001$; A vs. C: ***$p < 0.001$; A vs. D: $p < 0.001$; B vs. C: ***$p < 0.001$; C vs. D: ***$p < 0.001$)			

Is the physician who mainly treats you for your heart disease ACHD-certified?

	Total (N = 1,828)	Male (n = 777)	Female (n = 1,051)	Simple CHD (n = 398)A	Moderate CHD (n = 606)B	Complex CHD (n = 699)C	Others/unclassified CHD (n = 125)D
Yes	27.8% (*n* = 509)	25.4% (*n* = 197)	29.7% (*n* = 312)	16.1% (*n* = 64)	24.8% (*n* = 150)	39.9% (*n* = 279)	12.8% (*n* = 16)
No	6.1% (*n* = 111)	5.1% (*n* = 40)	6.8% (*n* = 71)	6.3% (*n* = 25)	5.8% (*n* = 35)	7% (*n* = 49)	1.6% (*n* = 2)
I do not know	66.15% (*n* = 1208)	69.5% (*n* = 540)	63.6% (*n* = 668)	77.6% (*n* = 309)	69.5% (*n* = 421)	53.1% (*n* = 371)	85.6% (*n* = 107)
Group differences		*$p < 0.05$			*$p < 0.001$		

Would you rather be treated by a pediatric cardiologist or an adult cardiologist?

	Total (N = 1,828)	Male (n = 777)	Female (n = 1,051)	Simple CHD (n = 398)A	Moderate CHD (n = 606)B	Complex CHD (n = 699)C	Others/unclassified CHD (n = 125)D
Pediatric cardiologist	28.5% (*n* = 521)	25.7% (*n* = 200)	30.5% (*n* = 321)	16.6% (*n* = 66)	25.7% (*n* = 156)	38.5% (*n* = 269)	24% (*n* = 30)
Adult cardiologist	30% (*n* = 549)	30.2% (*n* = 235)	29.9% (*n* = 314)	37.2% (*n* = 148)	32% (*n* = 194)	23.9% (*n* = 167)	32% (*n* = 40)
I do not know the difference	7.9% (*n* = 145)	9.7% (*n* = 75)	6.7% (*n* = 70)	9% (*n* = 36)	8.6% (*n* = 52)	6% (*n* = 42)	12% (*n* = 15)
I do not care	33.5% (*n* = 613)	34.4% (*n* = 267)	32.9% (*n* = 346)	37.2% (*n* = 148)	33.7% (*n* = 204)	31.6% (*n* = 221)	32% (*n* = 40)
		*$p < 0.05$			*$p < 0.001$		

N, sample size.

**Chi–squared test was used for the statistical analyses.*

***Kruskal–Wallis test was used for the statistical analyses.*

****Mann–Whitney U test was used for the statistical analyses.*

in comparison to male participants (30.5 vs. 25.7%). Furthermore, significant differences ($p < 0.001$) according to CHD severity were detected: patients with complex CHD preferred pediatric cardiologist in private practice more often (38.5%) than patients with simple CHD (16.6%) (**Table 2**).

Patient Age and Type of Main Treating Physician

With increasing age, there was also a change regarding the type of main treating physician. While 45.1% of the respondents in the youngest age group (18–22 years) were treated mainly by a pediatric cardiologist in private practice, only17.4% of the respondents older than 38 years of age were treated in this setting (**Figure 1**).

Rating Questions

Significant group differences were found regarding participants' rating of the information about their CHD that they received by their main treating physician ($p < 0.001$). While only 64.7% of patients with CHD not treated in a specialist setting felt well well-informed about their condition by their physician, patients treated in a specialist setting more often felt well-informed (pediatric cardiologist in private practice: 79.4%, ACHD clinic at a heart center: 76.8%, adult cardiologist in private practice: 76.4%) (**Table 3**).

Likewise, the question regarding participants' trust in their treating physician yielded significant group differences ($p < 0.001$) (**Table 3**). The highest degree of trust was reported by those patients who were mainly treated by a pediatric cardiologist (**Table 3**).

DISCUSSION

According to the German health care system, patients with CHD may not generally be treated by a pediatric cardiologist in private practice once they have turned 18 years (25). The present study shows indeed, that, with increasing age, patients are less likely to be treated by a pediatric cardiologist in private practice. However, as many as 17.4% of the patients older than 38 years are still treated by a pediatric cardiologist in private practice. Transition from pediatric to an age-appropriate adult medical care, as defined by the transition concept (9, 10), can, therefore, be considered as being only partially successful in Germany based on these results. Adult patients with more complex underlying heart disease are those being mainly treated in a specific ACHD clinic at a heart center or by a pediatric cardiologist in private practice. The relatively large proportion of patients continuing to attend general cardiologists, not specializing in ACHD, supports the concept to provide additional training for adult cardiologists in the field of CHD. To this end, a process of ACHD certification (24) was established in Germany based on recommendations for improving the quality of the interdisciplinary care for ACHD (23). The main intention was to enable, both, pediatric cardiologists to treat adult patients, as well as to provide adult cardiologists with training and experience in the treatment of complex CHD. It is hoped that this addresses the challenges associated with the continuously growing and aging group of CHD patients (14) and ensure that patients receive the necessary support and medical care throughout their lives (24). The fact that a large majority of the surveyed patients did not know the meaning of the term "ACHD-certified," as well as their ignorance regarding the fact of whether their treating physician is actually ACHD-certified, which shows that this certification

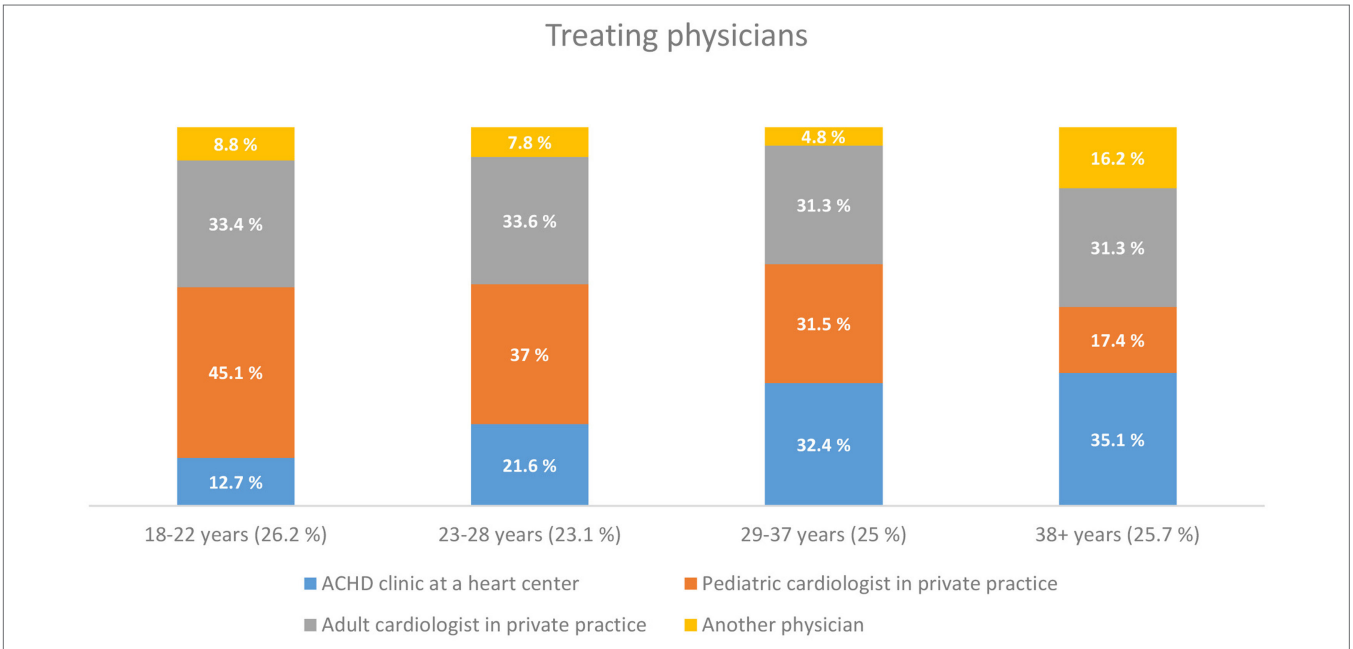

FIGURE 1 | **Treating physicians**.

TABLE 3 | Descriptive statistics (subjective patient statements).

Do you understand the explanations given by your physician concerning your heart defect?					
	Total (N = 1,828)	**ACHD clinic at a heart center (n = 465)A**	**Pediatric cardiologist in private practice (n = 598)B**	**Adult cardiologist in private practice (n = 592)C**	**Another physician (n = 173)D**
Low	4% (*n* = 73)	3.7% (*n* = 17)	4% (*n* = 24)	4.2% (*n* = 25)	4% (*n* = 7)
Medium	17.6% (*n* = 325)	17.8% (*n* = 83)	16.9% (*n* = 101)	17.4% (*n* = 103)	22% (*n* = 38)
High	78.2% (*n* = 1430)	78.5% (*n* = 78,5%)	79.1% (*n* = 473)	78.4% (*n* = 464)	74% (*n* = 128)
Group differences			$^{**}p = 0.583$		
Do you feel well-informed about your heart defect by your treating physician?					
	Total (N = 1,828)	**ACHD clinic at a heart center (n = 465)A**	**Pediatric cardiologist in private practice (n = 598)B**	**Adult cardiologist in private practice (n = 592)C**	**Another physician (n = 173)D**
Low	4.6% (*n* = 85)	4.1% (*n* = 19)	3.5% (*n* = 21)	4.9% (*n* = 29)	9.3% (*n* = 16)
Medium	19% (*n* = 347)	19.1% (*n* = 89)	17.1% (*n* = 102)	18.8% (*n* = 111)	26% (*n* = 45)
High	76.4% (*n* = 1396)	76.8% (*n* = 357)	79.4% (*n* = 475)	76.4% (*n* = 452)	64.7% (*n* = 112)
Group differences	$^{**}p < 0.001$ (A vs. D: $^{***}p < 0.01$; B vs. D: $^{***}p < 0.001$; C vs. D: $^{***}p < 0.01$)				
How well do you rate your knowledge regarding your heart defect?					
	Total (N = 1,828)	**ACHD clinic at a heart center (n = 465)A**	**Pediatric cardiologist in private practice (n = 598)B**	**Adult cardiologist in private practice (n = 592)C**	**Another physician (n = 173)D**
Low	6.8% (*n* = 125)	5.4% (*n* = 25)	7% (*n* = 42)	6.9% (*n* = 41)	9.8% (*n* = 17)
Medium	38.8% (*n* = 710)	35.7% (*n* = 166)	41.5% (*n* = 248)	39.2% (*n* = 232)	37% (*n* = 64)
High	54.3% (*n* = 993)	58.9% (*n* = 274)	51.5% (*n* = 308)	53.9% (*n* = 319)	53.2% (*n* = 92)
Group differences			$^{**}p = 0.089$		
How much do you trust your treating physician?					
	Total (N = 1,828)	**ACHD clinic at a heart center (n = 465)A**	**Pediatric cardiologist in private practice (n = 598)B**	**Adult cardiologist in private practice (n = 592)C**	**Another physician (n = 173)D**
Low	3.2% (*n* = 59)	2.4% (*n* = 11)	2.2% (*n* = 13)	3.7% (*n* = 22)	7.5% (*n* = 13)
Medium	16.8% (*n* = 307)	15.5% (*n* = 72)	13.2% (*n* = 79)	18.9% (*n* = 112)	25.4% (*n* = 44)
High	80% (*n* = 1,462)	82.2% (*n* = 382)	84.6% (*n* = 506)	77.4% (*n* = 458)	67.1% (*n* = 116)
Group differences	$^{**}p < 0.001$ (A vs. D: $^{***}p < 0.001$; B vs. C: $^{***}p < 0.01$; B vs. D: $^{***}p < 0.001$; C vs. D: $^{***}p < 0.01$)				

N, sample size.
**Chi-squared test.*
***Kruskal–Wallis test.*
****Mann–Whitney U test.*

measure is not appreciated and understood as a quality criterion by many patients. Therefore, despite the fact that especially patients with complex CHD prefer treatment at specialized ACHD centers, the question of whether the treating physician is ACHD-certified seems to play only a marginal role in choosing a particular center/physician.

One may also question the obligatory shift from pediatric to adult cardiology care in the German health care system. The main problem is that it may prevent a pediatric physician from caring for a patient known to him/her since the patient's early childhood, just because of an age limit that could be regarded by some as arbitrary. This could lead to patients being less compliant with their care. This may be one possible explanation for the major problem of ACHD patients being "lost to follow-up" (32, 33). On the other hand, advocates of the transition system rightly argue that adults with CHD have very different needs from children with the conditions requiring particular expertise and training on behalf of the main treating (pediatric-) cardiologist. Resolving the question on the optimal organization of care for ACHD patients is beyond the scope of the current report, but our study provides important insights into the current status of treatment, patient education, and patient views on this topic in a contemporary cohort of German ACHD patients.

Limitations

Since this is a cross-sectional study, we provide descriptive information and report on associations rather than claiming to report causal relationships between parameters. Moreover, the results reflect respondents' subjective statements. The results may not be applicable to patients outside Germany, since they are affected by the life situation of the patients, as well as the organization of the health care system.

One might assume that patients registered in the NRCHD have a greater interest in CHD and therefore know more about this condition than German patients who are not registered.

Since the CHD patients have been invited to participate in the survey by emails, *via* websites and social networks, no reliable response rate can be specified. Therefore, we cannot guarantee that the sample of patients participating in the online survey is representative for the ACHD community at large. However, a previous study has showed that the patient population included in the register is representative. In addition, by involving large national patient organizations, we aimed to increase the reach of the survey and thus also capture patients not necessarily linked to major heart center. This should reduce bias related to more complex patients tending to be more likely associated to tertiary care and thus included in the register.

CONCLUSION

Reassuringly, ninety percent of the participants were treated by medical specialists. Many patients made use of specific ACHD clinics at a heart center or were seen by pediatric/adult cardiologists in private practice. However, a sizeable proportion of patients was found to not being linked to recognized ACHD specialists, with approximately one-third of all respondents not in continuous medical care at a specific ACHD clinic/heart center. The trust in the treating physician seems to play a significantly more important role for the surveyed patients than an existing ACHD certification. Overall, there is still a major need for improvement of the (medical) care of ACHD patients.

AUTHOR CONTRIBUTIONS

PH, HK, GB, ES, RK, RN, G-PD, OT, and UB took responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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MINI REVIEW
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Mental Health Problems in Parents of Children with Congenital Heart Disease

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This review will provide a concise description of mental health problems in parents of children with a (non-syndromic) congenital heart disease (CHD) during different stressful periods. Predictors of these problems and also implications for clinical practice will be mentioned. Having a child with CHD can be very stressful for parents, who have to face overwhelming emotions and also extra physical, financial, and other practical challenges. Parental distress has been reported in 30–80% of parents and appears not to be related to severity of CHD. Parental mental health, parenting, the parent–child relationship, and parental quality of life can all be affected. Parents, and especially mothers, are at risk of psychological distress, anxiety, depression, somatization, hopelessness, and posttraumatic stress symptoms, which in turn may influence mother's responsiveness. In the long term, the majority of parents adapt successfully to living with a child with CHD, but approximately 40% report a need for psychosocial care. These families may be helped by early psychosocial interventions to alleviate stress and reduce children's emotional and behavioral problems. A holistic approach to early psychosocial interventions should aim at improving coping and enhance parenting. During routine medical checkups, medical professionals should ask about parental stress, family functioning, and psychosocial functioning of the child and, when needed, adequate psychosocial care should be provided.

Keywords: children, congenital heart disease, parents, stress, psychopathology

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INTRODUCTION

Approximately 36,000 infants (1% of total live births) are born with a congenital heart disease (CHD) in the USA each year (1). It is well known that due to huge improvements in the medical and surgical treatment of CHD in the last three decades, 85% of infants are expected to survive (2). In a retrospective cohort study, Oster et al. found that 1-year survival for infants with critical CHD improved from 67.4% for the 1979–1993 birth era to 82.5% for the 1994–2005 birth era ($P < 0.001$) (2). Because of the improved survival rates, more and more studies have looked into the psychological outcomes of children with CHD and their parents. Having a child with CHD can be very stressful for parents; the overwhelming emotions and experiences at the time of diagnosis, cardiac surgery, and thereafter may impact parental quality of life and their capacity for optimal parenting. Research indicates that

parents, and especially mothers of children with CHD, report mental health problems (such as depression, anxiety, and feelings of guilt), adjustment problems, and poor quality of life more often than parents of healthy children or children with other medical problems (3, 4). These parental mental health problems can be present during different phases of the lives of the children and their medical trajectories. A recent systematic review revealed that up to 30% of parents of children with critical CHD have posttraumatic stress (PTS) symptoms, 25–50% of them reported symptoms of depression and/or anxiety and 30–80% severe psychological distress, particularly shortly after children's cardiac surgery (5). In addition, parents have to face various extra physical, financial, and other practical challenges.

In this chapter, we give a short overview of parental mental health problems across different stressful or even traumatic periods, e.g., pre- and postnatal diagnosis, the time around cardiac surgery and hospital admissions, and parental well-being on the long term. Due to limited space, this mini review does not have the aim to give a complete systematic review, but rather aims to describe the most prominent problems concerning parents of children with CHD (**Table 1**).

PARENTAL MENTAL HEALTH PROBLEMS AROUND THE TIME OF CHILD'S CHD DIAGNOSIS

Several studies showed that during the period of diagnosis, parents of children with CHD experience more psychopathology (e.g., anxiety, depression, and somatization) compared to parents of children with other medical illnesses or healthy controls (3, 6, 7). Parents can experience difficulties at different time points. One possible stressful period is the time around the child's diagnosis.

As to timing of diagnosis of CHD (e.g., prenatal, postnatal), Fonseca et al. showed that parents of children with a congenital anomaly (40% of which were CHD) were more distressed compared to parents of healthy children, even if they had similar quality of life (4). Interestingly, learning the diagnosis in the prenatal period was related to a higher maternal quality of life compared to receiving the diagnosis after the baby was born.

Bevilacqua et al. found no differences in stress and depression levels in both fathers and mothers, who received the diagnosis of CHD in their child prenatally or postnatally (8). However, mothers who had received the diagnosis prenatally were more depressed, while those who had received a postnatal diagnosis were more stressed. In this study, parental self-reported stress and depression levels within 2 weeks after hospitalization of their infants in the first 3 months of life were significantly higher in mothers compared to fathers.

In a study of Cantwell-Bartl and Tibballs, of the total 18 parents whose infants were diagnosed with hypoplastic left heart syndrome (HLHS) *in utero*, eight of nine mothers and six of nine fathers had posttraumatic stress disorder (PTSD) (9). Of those parents whose infants were diagnosed with HLHS postbirth, six of seven mothers had acute stress disorder (ASD) and one mother had PTSD. Furthermore, two of the four fathers had ASD and one father had PTSD. These parents were clinically assessed with a semistructured interview and the PTSD module of the Structured Clinical Interview for Diagnosis. Only five parents were free of traumatic symptoms. This was the first study with parents of infants with HLHS in the ICU. The high prevalence of traumatic stress of parents in this study is related to the multiple stressors experienced by them, including the CHD diagnosis received after birth of their infant (for 50% of parents) and the life-threatening nature of HLHS, the ICU environment, and surgery.

Fischer et al. studied parental anxiety levels during the first month of their neonates' life with CHD (upon hospital discharge), using the State Trait Anxiety Scale (STAI) (10). They found low (5% with significant and 2% with borderline) trait anxiety scores, indicating stable personality levels of anxiety in caregivers, whereas higher numbers of caregivers reported clinically significant (5%) and borderline (14%) state anxiety. Higher education was associated with higher level of state and trait anxiety.

In a Norwegian Mother and Child Cohort Study ($n = 36{,}437$), Solberg et al. studied a subgroup of 141 children with CHD. They found that postpartum mental health of mothers of infants with severe (but not mild/moderate) CHD was different compared to that of cohort controls at 6, 18, and 36 months postpartum. The mothers of CHD children had been experiencing significantly elevated levels of depression and anxiety symptoms (7, 11). In the same cohort, CHD was a substantial risk factor for parental mental health problems in children and their mothers at all time points (12). Both familial and individual factors contributed to risk for developing mental health problems, and mutual influences between mother's and child's mental health at 18 and 36 months over time were found.

In sum, despite different methodologies, most studies agree that the period of the child's CHD diagnosis is generally a stressful period for parents, which may jeopardize the parental mental health. Nevertheless, the mentioned studies have limitations such as small sample size (8–10), reliance on retrospective memory, low participation rate and attrition (7, 11), oversimplification in CHD severity grading (7, 11), use of self-reports, lack of clinical assessment of parental mental health problems (8, 11), and lack of data on possible confounding factors (11).

PARENTAL MENTAL HEALTH PROBLEMS AFTER CHILD'S CARDIAC SURGERY

Parents of children with CHD undergoing cardiac surgery may also be at increased risk for psychological malfunctioning particularly in the weeks and months immediately following cardiac surgery (5, 13). In the study of Vrijmoet-Wiersma et al., predictive factors for increased parental anxiety appeared to be: the time interval since last procedure, the number of surgeries, and ethnicity (14).

Preprocedural mental health of parents of patients with (a) cyanotic CHD was studied by Üzger et al. (15). They found that an upcoming angiography was associated with depression and anxiety in parents of children with CHD. Mothers of children with cyanotic CHD had significantly higher levels of depression and anxiety compared to mothers of children with acyanotic CHD.

TABLE 1 | Details of studies included in the mini review.

Reference	Population studied	Measures	Risk factors	Main findings/types of problems
Parental mental health problems at the time of diagnosis				
Lawoko and Soares (3)	*N* = 632 parents of children with congenital heart disease (CHD; 58% women)	Symptom Checklist – 90 – Revised (SCL – 90 – R). The Hopelessness Scale	Gender: mothers had more severe symptoms of depression, anxiety, somatization, and hopelessness than fathers. Parental caregiving burden, feeling dissatisfaction about care, social isolation, and financial difficulties were associated with an elevated risk of long-standing parental psychopathology	Parental depression (18%), anxiety (16–18%), somatization (31–38%), and hopelessness (16%)
Fonseca et al. (4)	*N* = 42 infants with congenital anomalies (40% CHD) and *N* = 42 healthy controls	Symptom Inventory-18, World Health Organization Quality of Life-Brief instrument	Being a mother and postnatal diagnosis are risk factors for more adjustment difficulties	Parents of infants with a congenital anomaly had higher distress than parents of healthy infants
Jackson et al. (6)		Systematic review of 25 studies that were selected, using the PRISMA guidelines	Families with fewer psychosocial resources and lower support are at risk of higher parental psychological distress	Higher anxiety, depression, somatization, and hopelessness in parents of children with CHD compared to parents of healthy children orthose with other diseases
Solberg et al. (7)	*N* = 162 mothers of infants with CHD and *N* = 44,400 mothers of healthy controls within the Norwegian Mother and Child Cohort Study	Hopkins Symptom Checklist (SCL-8)	CHD was a substantial risk factor for parental mental health problems	Mothers of CHD children had increased depression and anxiety compared to controls; mothers of infants with severe CHD had different postpartum mental health compared to healthy controls at 6, 18, and 36 months postpartum
Bevilacqua et al. (8)	*N* = 38 parental couples of infants with CHD	General Health Questionnaire-30 (GHQ-30), Beck Depression Inventory (BDI), Quality of Life: SF-36	Prenatal diagnosis was associated with higher depression in mothers and postnatal diagnosis with more maternal stress	Mothers had higher stress and depression levels, compared to fathers (81.8 versus 60.6 and 45.7 versus 20.0%, respectively)
Cantwell-Bartl and Tibballs (9)	*N* = 16 mothers and *N* = 13 fathers	Structured Clinical Interview for Diagnosis-Clinical Version [posttraumatic stress disorder (PTSD) module]		The majority of parents (88% of mothersand 66% of fathers) had PTSD (only five parents were free of traumatic stress)
Fischer et al. (10)	*N* = 38 neonates	State Trait Anxiety Scale (STAI)	Higher education and less medication associated with higher parental anxiety	Low trait and higher state anxiety scores in parents
Solberg et al. (11)	*N* = 141 mothers of infants with CHD and *N* = 36,437 mothers from the Norwegian Mother and Child Cohort Study	SCL-8	Severity of child's CHD is associated with higher levels of depression and anxiety symptoms	Mothers of infants with severe CHD are at risk of anxiety and depression from delivery to 36 months postpartum
Landolt et al. (12)	*N* = mothers of 408 children with CHD	Fussy/Difficult Scale from the Infant Characteristics Questionnaire, Child Behavior Checklist, SCL-8	More negative child behavior at 18 months was associated with poorer maternal mental health at 36 months in CHD and controls	CHD explained 31% and 39% of the variance in child and maternal mental health problems
Parental mental health problems at postsurgery period				
Woolf-King et al. (5)		A systematic review of 30 studies that were selected using the PRISMA guidelines		30% of parents have PTS symptoms, 25–50% depression/ anxiety symptoms, and 30–80% severe distress
Helfricht et al. (13)	*N* = 135 mothers and *N* = 98 fathers of 139 children with CHD undergoing surgery	Posttraumatic Diagnostic Scale	PTS symptom severity at discharge predicted PTSD severity 6 months later	16.4% of mothers and 13.3% of fathers had acute PTSD; 15.7% of mothers and 13.3% of fathers had PTS symptoms
Vrijmoet-Wiersma et al. (14)	*N* = 114 mothers and *N* = 82 fathers of 131 children	Pediatric Inventory for Parents-short form, GHQ, Parental Stress Index-short form, STAI, Child Vulnerability Scale	Number of surgical procedures, time past since last one, and ethnicity were risk factors for higher parental anxiety	Parents of children with CHD had higher levels of perceived vulnerability than parents of healthy children; state anxiety was higher in mothers of children with CHD
Üzger et al. (15)	*N* = parents of 73 patients with CHD undergoing cardiac catheterization	BDI, Beck Anxiety Inventory	Cyanosis: mothers of cyanotic children had more anxiety and depression than mothers of acyanotic children	Increased parental depression and anxiety symptoms in parents of children with CHD

(*Continued*)

TABLE 1 | **Continued**

Reference	Population studied	Measures	Risk factors	Main findings/types of problems
Hearps et al. (16)	*N* = 39 caregivers (28 mothers) of 29 children with CHD	Adapted version of Psychosocial Assessment Tool	Increased risk for psychosocial problems is associated with higher emotional distress (in 38.5% of parents)	61.5% of parents at risk comparable to that of the general population, 35.9% at subclinical level, and 2.6% at clinical risk
Farley et al. (17)	*N* = parents of 52 pediatric heart transplant recipients	Questionnaires on illness-related parenting stress and PTS symptoms		19% of parents had PTSD and almost 40% of them had moderately severe to severe PTS symptoms
Nelson and Gold (19)		A review of descriptive, observational, and controlled studies on pediatric intensive care unit and PTSD	More serious disease was associated with PTSD development. Positive association between children's PTS symptoms and their parents' symptoms. Mothers at increased risk to develop PTSD (and more severe PTSD) compared to fathers	PTSD in 5–28% and PTS symptoms in 35–62% of parents of children admitted to intensive care unit
Helfricht et al. (20)	*N* = 61 parents of children following surgery and *N* = 52 patients with an acute cardiac event	German version of Acute Stress Disorder Scale (ASDS)	Surgery versus acute cardiac event	25% of parents of children with CHD met diagnostic criteria for ASD
Franich-Ray et al. (21)	*N* = 77 mothers and *N* = 55 fathers of infants who underwent cardiac surgery before 3 months of age	ASDS	Gender: mothers had higher ASD mean scores than fathers for all symptoms (except dissociation)	33.8% of mothers and 18.2% of fathers had ASD
Van Horn et al. (22)	*N* = 38 mothers of children with CHD aged 3–16 years	Modified Semistructured Interview (developed by Beardslee et al., 1992)	Mothers' perceptions of medical severity were associated with distress about psychosocial issues postdischarge	Maternal distress, anxiety, and depressed mood decreased postdischarge
López et al (23)	*N* = 40 parents of children with CHD and *N* = 115 parents of healthy children	GHQ, Basic Psychological Needs Scales, Self-Determination Scale, Beck Hopelessness Scale, a socioeconomic survey		Children's surgery decreased parental hopelessness. Parents of children with CHD had worse GHQ scorings than parents of healthy children
Longitudinal studies of parental mental health problems				
Lawoko and Soares (3)	*N* = 632 parents of children with CHD (58% women)	Symptom Checklist – 90 – Revised (SCL – 90 – R). The Hopelessness Scale	Parental caregiving burden, feeling dissatisfaction about care, social isolation, and financial difficulties were associated with a higher risk of long-term parental mental health morbidity	Parental depression (18%), anxiety (16–18%), somatization (31–38%), and hopelessness (16%) at both measurement points
Lawoko and Soares (24)	*N* = 1,092 parents of children with CHD, *N* = 112 parents of children with other diseases, and *N* = 293 parents of healthy children	Symptom Checklist – 90 – Revised (SCL – 90 – R). The Hopelessness Scale	Employment status and financial situation were risk factors for parental distress and hopelessness	Parents of children with CHD at higher risk of distress and hopelessness. Mothers within all parent groups had higher distress and hopelessness than fathers. Fathers of children with CHD were doing worse than fathers of the other groups
Berant et al. (25)	*N* = 63 mothers of newborns with CHD	Mothers' interview on mental health and attachment style, Children's Apperception Test	Maternal avoidant attachment at initial assessment was the best predictor of worsening of her mental health at 7-year follow-up	Mothers of children with severe CHD were more vulnerable in terms of their mental health
Menahem et al. (26)	*N* = parents of 39 children	Parents were assessed (e.g., mental health, locus of control) prior to and 12–50 months following their children's surgery		Mothers with increased anxiety and a tendency to attribute events to chance greater than normal; their anxiety decreased at follow-up

In Hearps et al.'s sample, the majority of parents appeared to have adjusted to the acute stress of their infant's CHD 4 weeks following cardiac surgery. However, 38.5% of them were classified at increased psychosocial risk [35.9% at a targeted (/subclinical) and 2.6% at a clinical level]. This risk was measured using the Psychosocial Assessment Tool (PAT), a brief parent report screener that was adapted to include also sleeping, feeding, crying, and bonding difficulties. PAT scores were associated with higher

levels of emotional distress compared to universal psychosocial risk (the lowest 61.5% of parents) (16). As the authors report, the distribution of risk for psychosocial problems in parents of CHD children undergoing surgery is comparable to that of parents of children with other serious pediatric diagnoses such as pediatric cancer. There were no differences between families of infants who received prenatal versus postnatal diagnosis or single ventricle versus biventricular repair. In addition, a higher parent education significantly predicted a lower total psychosocial risk score.

Farley et al. found a PTSD prevalence of 19% in parents of children who underwent pediatric heart transplantation (17). This is a clearly heightened risk in comparison to a PTSD lifetime prevalence of 5.6% in the general population (18). This high rate of PTSD is comparable to that of parents, following their child's admission to the pediatric intensive care unit (10.5–21%) (19). Fifty-six percentage of the CHD parent sample showed moderate levels of PTSD symptoms and 39% indicated moderately severe to severe PTSD symptoms.

Helfricht et al. reported that acute PTS symptoms in parents following discharge from hospital after cardiopulmonary bypass surgery in their child are a major risk factor for the development of chronic PTSD. Their research showed that following discharge, 16.4% of mothers and 13.3% of fathers of CHD children met diagnostic criteria for acute PTSD, using the Posttraumatic Diagnostic Scale. Another 15.7% of mothers and 13.3% of fathers experienced significant PTS symptoms. Six months after surgery, PTSD rates were 14.9 and 9.5%, respectively. In another study, Helfricht et al. found that 25% of parents of children with CHD met diagnostic criteria for ASD assessed with the German Acute Stress Disorder Scale (20).

Almost similar levels of ASD were found by Franich-Ray et al. in 77 mothers and 55 fathers of infants (younger than 3 months old), 1 month after their child was discharged from hospital following cardiac surgery (21). More specifically, one-third of mothers and almost one-fifth of fathers experienced ASD symptoms. Most of them experienced at least one symptom at a clinical level, while dissociative symptoms were the most commonly experienced group of symptoms.

Van Horn et al. studied mothers of children with CHD and their concerns during hospitalization and 2–4 weeks after discharge from hospital (22). Distress due to concerns decreased postdischarge, as did mother's anxiety and depressed mood.

In a Latin American study (Chile), parents of children with CHD had a decreased well-being (measured with the General Health Questionnaire-12) compared to parents of healthy children. On the other hand, they had a similar level of agency (a concept from developmental studies defined as "the ability to act on behalf of what you value and have a reason to value") (23). Their children's surgery significantly decreased parental feelings of hopelessness, but had no influence on their well-being or agency.

In sum, most of the reviewed studies show that in the period surrounding a child's cardiac surgery, parents are at elevated risk for developing mainly traumatic reactions, i.e., ASD and PTSD, but also anxiety and depression symptoms; psychological distress may gradually decrease following cardiac surgery. Limitations of reviewed studies include, e.g., small sample size or use of non-standardized instruments (23), underestimation of ASD (21), assessment of mental health symptoms "only," and not of specific psychiatric diagnoses (13–15, 17, 20, 21, 23).

LONG-TERM PARENTAL MENTAL HEALTH PROBLEMS

Several studies investigated parental mental health problems at longer term (after at least 1 year or longer thereafter) following diagnosis or cardiac surgery of their child. In a longitudinal study, Lawoko and Soares studied psychological morbidity and its determinants in parents of children with CHD, with a 1-year follow-up interval. Parents reported a variety of psychological problems: depression (18%), anxiety (16–18%), somatization (31–38%), and hopelessness (16%) during both measurement points. Moreover, 7–22% reported persisting problems during the 1-year follow-up period. Mothers reported more severe mental health problems than fathers. Children's clinical severity did not explain parents' psychological morbidity over time. Nevertheless, parental caregiving burden, feeling dissatisfaction about care, social isolation, and financial difficulties were associated with an elevated risk of long-standing parental psychopathology. In their previous study, the same researchers found that parents of children with CHD overall were at higher risk of distress and hopelessness than parents of children with other diseases and parents of healthy children (24). Across all parent groups, mothers had higher levels of distress and hopelessness than fathers, with the highest levels among mothers of children with CHD compared to mothers in the other groups. Fathers of children with CHD were doing worse than fathers belonging to the other groups.

In a 1-year and 7-year follow-up study of children with CHD, maternal avoidant attachment at the time of diagnosis was the best predictor of worsening of mothers' mental health and maternal satisfaction over this period, especially in a subgroup of whose children had severe CHD (25). In addition, mothers' attachment insecurities to their own and their children's psychological functioning (both anxiety and avoidance) at the time of diagnosis were associated with their children's emotional problems and children's poor self-image 7 years later.

In the study of Menahem et al., a substantial increase in the emotional distress, e.g., anxiety of mothers of children with CHD at the time of surgery significantly resolved by 12–50 months following the surgery while they still seemed not to feel in "control" at follow-up (26). At baseline, these mothers reported increased anxiety and a tendency to attribute events to luck and/or chance greater than community norms.

In sum, the few longitudinal studies on mental health problems of parents with CHD available show conflicting results, i.e., decline of parental symptoms over time or persistence, especially in more severe CHD cases.

CLINICAL IMPLICATIONS—THE NEED FOR PSYCHOSOCIAL CARE

Despite high variability in methodologies and measurements used in outcome studies, it can be concluded that parents of

children with CHD experience numerous stresses and mental health problems. High percentages of them show traumatic stress, anxiety, depression, and other psychiatric morbidities (5, 9, 22). Levert et al. have recently reported that more than 40% of parents and more than 50% of their children with CHD reported a need for psychosocial care on each of five domains studied, i.e., physical/medical, emotional, social and educational/occupational functioning, and health behavior (27). Needs for psychosocial care for parents themselves were highest for parents of 0–12-year-old children. Parents and/or patients reported that they would like to be referred to mental health professionals in case of problems on the domains studied.

The PICU environment, where also the diagnosis is given for many children with CHD, may impact the parent–infant attachment and parental adaptation. The PICU staff may, therefore, help parents in dealing with their new traumatic situation (9). This can be done by providing parents information and psychoeducation, involving them in taking care of their infant as much as possible and strengthening their role as parents, to enhance bonding with their child. Also, other studies point to the need for providing support both to children/adolescents with CHD and their parents, especially mothers (12). There is a need for early identification and screening of parents at risk of stress and mental health problems. Specific interventions to improve parental coping and adjustment are needed. Practitioners working with these children and families should ask about, e.g., parental mental health, stress, and family functioning, in the context of routine medical checkups (28). In this modern digital era, we recommend to screen for mental health problems and parental stress during outpatient consultations, by having parents complete questionnaire digitally on an iPad, in the waiting room during outpatient consultations.

Considering the findings of studies on psychosocial interventions to promote adjustment in families of child with CHD, a holistic approach is recommended (6). The pediatric cardiology group from Belfast (United Kingdom) has highlighted the importance of maternal mental health for child behavioral outcomes at 1-year follow-up. Their psychosocial intervention has been shown to have a positive impact on maternal mental health and functioning of families with children with CHD (29).

Finally, parents and families can be helped by educational interventions such as the use of narrative therapy, strengthening protective factors, cognitive behavioral techniques (relaxation, helpful thoughts, and cognitive restructuring), and provision of psychoeducation to deepen parents' understanding of their child with CHD (3).

CONCLUSION

Despite great methodological variability between reviewed studies, the majority of studies show that parents, and especially mothers, of children with CHD are at higher risk and experience a variety of mental health problems (e.g., PTS, anxiety, depression) at different time periods of their offspring medical condition. Those parents with mental health problems can be helped by mental health professionals. In addition, prospective studies of parental mental health problems, with larger samples of families and use of standardized instruments and interviews.

AUTHOR CONTRIBUTIONS

All the authors (GK, MM, and EU) have substantially contributed to the conception of the work. GK has drafted the manuscript, and MM and EU revised it. All the authors (GK, MM, and EU) have made a final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Factors Influencing Neurodevelopment after Cardiac Surgery during Infancy

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Short- and long-term neurodevelopmental (ND) disabilities with negative impact on psychosocial and academic performance, quality of life, and independence in adulthood are known to be the most common sequelae for surviving children after surgery for congenital heart disease (CHD). This article reviews influences and risk factors for ND impairment. For a long time, the search for independent risk factors was focused on the perioperative period and *modalities of cardiopulmonary bypass (CPB)*. CPB operations to ensure intraoperative vital organ perfusion and oxygen supply with or without circulatory arrest or regional cerebral perfusion bear specific risks. Examples of such risks are embolization, deep hypothermia, flow rate, hemodilution, blood gas management, postoperative hyperthermia, systemic inflammatory response, and capillary leak syndrome. However, influences of these *procedure-specific risk factors* on ND outcome have not been found as strong as expected. Furthermore, modifications have not been found to support the effectiveness of the currently used neuroprotective strategies. *Postoperative factors,* such as need for extracorporal membrane oxygenation or assist device support and duration of hospital stay, significantly influence ND parameters. On the other hand, the so-called "innate," less modifiable *patient-specific risk factors* have been found to exert significant influences on ND outcomes. Examples are type and severity of CHD, genetic or syndromic abnormalities, as well as prematurity and low birth weight. Structural and hemodynamic characteristics of different CHDs are assumed to result in impaired brain growth and delayed maturation with respect to the white matter. Beginning in the fetal period, this so-called *"encephalopathy of CHD"* is suggested a major innate risk factor for pre-, peri-, and postoperative additional hypoxic or ischemic brain injury and subsequent ND impairment. Furthermore, MRI studies on brain volume, structure, and function in adolescents have been found correlated with cognitive, motor, and executive dysfunctions. Finally, *family and environmental factors* independently moderate against ND outcomes. In conclusion, the different mediating factors may exert independent effects on ND and interactive influences. Implications for the future comprise modifying clinical risk factors, such as perioperative cerebral oxygen delivery, conducting brain MRI studies in correlation to ND outcomes, and extending psychosocial interventions leading to adequate resilience.

Keywords: risk factors, neurodevelopment, congenital heart disease, cardiac surgical procedures, cardiopulmonary bypass, brain MRI, encephalopathy

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INTRODUCTION

The prevalence of congenital heart disease (CHD) is about 1 in every 100 live births. About one-third of CHD cases is in critical need of surgical intervention in neonatal or infant age (1). Since the 1980s, advanced diagnostic technologies, neonatal cardiopulmonary bypass (CPB) operations enabling early correction of complex congenital heart defects, and improved postoperative care have markedly increased life expectancy: today more than 90% of CHD patients survive into adulthood. At the same time, these patients are at remarkable risk of short- and long-term neurodevelopmental (ND) impairment. This can have negative impact on psychosocial and academic performance, quality of life, and independence in adulthood (2–6).

The present article discusses causes and factors mediating risk for ND disabilities from neonatal to adolescent age in CHD patients after cardiac surgery during infancy.

INFLUENCING FACTORS ON NEURODEVELOPMENT: INNATE AND MODIFIABLE PARAMETERS

Risk factors for brain injury and consecutive ND disabilities in infants, children, and adolescents with CHD after cardiac surgery in infancy may exert independent, cumulative, and synergistic influences. They comprise patient-specific (mostly innate and not modifiable) and procedure-specific (in part modifiable) parameters (**Figure 1**).

For a long time, the search for independent factors mediating risk for ND impairment has focused on the perioperative period and modalities of CPB. CPB operations to ensure intraoperative vital organ perfusion and oxygen supply with or without circulatory arrest or regional cerebral perfusion bear specific risks. Examples for such risks are embolization, deep hypothermia, flow rate, hemodilution, blood gas management, postoperative hyperthermia, systemic inflammatory response, and capillary leak syndrome (7–11). Though numerous modifications of these factors have been performed over time, ND outcomes have not improved accordingly (12, 13). In a recent analysis of >1,700 CHD patients from across the world who were born between 1996 and 2009 and had cardiac surgery at age <9 months, only modest improvements in the significantly reduced ND outcomes (psychomotor developmental index—PDI and mental developmental index—MDI) of the Bayley Scales of Infant Development-II at a mean age 14 months have been observed (14). Moreover, CPB management factors explained only about 1% of test results' variance. Longer support time was hypothesized to be a surrogate for operative complexity. Postoperative parameters like need for extracorporal membrane oxygenation or ventricular assist device support and longer postoperative length of hospital

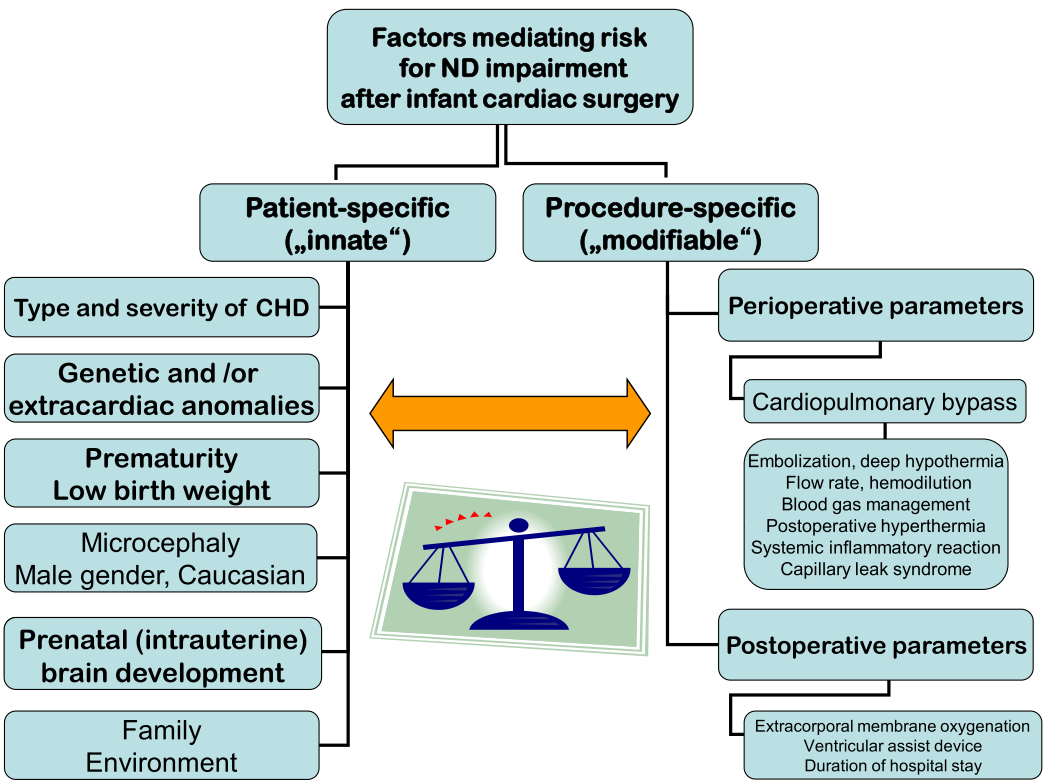

FIGURE 1 | Factors-mediating risk for neurodevelopmental impairment after infant cardiac surgery.

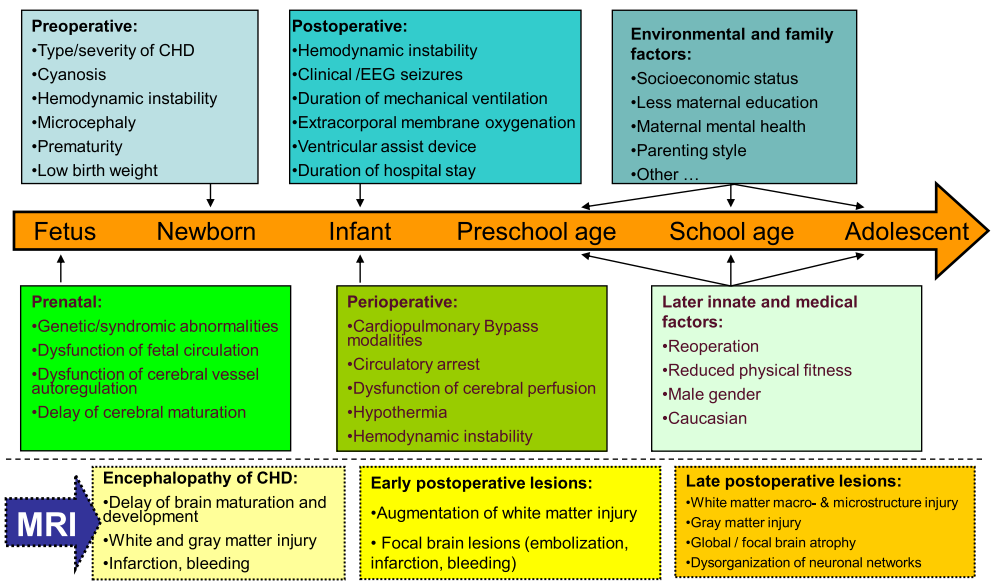

FIGURE 2 | **Factors-influencing neurodevelopmental outcomes in relation to brain magnetic resonance imaging**.

stay were associated with lower ND results. In total, measured intraoperative and postoperative factors accounted for 5% of the variances in PDI and MDI (15).

There is a strong evidence that less modifiable innate patient characteristics and socioeconomic environmental factors have an important impact on ND outcomes (14, 16–19). In addition to type and severity of CHD, prematurity, lower birth weight, white race, and genetic or extracardiac anomalies have been assessed as predicting lower PDI. Lower birth weight, male gender, less maternal education, and genetic or extracardiac anomalies were independent risk factors for lower MDI (14). In general, genetic disorders are found in about 30% of patients with CHD. This includes chromosomal disorders, microdeletions, or mutations. However, only about one-third of the variance in ND outcomes early after cardiac surgery in infancy can be explained by the known innate patient and preoperative risk factors. Further genetic and epigenetic factors (changes in proteins affecting gene regulation) (20) or genetic polymorphisms such as the apolipoprotein E affecting the resilience capability of the brain (18) may exert influences on ND outcomes.

In addition, psychosocial factors comprising family and environmental parameters moderate against, or augment adverse ND behavioral and school outcomes. Family factors comprise parenting style such as overprotection, maternal mental health, and worry. They are able to exert significant influence on cognitive outcomes. Socioeconomic status is considered the most important environmental factor (21, 22).

ENCEPHALOPATHY OF CHD: DELAYED MATURATION, INJURY, AND NEURODEVELOPMENT

There is evidence that structural and hemodynamic characteristics of different congenital heart defects lead to autoregulation mechanisms in the brain in case of hypoperfusion or hypoxia by vasodilatation of the cerebral arteries with increased diastolic flow and decreased cerebrovascular resistance (23, 24). It has been assumed that prolonged periods of this autoregulation may lead to delayed maturation of the fetal oligodendrocytes, reduced myelinization, and increased vulnerability of the brain (25–28). However, in fetuses with single ventricular heart, decreased cerebrovascular resistance has been found associated with higher PDI scores at the age of 14 months (29, 30). It remains unclear whether fetal cerebral blood flow alterations predict ND outcomes later in childhood.

Fetal brain perfusion disturbance has been supposed to result in impaired brain growth and maturation with respect to the white matter. Neuropathological studies indicate that the brain disturbance of infants with CHD consists predominantly of cerebral white matter injury (WMI). This result is comparable to periventricular leucomalacia as described in preterm infants (31, 32).

During the last decade, structural and functional brain MRI studies in CHD fetuses, neonates before and after cardiac surgery, and adolescents have given increasing evidence of brain abnormalities in relation to factors mediating ND disabilites (**Figure 2**).

In MRI studies, the term "cerebral white matter immaturity" has been suggested (33–35), and a rate of 20–50% of WMI in newborns prior to surgery, which is dependent on the severity of the underlying CHD, has been detected (36–39). Brain MRI studies have also shown smaller brain volumes, abnormal brain metabolism and decreases in cortical folding, and gyral development in CHD fetuses (27, 40). However, the predictive value of brain abnormalities detected *in utero* MRI on postnatal preoperative brain injury is limited. Further postnatal studies prior to cardiac surgery are needed (41). In newborns with complex CHD prior to surgery (42–46), smaller preoperative brain volumes, abnormal brain metabolism and decreases in cortical folding, and gyral development were also detected. These were associated with a poor behavioral state regulation (43). Brain maturation has been found delayed by 1 month in newborns with transposition of the great arteries or hypoplastic left heart syndrome (34). Associations between lower brain maturity at birth and increased preoperative and postoperative brain injury (47) as well as ND impairment at the age of 2 years (38) suggest that the so-called "encephalopathy of CHD" (48, 49) may increase the vulnerability of the brain to hypoxia or ischemia. This is especially true in the setting of the surgical and perioperative management, and also in terms of a longer preoperative period between birth and surgery (50). After cardiac surgery, more than 50% of the neonates provide MRI signs of WMI (36–38).

In summary, the brain immaturity and abnormality in infants with CHD seem to be a complex disturbance with destructive and developmental elements, similar to the encephalopathy first described in premature infants (51). Beginning in the fetal period, the encephalopathy of CHD is a major innate risk factor for preoperative, perioperative, and postoperative additional hypoxic or ischemic brain injury and subsequent ND impairment.

There are also important implications in long-term follow-up linking brain abnormalities in CHD to later ND delay. Brain volumes, including hippocampal volume, remain smaller into adolescence. They are accompanied by reduced ND outcomes (52, 53). MRI macrostructural brain abnormalities (54) and regions of reduced white matter microstructure (55) in TGA adolescents have been found correlated with neurocognitive decline. Diminished white matter microstructure may contribute to cognitive compromise in adolescents who underwent open-heart surgery in infancy. Recently, special brain MRI investigations have suggested that disorganization of neuronal networks may contribute to increased attention deficiency hyperactivity disease symptoms in adolescents with TGA (56).

CONCLUSION

Besides physical morbidity, ND and psychosocial disabilities are the most common long-term risks of critical CHD. Surgical factors seem to be less important than innate patient and preoperative factors and postoperative events in predicting ND outcomes after cardiac surgery in infancy. Since the variance in percentage explained by the considered clinical variables is quite low, as-yet unknown intrauterine and genetic factors should be investigated. The risk of delayed brain maturation and brain injury evaluated by MRI in fetuses and in neonates with CHD prior to cardiac surgery is of importance.

While the predisposing factors for ND disorders are predominantly innate and while only a few of them are modifiable, research focuses on new approaches for neuroprotection. Examples for such research are cerebral vascular autoregulation monitoring, new perioperative brain biomarkers, and perioperative EEG monitoring. Sophisticated longitudinal brain MRI studies with systematic correlation to ND outcomes aim at an improved risk stratification and therapy for the CHD population.

AUTHOR CONTRIBUTIONS

HH-G is the only author of the manuscript and contributed concept, text, and reference list.

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Intellectual Functioning in Children with Congenital Heart Defects Treated with Surgery or by Catheter Interventions

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Background: Studies suggest that children with congenital heart defects (CHD) are at risk for adverse intellectual functioning. However, factors related to lower intellectual functioning in this group are largely unknown. This study describes intellectual functioning in children with CHD in relation to severity of the heart defect, the child's age, and the socioeconomic status of the family (SES).

Methods: Two hundred twenty-eight children treated with surgery or by catheter technique were tested using the Wechsler intelligence scales to determine full scale IQ (FSIQ). FSIQ was then analyzed in relation to age (3-, 5-, 9-, and 15-year olds), severity of the diagnosis (mild, moderate, and severe), and SES (low, medium, and high). The median age was 70 months (5.8 years) with a range of 162 months [30 months (2.5 years) to 192 months (16.0 years)].

Results: The total mean score on FSIQ was 100.8 (SD = 14.5). Children with severe CHD had significantly lower FSIQ than children with mild and moderate CHD, and 9- and 15-year olds had significantly lower FSIQ compared to the 3-year olds. Children from families with low SES had significantly lower FSIQ than children from medium SES and high SES families. No interaction between severity of diagnosis, age, and SES was found for FSIQ.

Conclusion: Eighty-three percent of the children with CHD performed at or above average with respect to FSIQ. SES and severity of diagnosis had significant main effects on FSIQ. These factors should be considered when planning interventions and follow-up programs for children with CHD.

Keywords: intellectual functioning, neurodevelopment, congenital heart defects, cardiac treatment by surgery or by catheter interventions

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INTRODUCTION

Because children with congenital heart defects (CHD) now live longer due to advances in surgical and catheter techniques, their neurodevelopment, including intellectual functioning, has become a major area of concern (1, 2), attracting both clinical and research interest (3).

Severity of the heart diagnosis in children with CHD has been suggested as an important predictor for intellectual functioning: the more severe the heart diagnosis, the higher the risk for lower intellectual functioning (4) and poorer academic performance (5). Results, however, are not consistent. A study comparing univentricular and biventricular patients showed no significant group differences with respect to intellectual functioning; that is, both groups scored within the norms. However, when assessing specific neuropsychological functions within the domains of attention and executive and sensorimotor functioning, only the univentricular patients had lower scores compared to the matched controls (6).

The use of wide age ranges when measuring intellectual functioning in children with CHD have made it difficult to compare studies (5). A meta-analysis described a significant relation between older age and better cognitive functioning. Further analysis disclosed that when excluding patients with the more severe diagnosis, the age effect disappeared, implying that age effects were observed because patients with the more severe diagnosis were often tested at an earlier age (5). Some studies [e.g., Oates et al. (7)], however, have not found correlations between age and intellectual functioning (8).

The relation between SES and intellectual functioning is well investigated in the normal population (9–13) as well as in children with CHD (14–16). Intellectual outcomes in children with CHD are often shown to be related to maternal education (17), comorbidity (i.e., velocardiofacial syndrome), and low SES (18, 19). In a study of cardiac arrest in children with heart disease, higher SES correlated with higher intellectual functioning, lower levels of behavioral problems, and lower levels of parental stress (20). In studies done in healthy populations, intellectual functioning is positively related to SES (21).

Scientific knowledge on neurodevelopment in children with CHD, and specifically, intellectual functioning, is still incomplete. Previous studies have been limited to small groups of patients (22, 23) with a specific diagnosis (17, 24–26), have been overly restricted, specific, or unclear with respect to age groups (27–29), and have been limited to specific surgical procedures (26, 30). Using the intelligence quotient (FSIQ) score, the aim of the present study was to investigate intellectual functioning in children with CHD treated with surgery or by catheter techniques and to investigate if intellectual functioning was related to severity of the heart diagnosis, child age, or socioeconomic status of the families. The following hypotheses were tested:

1. Children with severe CHD have lower intellectual functioning than children with mild and moderate CHD,
2. Older children have lower intellectual functioning than younger children with CHD,
3. Children with CHD living in families with low SES have lower intellectual functioning than children in families with higher SES,
4. There is an interaction effect of severity of diagnosis and SES: children with low SES and severe CHD have lower intellectual functioning compared to children with high SES and severe CHD.

MATERIALS AND METHODS

Participants

Participants were tested over a 7-year period (2008–2015). In the beginning, only children with severe CHD living in the Gothenburg area were included. As time and financial resources allowed, children with severe CHD were recruited from the whole region of Västra Götaland. Later, children with milder CHD (a larger population) were recruited to obtain comparison groups of comparable sizes. Using the medical records of children living in the Västra Götaland Region (VGR), we know that 1,133 children were treated with surgery or catheter interventions for CHD at Queen Silvia Children's Hospital in Gothenburg, Sweden during the data collection period. Children with chromosomal defects and disabilities known to influence intellectual functioning ($N = 144$) were excluded. The invited families were required to speak, read, and write Swedish and to provide a signed consent. All eligible children with severe CHD ($N = 99$) and 432 (of 890) children with milder CHD were invited. We were unable to locate some patients, and some patients did not want to participate for different reasons (e.g., lack of time, not wanting to worry the child who had a mild CHD and were unaware of any difficulties, and did not speak Swedish). In total, 531 patients were invited (**Figure 1**); of these, 237 children and their families (44.9%) agreed to participate in the study. Participation rate was higher in the severe group than in the milder groups. All children met with a clinical psychologist at their local hospital for a psychological evaluation.

Four hospitals participated in the gathering of data: The Queen Silvia Children's Hospital, North Älvsborg County Hospital, Southern Älvsborg Hospital, and Skaraborg Hospital Skövde; most of the testing was done by the same psychologist, however, the groups of psychologists testing the children met regularly to assure test reliability. Nine of the tested children were not included in the analyses: two 3-year olds were unable to complete the tests; two 5-year olds had unreliable test results (one was given a neuropsychiatric diagnosis); and one 15-year old refused to finish the testing. Four 9-year olds were not tested with the Wechsler scales. As a result, 228 children (42.9% of those invited) completed testing with Wechsler scales at age 3, 5, 9, or 15 years (**Table 1**) and are included in the analyses; 111 (48.7%) were girls and 117 (51.3%) boys. Approval from the ethics committee in Gothenburg, Sweden was obtained on September 20, 2011 (ref. no. 391–11).

Intellectual Assessment

The Swedish versions of the Wechsler Scales of Intelligence (31, 32) were used to assess general intellectual functioning. The Wechsler Preschool and Primary Scale of Intelligence – third edition (WPPSI–III Swedish version) was used to test the 3- and 5-year-old children, and the Wechsler Intelligence Scale for Children – fourth edition (WISC–IV Swedish version) was used to test the 9- and 15-year-old children. Only core subtests were used to compute the full scale IQ (FSIQ). Analysis of verbal IQ (VIQ) and performance IQ (PIQ) did not show significant differences, so we report only FSIQ since it is the most robust

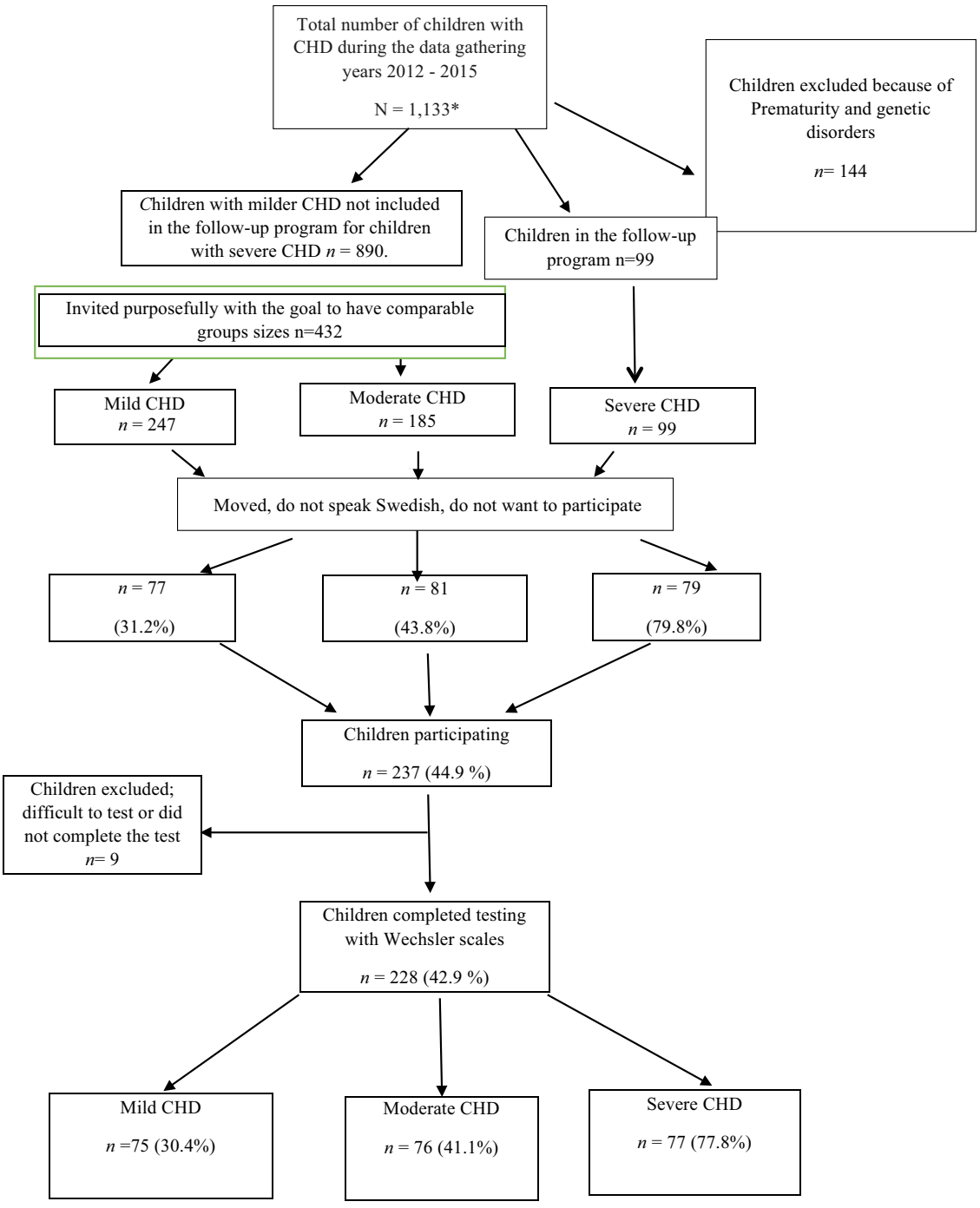

FIGURE 1 | **Study population**. *Children treated with surgery or by catheter interventions for CHD.

measure of intellectual functioning. The children assessed with the WPPSI–III in the 2:6–3:11 age band were administered only five subtests: receptive vocabulary, block design, information, object assembly, and picture naming. For the children in the 4:0–7:3 age band, eight subtests were administered: information, vocabulary, word reasoning, block design, matrix reasoning, picture concepts, coding and symbol search. The children assessed with the WISC–IV, designed for children of 6:0–16:11 age, were assessed using 10 core tests: Similarities, vocabulary, comprehension, block design, matrix reasoning, digit span, coding and symbol search. The Swedish versions of the WPPSI–III and the WISC–IV are based on UK standardization data. Data have

TABLE 1 | Participants grouped by the severity of their cardiac diagnosis and the targeted age for assessment.

CHD	AGE				
	3 years	5 years	9 years	15 years	*N* (%)
	Min. 2.5 years, max 3.8 years	Min. 4.5 years, max 6.0 years	Min. 7.6 years, max 10.4 years	Min. 13.9 years, max 16.0 years	
Mild	19	17	19	18	73 (32.0)
Moderate	20	17	24	17	78 (34.2)
Severe	26	19	18	14	77 (33.8)
N (%)	65 (28.5)	53 (23.2)	61 (26.8)	49 (21.5)	228 (100)

111 children (48.7%) were girls and 117 children (51.3%) were boys.

shown that previous British and Swedish versions of the Wechsler scales are comparable (31) as both measure similar constructs and their norms are highly consistent (33).

The Wechsler scales of IQ are based on the normal distribution curve with a mean score of 100 (SD 15); 68% of children in a population are expected to have an IQ score between 85 (−1 SD below the mean) and 115 (+1 SD above the mean), 14% are expected to have an IQ score between 116 and 130 (+2 SD), 14% are expected to have an IQ score between 84 and 70 (−2 SD), 2% are expected to have an IQ score between 131 and 145 (+3 SD), and 2% are expected to have an IQ score between 69 and 55 (−3 SD).

Cardiac Diagnosis and Severity

The children in the study had a wide range of cardiac diagnoses and were divided into three groups. Recruitment of children with moderate and mild CHD was done with the aim of having approximately equal numbers of children as in the severe group (see **Table 1** for distribution of these groups). The three severity groups were based on the risk the child had for further complications and their cardiac diagnosis: (1) the mild group – children usually treated once with surgery or by catheter intervention with little risk for further complications and who were, in most cases, no longer followed up, e.g., atrial septal defect, ventricular septal defect, persistent ductus arteriosus, isolated coarctation of the aorta, and pulmonary stenosis; (2) the moderate group – children who had been treated with surgery and/or catheter intervention and were followed up regularly since there were risks for further complications, e.g., transposition of the great arteries, tetralogy of Fallot, complete AV defect, total anomalous pulmonary venous drainage, and aortic stenosis; and (3) the severe group – children with complex heart defects for whom long-term prognosis was uncertain and serious complications were not uncommon, e.g., univentricular heart lesions, pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals, and heart transplantation.

Age

Testing was performed between 2008 and 2015. Families of children who met the inclusion criteria were invited when children were at the right age for testing. Children were tested as toddlers (3 years), pre-schoolers (5 years), school aged (9 years), or teenagers (15 years) (±6 months from their birthday), recruitment of patients from the moderate and mild CHD-group was done purposefully to get equal number of children in each age group to match the severe group. Ages for data gathering were chosen to the match the follow-up program for children with CHD at Queen Silvia Children's Hospital in Gothenburg.

Socioeconomic Status

The Hollingshead "Four Factor Index of Social Status" was used to determine socioeconomic status index (SES) for each family. This index weighs education, occupation, and employment status to determine a composite score of social status.[1] From our sample of 228 children, 366 parents (202 mothers and 164 fathers) answered the questionnaire. In 17 families, none of the parents provided data on SES and for 154 families, both parents answered the questionnaire. When both parents provided data, we followed the Hollingshead manual's requirements and divided the sum of their scores by two to create a SES index for the family (see text footnote 1). Based on a *Z*-transformation, three SES groups were formed: low (−1 SD), medium (±1 SD), and high (+1 SD). The scores on the index ranged from 3 to 66; the mean score for our sample was 43.6 (SD = 12.5), indicating that, on average, our patients came from medium to high SES families. Previous studies have shown an average SES of 37.0 (SD = 11.7) in the Swedish population (13).

Statistical Analysis

SPSS 20.0 was used for the statistical analyses. The dependent variable – FSIQ – was normally distributed and therefore parametric tests were used. For between-group comparisons of intellectual functioning (FSIQ) in relation to age (3-, 5-, 9-, and 15-year olds), severity levels (mild, moderate, and severe) and SES (low, medium, and high), we used analysis of variance (ANOVA) with eta-square to analyze effect size, interpreting 0.02 as small, 0.13 as medium, and 0.26 as large effect size (34). For the *post hoc* tests, Bonferroni was used. All variables were check for normality. For non-parametric statistics, we used cross tabs and chi-square test ($p \leq 0.05$ statistically significant).

RESULTS

Intellectual Functioning

For the 228 children, the total mean score for FSIQ was 100.8 (SD = 14.5), displayed in **Figures 3–6** with a horizontal line.

[1] Adams J, Weakliem DL. August B. Hollingshead's "four factor index of social status": from unpublished paper to citation classic. *Yale J Sociol* (2011) 8:11–20.

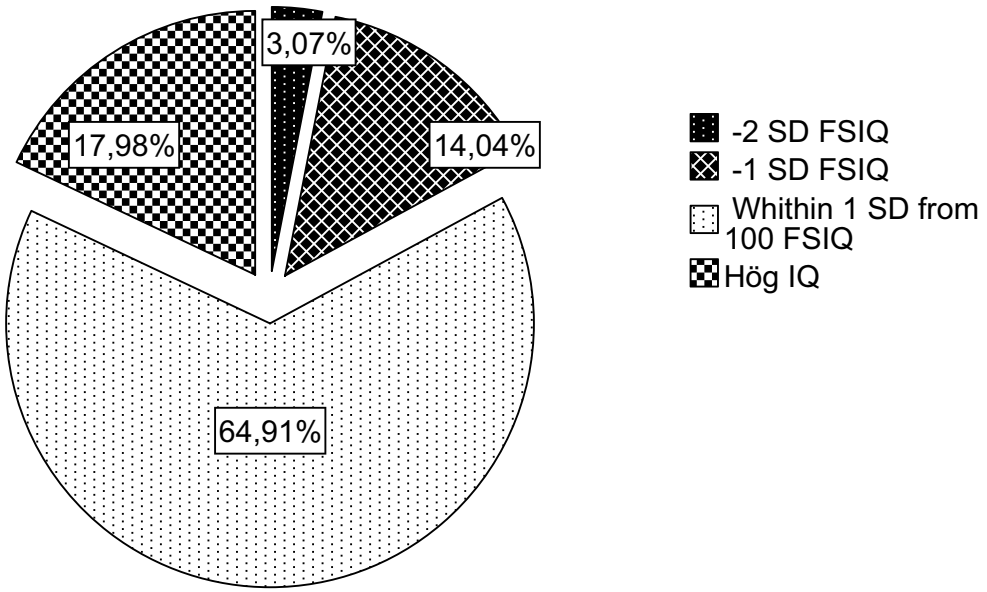

FIGURE 2 | **Proportion of children performing in the normal range (±1 SD) and over (+1 and SD) and under (−1 and −2 SD)**.

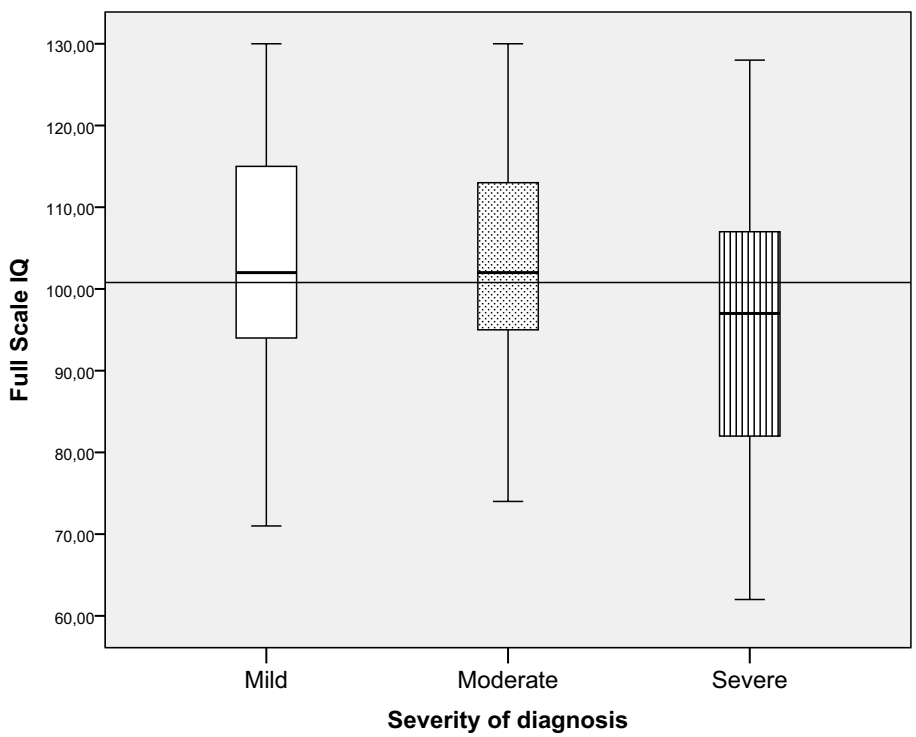

FIGURE 3 | **FSIQ in relation to severity of diagnosis**.

No significant differences were found between boys and girls. **Figure 2** shows the distribution of children performing within the normal range and ±1 and ±2 SD compared to norms.

In the following sections, FSIQ will be presented in relation to severity of diagnosis, age, and SES. We begin each section by presenting FSIQ as a continuous variable, followed by presenting FSIQ as a categorical variable [i.e., the proportion of children performing within the normal range, ±1 SD, +1 SD (no child over +2 SD), and −1 and −2 SD in relation to severity of diagnosis, age, and SES]. See **Table 2** for descriptive data.

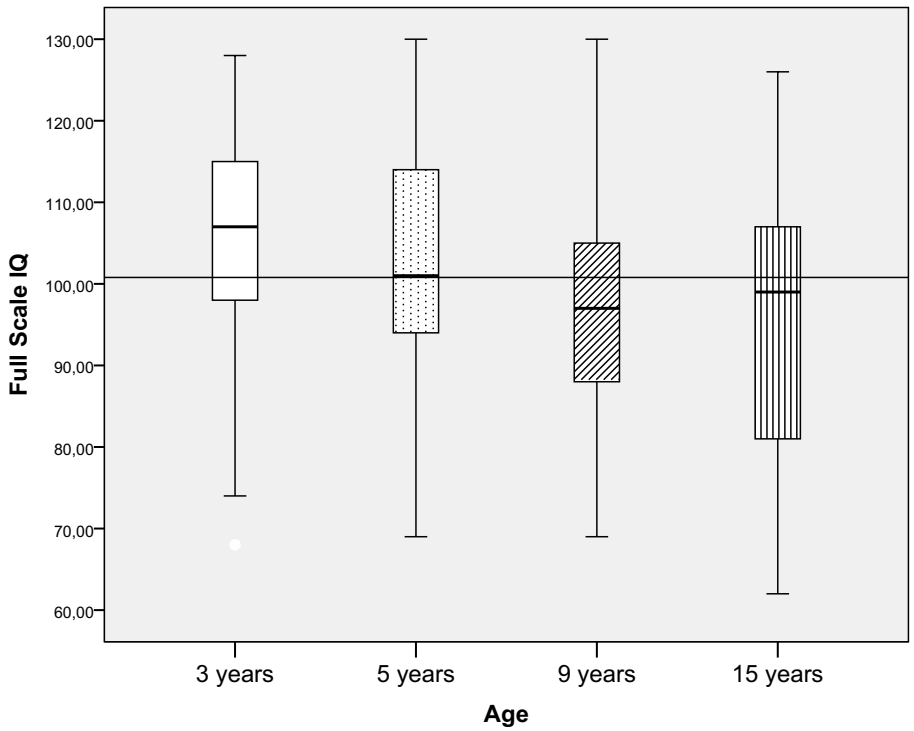

FIGURE 4 | **FSIQ in relation to age**.

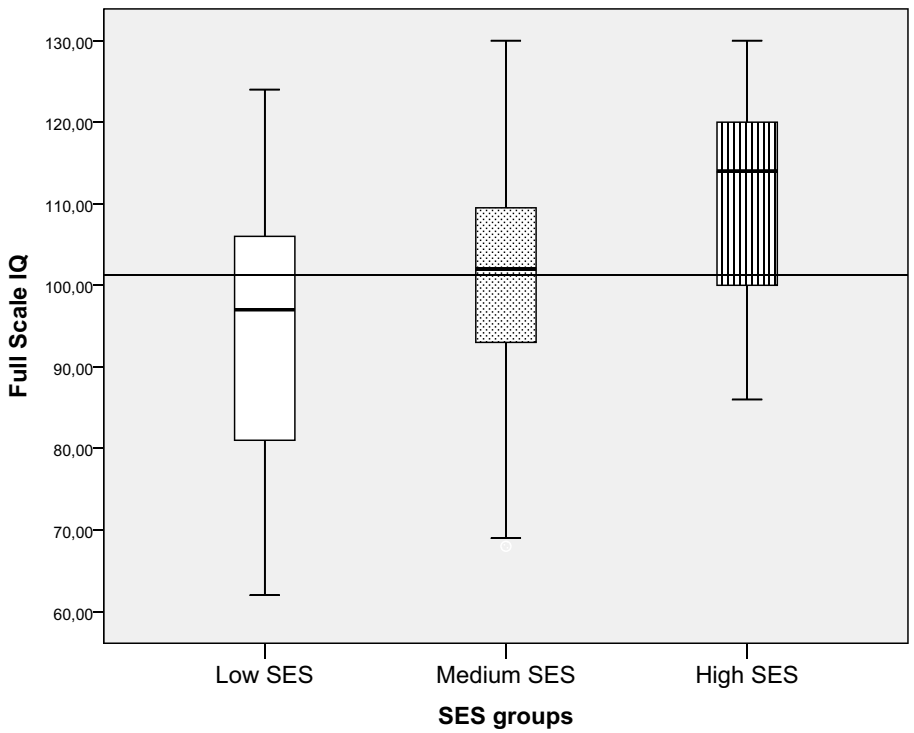

FIGURE 5 | **FSIQ in relation to SES**.

Intellectual Functioning in Relation to Severity of Diagnosis

Children in the severe CHD group had significantly lower FSIQ (mean = 95.8, SD = 16.0) than children in the mild CHD group (mean = 103.6, SD = 13.6) and the moderate CHD group (mean = 103.2, SD = 12.6) [F (2, 227) = 7.3, $p = 0.001$, $\eta_p^2 = 0.06$], see **Figure 3**. The effect size was small for distribution of children from the different severity groups performing within the normal range and ±1–2 SD. More children with severe CHD had FSIQ below −1 SD (32.5%) than children with milder forms of CHD (9.3%) [λ^2 (df 6) = 23.7 $p < 0.001$]. **Table 3**.

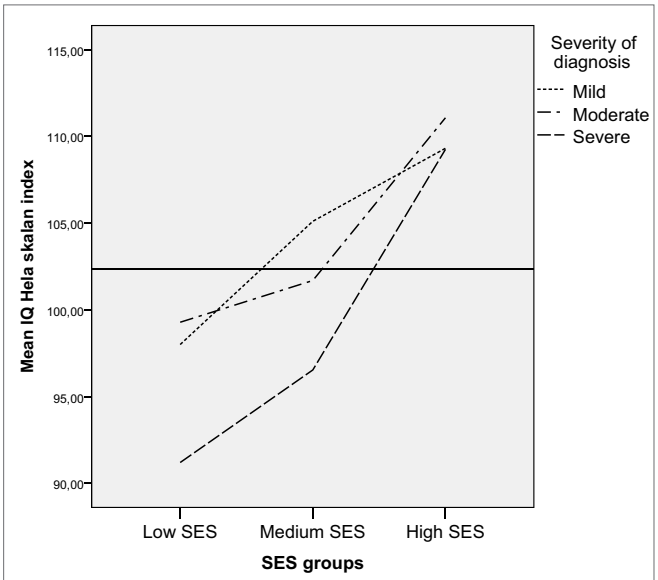

FIGURE 6 | FSIQ in relation to SES and severity of the cardiac diagnosis.

Intellectual Functioning in Relation to Age

Intellectual functioning was significantly lower for the 9-year olds (mean = 98.0, SD = 13.1) and 15-year olds (mean = 96.1, SD = 15.9) compared to the 3-year olds (mean = 105.6, SD = 13.6) [F (3, 227) = 5.3, $p = 0.001$, $\eta_p^2 = 0.07$], and the effect size was small. However, when children were divided into categorical IQ-groups (low, average, and high intellectual functioning), there were no significant differences in the proportion of children in the groups in relation to age (**Figure 4**; **Table 2**).

Intellectual Functioning in Relation to SES

Children from families with low SES had significantly lower intellectual functioning (mean = 94.9, SD = 16.4) compared with both the medium SES (mean = 101.0, SD = 13.2) and the high SES group (mean = 110.0, SD = 12.6). The high SES group also had significantly higher FSIQ than the medium SES group [F (2, 210) = 11.3, $p = 0.000$, $\eta_p^2 = 0.10$]. The effect size was of medium size. When children were divided into categorical IQ-groups (low, average, and high intellectual functioning), a higher

TABLE 2 | FSIQ mean and SD by severity of cardiac diagnosis, and age or SES.

	Mild CHD		Moderate CHD		Severe CHD		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AGE								
3 years (n = 65)	109.5	11.0	108.9	12.4	102.0	14.8	105.6	13.6
5 years (n = 53)	107.9	12.1	104.4	12.5	95.7	15.2	102.4	14.2
9 years (n = 61)	101.1	12.5	99.1	12.6	93.3	13.9	98.0[a]	13.2
15 years (n = 49)	95.8	15.6	100.8	11.3	90.9	20.6	96.1[a]	15.9
Total (n = 228)	103.6	13.6	103.1	12.6	95.8	16.0	100.8	14.5
SES								
Low (n = 41)	98.0	15.5	99.3	17.7	91.2	16.5	94.9[c]	16.4
Medium (n = 136)	105.1	11.8	101.7	11.6	96.5	15.0	101.0	13.2
High (n = 34)	109.3	12.9	111.1	12.1	109.3	16.8	110.0[d]	12.6
Total (n = 211)	104.6	13.2	103.2	12.8	95.5[b]	15.9	101.3	14.4

[a]*Intellectual functioning was significantly lower for the 9- and 15-year olds compared to the 3-year-olds [F (3, 227) = 5.3, p = 0.001, $\eta_p^2 = 0.07$].*
[b]*Children in the severe CHD group had significantly lower FSIQ than children in the mild CHD group and the moderate CHD group [F (2, 227) = 7.3, p = 0.001, $\eta_p^2 = 0.06$].*
[c]*Children from families with low SES had significantly lower intellectual functioning compared with both the medium SES and the high SES group (mean = 110.0, SD = 12.6).*
[d]*The high SES group had significantly higher FSIQ than the medium SES group [F (2, 210) = 11.3, p = 0.000, $\eta_p^2 = 0.10$].*

TABLE 3 | Proportion of children with low, average, or high intellectual functioning in relation to severity of diagnosis.

	Mild CHD n (%)	Moderate CHD n (%)	Severe CHD n (%)	Total n (%)
Low FSIQ (−1 and −2 SD)	7 (9.6)	7 (9.0)	25 (32.5)[a]	39 (17.1)
Average FSIQ (within ±1 SD)	48 (65.8)	56 (72.0)	44 (57.1)	148 (64.9)
High FSIQ (+1 SD IQ)	18 (24.7)	15 (9.2)	8 (10.4)	41 (18.0)
Total n (%)	73	78	77	228 (100)

[a]*More children with severe CHD had FSIQ below −1 SD (32.5%) than children with milder forms of CHD (9.3%) [λ^2 (df 6) = 23.7 p < 0.001].*

TABLE 4 | Proportion of children with low, average, or high intellectual functioning in relation to SES.

	Low SES *n* (%) mean and SD	Medium SES *n* (%)	High SES *n* (%)	Total *n* (%)
Low FSIQ (−1 and −2 SD)	14 (34.1)[a]	20 (14.7)	1 (2.9)	35 (16.5)
Average FSIQ (within ±1 SD)	22 (53.7)	97 (71.3)	17 (50.0)	136 (64.5)
High FSIQ (+1 SD IQ)	5 (12.2)	19 (14.0)	16 (47.1)	40 (19.0)
Total *n* (%)	41 (19.4)	136 (64.5)	34 (16.1)	211 (100)

[a]*A higher proportion of children from families with low SES had FSIQ below −1 SD compared to children from families with average or high SES [λ^2 (df 6) = 33.0 $p < 0.01$].*

proportion of children from families with low SES had FSIQ below −1 SD (34.1%) compared to children from families with average (14.7%) or high SES (2.9%) [λ^2 (df 6) = 33.0 $p < 0.01$] (**Figure 5**; **Table 4**).

Interaction Effects

We found no interaction effect between severity of diagnosis and SES for FSIQ. Using ANOVA to control for the effect of SES on FSIQ, we found that the effect size for severity of diagnosis on FSIQ decreased from.06 to.05 after controlling for SES, but the differences in FSIQ between the severity groups remained significant. Both SES and severity of CHD diagnosis had significant main effects on FSIQ. When children were divided into categorical IQ-groups (low, average, and high intellectual functioning), a larger proportion of children both diagnosed with severe CHD and living in families with low SES performed in the low range of intellectual functioning more often than children diagnosed with severe CHD living in families with medium and high SES (**Figure 6**) [Pearson chi-square (df 6) = 25.6, $p < 0.01$]. Among those children having low SES and a severe CHD 8 of 20 (40%) had low IQ (−1 or 2 SD); those having medium SES and severe CHD 13 of 43 (30%) had low IQ, and those with high SES severe CHD, 1 (of 4) had low IQ.

DISCUSSION

In our study of 228 Swedish children with CHD treated with surgery or by catheter technique, the mean score on FSIQ in Wechsler Scales of Intelligence was 100.8 (SD = 14.5). This finding indicates that children with CHD treated with surgery or by catheter interventions as a group performed within the normal range on overall intellectual functioning, a result that contradicts some early studies such as the ones presented in a literature review by Amianto, et al. (8). In this literature review, some studies reported that CHD in children was related to lower intellectual functioning; however, other studies found normal performance in these children not only with respect to general intelligence but also with respect to academic results, learning abilities, and visuospatial abilities (8).

Although 65% of children in the present study performed within the normal range, 17% had scores −1 or −2 SD below the mean, and 18% had scores +1 SD above the mean. When comparing subgroups of children with CHD, some children are clearly more at risk than others in terms of intellectual functioning. As hypothesized, intellectual functioning in children with CHD was related to severity of diagnosis, age, and SES.

In this study, we created similarly sized diagnosis groups with diverse severity levels to avoid focus on specific heart defects, a limitation of many other studies (17, 24–26). The results show that children with severe CHD had significantly lower intellectual functioning than children with mild or moderate CHD. This finding agrees with studies reporting that children with milder forms of CHD, such as ventricular septal defect, present lower incidence of neurodevelopmental problems than children with more severe forms of CHD (6, 35). The fact that children with more severe forms of CHD present higher risk for neurodevelopmental problems suggests that cognitive problems could be related to intraoperative factors and to the surgery procedures themselves (36). Although some studies have evaluated the risks that specific surgery techniques confer on children's intellectual functioning, no clear relation has been proven (29). However, genetic comorbidities and neurological status before surgery are shown to be significant (37). Brain development during fetal and early postnatal life has shown to be influenced by environmental conditions such as maternal stress, and this psychosocial strain in turn influences intellectual functioning (38, 39). A study measuring brain size in infants with CHD found that although brain size in these children was smaller than in healthy term infants, cerebral grow rates were comparable with the cerebral growth rates of the controls (4), and there were no significant differences in neurodevelopmental outcomes in pre-term-born infants with CHD compared to term-born infants (40, 41). Studies have highlighted the long-term effects of preoperative status (42, 43) and of the surgical procedures, which are determined by the severity of the heart defect (1, 2, 23). In the present study, the SD in the severe group was shown to be wider than in the mild and moderate groups, i.e., the difference in intellectual functioning between the lowest and highest performance in the severe group was larger than in the mild or moderate groups. This finding has also been observed in previous studies (25, 44, 45).

Because using unrestricted or very restricted age groups is a well-known problem in many previous studies (27–29), we created specific comparable age groups. Results showed that children in the older groups (9- and 15-year olds) had significantly lower intellectual functioning compared to the 3-year olds. Three-year olds were assessed with WPPSI–III, and the 9- and 15-year olds were assessed with WISC–IV, a choice that probably influenced the results. Although good correlations have been established between these instruments, the WPPSI–III produces slightly higher scores than the WISC–IV. In addition, as children become older and progress through school, the demands on their intellectual functioning increase. Even though intellectual functioning is one of the best predictors of school performance, there are specific cognitive functions that influence learning (e.g., attention and memory). These specific cognitive factors are not targeted in the FSIQ of the Wechsler scales. Deficits in specific

cognitive factors were shown in one study of children with CHD tested at age 5 and 10 years; despite stable intelligence scores, the risk for cognitive deficits increased with age (42). Difficulties with specific cognitive functions – e.g., attention, working memory, and processing speed – may not impact general performance in a test situation such as the Wechsler scales of intelligence but may become evident in everyday situations as demands in school increase with age. The clinical experience is that children with CHD more often require special education and learning interventions when they are older. Future research should target specific cognitive domains such as attention, working memory, and executive function in children with CHD in relation to FSIQ and school performance.

Our results showed a significant relation between SES and intellectual functioning in children with CHD. Children from families with low SES had significantly lower intellectual functioning compared with both the medium SES and the high SES groups. This goes in line with studies carried out in healthy populations in which intellectual functioning is believed to be determined by socioeconomic status (21, 46). Results in our study showed that the high SES group also had significantly higher FSIQ compared to the medium SES group. Larger proportion of the children from families with low SES had FSIQ below −1 SD compared to children from families with average or high SES. Yet, it is important to interpret these results cautiously since our sample had very small subgroups. This finding, however, corresponds with previous studies showing that parental education (28), environmental processes (15, 47), and parental stress (48) are related to intellectual functioning in children with CHD (14). Furthermore, studies reporting results of interventions aimed to promote intellectual functioning, development, emotional adjustment, and resilience in children with CHD have shown that reduced levels of anxiety in mothers, good mental health in parents, and good family functioning are significant advantages not only for intellectual functioning (and fewer missed school days) but also for self-perceived health (49, 50).

In the ANOVA, no interaction effect was found between severity of diagnosis, age, and SES, probably because of the relatively small sample size. However, when using non-parametric test, children simultaneously exposed to severe CHD diagnosis and to low SES were found to more often perform in the low range of intellectual functioning. This finding also corresponds with previous studies showing that children with severe heart defects and lower SES are at greater risk for problems related to intellectual functioning (14, 51).

In sum, children with CHD as a group performed well on FSIQ, although we identified severity of the heart diagnosis and SES as factors related to increased risk for lower FSIQ in children with CHD. We believe that providing parents with specific and accurate information on the risks of lower intellectual functioning, supporting schools with psychoeducational advice, and introducing follow-up and intervention programs for families as early as possible are important steps to improving the outcomes for children with CHD. Therefore, children with severe CHD and children from low SES families should be assessed for further interventions and included in follow-up and intervention programs.

Limitations

This study is limited by the absence of a control group. Although believed to be reliable, norm data have limitations since we do not know if the groups are comparable on important background variables. Another limitation of this study is the use of only one dependent variable, FSIQ. Although intellectual functioning is one of the best predictors of school performance, it does not fully capture children's learning problems or behavioral difficulties. Therefore, we believe that future studies should address specific cognitive functions (e.g., executive function, attention, and memory functions) as often these functions are impaired in children seeking help for school problems in this group. Analysis of these functions together with FSIQ could give a more complete understanding of the problems presented in children with CHD.

The response rate in the severe group was much higher than the response rate in the mild group. We do not have background data on the non-responders, and there is a risk of response-bias. It is common that parents with higher education more often agree to participate in scientific studies compared to parents with lower education. It might also be the case that parents of children with more difficulties at school were more inclined to participate because they wanted a cognitive evaluation of their child and more support from the school. We know that FSIQ in our mild CHD group was normally distributed, and the FSIQ scores in the severe CHD group were skewed with lower values on FSIQ. Looking closer at the severity of diagnosis- and SES-relation, we could see that 23% of children in the mild group had high SES while only 7% of children in the severe group had high SES. FSIQ in the mild group could be systematically higher because parents with high IQ and higher education more often agreed to participate or FSIQ in the mild could be lower than expected because parents who were worried about their child more often agreed to participate. The moderate and severe groups' participation level was much higher, and the risk for systematic response bias lower, although it is possible that the most fragile families, such as families with very ill children and very low socioeconomic status, did not participate. More studies on larger samples are needed to confirm the results of the present study.

Because this is a cross-sectional study, effects should be interpreted with caution. The differences between age groups could be due to many factors. Factors such as older and less effective surgical techniques used in the older children and the fact that different tests were used in younger and in older children contribute to the uncertainty of the results. The WIPPSI is usually considered to produce higher FSIQ scores than the WISC, which may account for the higher scores among the 3-year olds. Also, cognitive assessment in younger children is more problematic and unstable than in older ones (52). Therefore, longitudinal studies of children with CHD are needed to develop an accurate picture of cognitive development.

AUTHOR CONTRIBUTIONS

CR has substantially contributed to the design of the work, the acquisition, analysis, and interpretation of the data. JS has substantially contributed to the design of the work, retrieval of patients, classification of severity of diagnosis, and

interpretation of the data. MT has substantially contributed to the acquisition, analysis, and interpretation of the data. MB has substantially contributed to the design of the work, analysis, and interpretation of the data. All authors – CR, JS, MT, and MB – have revised the work critically, approved of the final version, and agreed to it.

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MINI REVIEW
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Neuropsychological and Psychiatric Outcomes in Dextro-Transposition of the Great Arteries across the Lifespan: A State-of-the-Art Review

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Advances in prenatal diagnosis, perioperative management, and postoperative care have dramatically increased the population of survivors of neonatal and infant heart surgery. The high survival rate of these patients into adulthood has exposed the alarming prevalence of long-term neuropsychological and psychiatric morbidities. Dextro-transposition of the great arteries (D-TGA) is one of the most extensively studied cyanotic congenital heart defect (CHD) with regard to neurodevelopmental outcomes. Landmark studies have described a common neurodevelopmental and behavioral phenotype associated with D-TGA. Children with D-TGA display impairments in key neurocognitive areas, including visual–spatial and fine motor abilities, executive functioning, processing speed, and social cognition. As they grow older, they may face additional challenges with a worsening of deficits in higher order cognitive skills, problems in psychosocial adjustment and a higher-than-expected rate of psychiatric disorders, such as attention-deficit hyperactivity disorder, depression, and anxiety. The aim of this review is to summarize the available recent data on neuropsychological and psychiatric outcomes in individuals with D-TGA after the arterial switch operation. We present findings within a life-span perspective, with a particular emphasis on the emerging literature on adolescent and young adult outcomes. Finally, we propose avenues for future research in the CHD adult neuropsychology field. Among these avenues, we explore the potential mechanisms by which pediatric neurodevelopmental impairments may have lifelong adverse effects as well as alternative interventions that could optimize outcomes.

Keywords: dextro-transposition of the great arteries, neuropsychological outcomes, psychiatric disorders, cognitive, executive function, open-heart surgery

INTRODUCTION

Dextro-transposition of the great arteries (D-TGA) accounts for 5–7% of congenital heart defects (CHD), with a prevalence of 0.2 per 1,000 live births (1, 2). Individuals with D-TGA represent a unique and relatively homogeneous study cohort with the Arterial Switch Operation (ASO) being now the standard-of-care. Moreover, D-TGA is infrequently associated with extra-cardiac anomalies, including genetic abnormalities, reducing potential confounding variables in follow-up studies. Since the first successful ASO in 1975 (3), survival rates have significantly increased, resulting in a demographic shift: adults now outnumber children living with D-TGA (4, 5). Long-term outcomes in D-TGA, and in CHD population as a whole, pose a public health challenge for screening, diagnosis, and treatment. The aim of this state-of-the-art review is to integrate recent data on neuropsychological and psychiatric outcomes in D-TGA after the ASO within a life-span perspective. Finally, we propose avenues for future research, including discussion on the potential mechanisms of long-term impairments and interventions to optimize outcomes.

NEUROPSYCHOLOGICAL OUTCOMES IN CHILDREN WITH D-TGA

Much of our knowledge on the neuropsychological profile of children with CHD comes from decades of study of survivors of D-TGA. Although the prevalence of severe neurological disorders is very low in this population (6), neurodevelopmental impairments are consistently reported (7). Early development is characterized by mild to moderate delays in cognitive, motor, and language function, with scores on the Bayley Scales of Infant Development (BSID) 0.5–1 SD below the expected mean values (8–11). The Boston Circulatory Arrest Study (BCAS) offers one of the most comprehensive analyses of the neuropsychological phenotype of these patients (9, 12–14). This longitudinal prospective study followed-up children from infancy to adolescence. At 12 months, 20% of infants achieved a psychomotor score $\leq$80 on the BSID and were less vocal than expected, suggesting delays in expressive language development (9). Recent findings reported an improvement on early outcomes for infants with D-TGA. Andropoulos et al. (15) reported mean Cognitive scores on the BSID within the normal population range, although Language and Motor scores were 7–10 points lower than the expected means. Although evaluations in infancy are important for early interventions, they are not strongly predictive of long-term scores (16), which may lead to false negatives.

Several studies have characterized the cognitive outcomes of children with D-TGA. It has become clear that intelligence abilities, as measured by Full-scale IQ scores, are generally within the normal range (6, 17). Nevertheless, deficits are often apparent in specific neurocognitive areas. Speech and motor impairments were reported in both European (17, 18) and North-American studies (13, 19). Bellinger et al. (12, 13) reported below age-expected scores for 4- and 8-year-old children in visual–spatial skills, academic achievement, working memory, hypothesis generation, sustained attention, and higher order language skills. In general, lower-level skills were relatively intact, but children had difficulty integrating or coordinating these skills to achieve higher order goals (13).

There is growing awareness that executive functioning is particularly vulnerable in D-TGA (20–22). In the BCAS, 8-year children had substantial difficulties in metacognitive aspects of behavior, such as planning, organizational skills, and cognitive flexibility (13). Impairments were evident on both verbal and non-verbal tasks, with children tending to focus on isolated details at the expense of a coherent organization of elements (13, 23). Calderon et al. (24, 25) corroborated these findings in two cohorts of 5- and 7-year olds with D-TGA. In these studies, children had difficulties elaborating a strategy to achieve a goal, i.e., anticipating the right number of actions to reproduce a visual model. They also had deficits in attentional control and inhibition of automatic tendencies, as well as lower working memory. Executive functioning issues start early in preschool years. Calderon et al. (25) demonstrated that executive function impairments were common at the age of 5, in tasks measuring behavioral control, attention, working memory, and cognitive flexibility. Executive function deficits were also reported in children with other types of complex CHD (26, 27), suggesting that they are part of the "developmental signature" of critical CHD.

Recently, deficits in social cognition were described in children with D-TGA (24, 28, 29) manifested by difficulties to interpret social stimuli and situations, e.g., facial emotional expressions, self- and other's intentions. A significant proportion had difficulties in identifying the emotional and cognitive states of others (Theory of Mind deficits).

In sum, the cognitive and behavioral challenges faced by children with D-TGA place them at high risk of long-term learning disabilities and academic under-achievement (22). Indeed, nearly 50% requires early remedial services (e.g., psychotherapy, speech therapy, or educational support) (30).

ADOLESCENTS WITH D-TGA: COGNITIVE AND PSYCHIATRIC OUTCOMES

Cognitive Outcomes

To our knowledge, only two studies focused on the cognitive outcomes of adolescents with D-TGA corrected by ASO (14, 31). In the BCAS, 139 adolescents with D-TGA (16.1 $\pm$ 0.5 years old) were evaluated (14). Patients' mean scores were lower than the expected population means on tests assessing academic skills, visuo-spatial skills, long-term memory, executive functions, and social cognition. Frequencies of scores $\geq$1 SD or $\geq$2 SD below the normative mean were, respectively, 26 and 7% for academic skills composite, 35 and 17% for memory index, and 54 and 20% for visuo-spatial index (compared to the expected frequencies of 16 and 2%, respectively). By parent report, about one in five patients had attention or executive impairments in daily life. In the Aachen Study (17, 31, 32), 60 patients who underwent the ASO were followed-up from preschool to adolescence (16.9 $\pm$ 1.7 years old). Adolescents' IQ scores were not reduced compared to the population norms, but the frequency of IQ scores $\geq$2 SD below

the expected mean was increased, especially for Performance IQ (11%) (31).

Some study cohorts have included adolescents with D-TGA as well as other types of CHD (33–37), but investigations directly comparing the D-TGA and other CHD groups are scarce. In the study of Matos et al. (34), adolescents with cyanotic CHD scored lower than adolescents with acyanotic CHD on all cognitive domains assessed, although the difference was significant only for visuo-constructive abilities. Cassidy et al. (33) evaluated executive function in 352 adolescents with cyanotic CHD (D-TGA, TOF or single-ventricle anatomy requiring Fontan procedure) and 111 controls. D-TGA, TOF, and Fontan groups had lower performances than controls on cognitive flexibility and verbally mediated executive function skills. Only visuo-spatially mediated skills were higher in the D-TGA group compared to the other groups with CHD. Despite the relative preservation of these abilities in the D-TGA group, impairment (score $\geq$ 1.5 SD below the expected mean) was twice as frequent when compared to controls.

In sum, we observe a continuum between cognitive impairments observed in children and those detected in adolescents with D-TGA. These issues, which may increase with age (13, 14, 25), involve diverse domains but mostly attention, visuo-spatial abilities, and executive functions.

Psychosocial and Psychiatric Outcomes

Adolescence is a vulnerable time, when a variety of psychosocial and psychiatric problems emerge (38). Successful transition from childhood to adolescence depends on the development of effective self-management skills and a sense of autonomy (7). For individuals with CHD, it is also an opportunity for intervention before transitioning to adult health care (39). This is important, as mental health problems can predict future adjustment difficulties, such as unemployment, risk-taking behaviors, substance abuse, and suicidality (40). Although many adolescents with D-TGA do not have residual cardiac morbidities or health chronic conditions, they may still be at risk of poor psychosocial outcomes and mental health problems. Several studies identified increased incidence of internalizing problems (i.e., anxiety, somatic complaints, depressive symptoms) in adolescents with complex CHD when compared to general population (40–43). Externalizing problems were also consistently reported, on both parent and self-report measures (41, 44). However, because these studies typically include mixed types of CHD, it is difficult to draw inferences about the risk among individuals with D-TGA.

Few studies reported specifically on adolescents with D-TGA. Hövels-Gürich et al. (42) and Karl et al. (19) showed an increased risk of parent-reported psychosocial maladjustment in children and adolescents with D-TGA. In the BCAS, 16-year-olds with D-TGA were more likely than controls (35 versus 20%) to meet criteria for a lifetime psychiatric diagnosis, as evaluated by the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS) (45). They also had a greater proportion with Attention Deficit Hyperactivity Disorder (ADHD), both lifetime (19 versus 7% for referents) and current (16 versus 3% for referents). However, the frequencies of mood or anxiety disorders did not differ between groups. On the Children's Global Assessment Scale, which assesses psychosocial functioning in different life-settings, adolescents with D-TGA obtained poorer scores, and 15% fell within the range of pathological functioning. Parent- and self-reports of psychiatric symptoms in the D-TGA group also identified more depressive, anxiety, and post-traumatic stress symptoms. Impaired cognitive functioning and greater parental stress at 8 years were the strongest predictors of poor psychosocial and psychiatric outcomes at 16 years. Of note, the prevalence of psychiatric disorders in D-TGA is lower compared to other forms of critical CHD such as single-ventricle physiology (46). However, the rates of mental health disorders in D-TGA are much higher than those reported in the national US population (47).

Finally, neuropsychological and mental health morbidities can impede successful transition from pediatric to adult health care (7). Studies showed that adolescents with CHD struggle to successfully transit to adult care and assume control of their health-care management (48–50). Focused psychosocial care, including strategies for managing health and coping with medical decision-making, should be a key facet of the transition process (51). According to the American Heart Association's transition guidelines (39), a standard core educational curriculum should include topics related to lifestyle issues including learning disabilities, anxiety, depression, and high-risk behaviors. The transition process must also include facilitated access to mental health services (50).

ADULTS WITH D-TGA: EMERGING EVIDENCE

Despite the increased number of adults with D-TGA after the ASO (52), studies on their cognitive or psychological outcomes are infrequent. Thus, to our knowledge, no studies have focused specifically on the cognitive outcomes of adults who underwent the ASO. Two recent studies (53, 54) investigated the neuropsychological outcomes of adults with CHD, including D-TGA. However, in these cohorts, most of the adults with D-TGA had not undergone the ASO but the atrial switch procedure (operation often conducted in this population before the development of the ASO). In the study of Klouda et al. (53), adults with critical CHD (i.e., D-TGA or Fontan, $n = 24$, 32.8 ± 7.6 years old) had lower scores than expected in multiple domains: psychomotor speed, processing speed, sustained and executive attention, and on the overall, neurocognitive index. Tyagi et al. (54) observed that D-TGA adults ($n = 80$, 19–50 years old) scored worse than those with mild CHD ($n = 84$) on an overall neuropsychological index. Furthermore, proportions with cognitive impairments on at least three tests were higher in the D-TGA group (49%) compared to the mild CHD group (26%). Most of the impairments observed in CHD groups involved divided attention, executive functions, and fine motor function.

To our knowledge, no studies have investigated psychiatric risks specifically in adults who underwent the ASO. Two studies evaluated the psychological outcomes of adults who underwent the atrial switch procedure (55, 56), finding that approximately 20% met criteria for a psychiatric disorder. Studies comparing

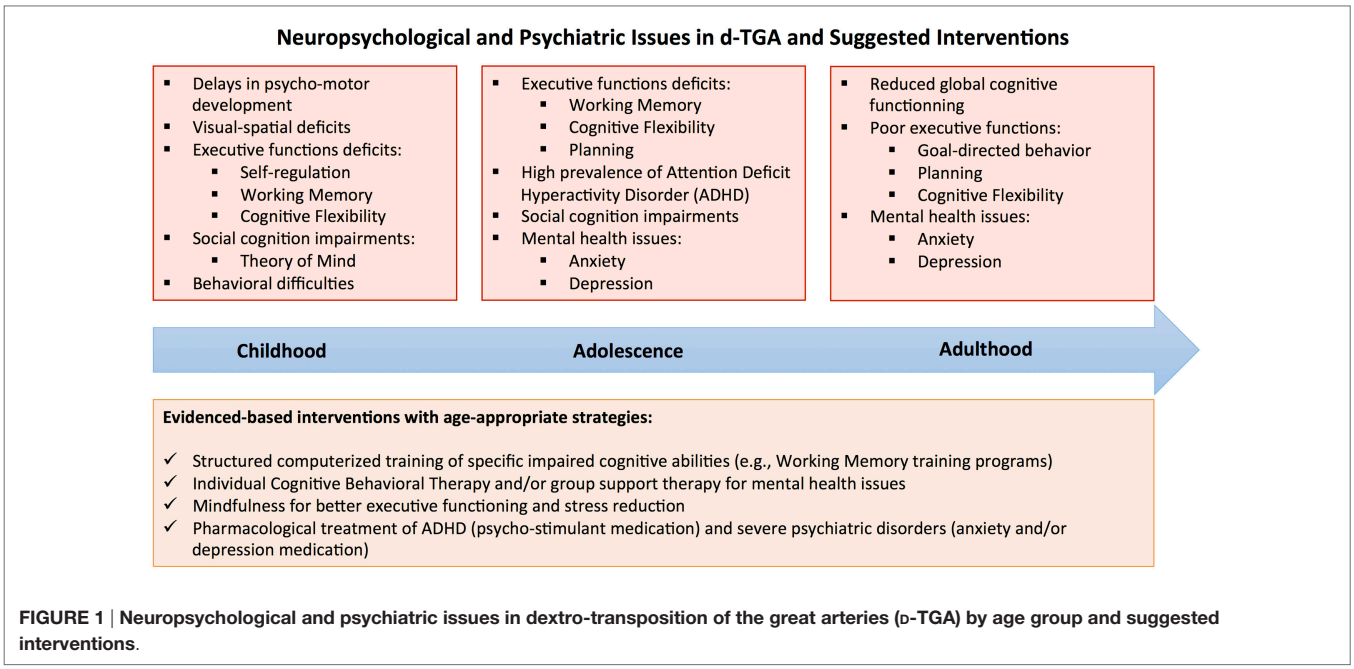

FIGURE 1 | Neuropsychological and psychiatric issues in dextro-transposition of the great arteries (D-TGA) by age group and suggested interventions.

results between cardiac diagnoses showed that psychological outcomes were worse among adults with cyanotic or complex CHD than among adults with acyanotic or mild CHD (41, 57, 58). Findings from mixed cohorts of adults with CHD show high rates of psychiatric disorders (59–62), with about 30% meeting diagnostic criteria for at least one lifetime mood disorder (i.e., major depressive disorder, bipolar disorder, etc.), and 26–28% for at least one anxiety disorder (i.e., generalized anxiety, social phobia, etc.) (61, 62). Findings on the frequency and severity of current anxiety-depressive symptoms assessed by self-report are mixed. Some studies found high symptomatology in adults with CHD (59, 61, 63–65), whereas others did not (66–72). According to several authors (60, 71–74), denial mechanisms or coping strategies are frequently used by CHD patients and could contribute to the favorable psychological outcomes sometimes suggested by self-assessments.

Many CHD patients with psychiatric disorders appear not to receive adequate treatment. Kovacs et al. (61) found that 69% of patients with a mood or anxiety disorder did not receive psychotherapy or psychotropic drugs. Other studies report that only 11–12% of patients receive psychological counseling, despite high rates of anxiety-depressive syndromes (62, 64). In adults with CHD, presence of a high depressive or anxiety symptomatology is associated with higher rates of unemployment (64), lower quality of life (QoL) (62, 64, 68), greater consumption of tobacco and alcohol (75), poorer adherence to treatment (76), and worse cardiac prognosis (65).

In summary, to date, few data are available on the cognitive and psychiatric outcomes of D-TGA adults after the ASO. Elevated risk of attentional and executive impairments and of mood and anxiety disorders may be prevalent. More research is needed to better understand the long-term cognitive and psychological trajectory of these adults and to investigate how cognitive and psychiatric disorders influence social interactions, employability, and achievement.

FUTURES AVENUES

Potential Mechanisms for Long-term Impairment

The mechanisms for lifelong cognitive and psychosocial difficulties in CHD are multifactorial. Early cognitive deficits play a decisive role (7). In children with D-TGA, lower full-scale IQ is associated with lower parent-reported psychosocial QoL (77). Moreover, as reported in other pediatric populations, such as children born preterm (78), a cascade of effects may be observed, where early deficits mediate the expression of new symptoms and/or the worsening of pre-existing impairments. In children with D-TGA, Calderon et al. (25) showed that deficits on some aspects of executive functioning (i.e., cognitive flexibility) became worse between the ages of 5 and 7, whereas more basic processes (e.g., motor control) tended to catch-up. Interestingly, Cassidy et al. (22) reported that reading and math difficulties of adolescents with D-TGA at age 16 were predicted by deficits in processing speed and executive function at age 8. Indeed, executive function deficits and difficulties in other key areas of neurodevelopment are often comorbid. In D-TGA, poor working memory adversely impacted children's language comprehension and mathematic skills (13) and poor inhibitory control was associated with deficits in social cognition (24). These weaknesses might result in more severe dysfunction as expectations increase with age. Patients with these cognitive challenges may find establishing and maintaining social relationships difficult, especially in adolescence and adulthood (20). Peer interactions and social cues (e.g., body language, irony, sarcasm) become

TABLE 1 | Overview of selected studies on neuropsychological and psychiatric outcomes for patients with D-TGA.

Reference	*n*, age (years), diagnosis	Neurocognitive or psychiatric assessment	Main results
Children			
Bellinger et al. (12)	*n* = 158, 4 years, D-TGA	– WPPSI revised, – Peabody Developmental Motor Scales, – Grooved pegboard, – Test for auditory comprehension of language, – Receptive one-word picture vocabulary test, – Expressive one-word picture vocabulary test, – Illinois test of psycholinguistic abilities.	• Lower than expected mean scores in general intelligence (IQ), expressive language, visual-motor integration, motor function, and oromotor control.
Bellinger et al. (13)	*n* = 155, 8 years, D-TGA	– WISC III, – WIAT, – Wide range assessment of memory and learning, – Developmental test of visual–motor integration, – Test of variables of attention, – Rey–Osterrieth complex figure, – Verbal fluency, – Wisconsin card sorting test, – Trail making test, – Formulated sentences subtest of the clinical evaluation of language fundamentals, – Controlled oral word association test, – Grooved pegboard.	• Lower than expected scores in academic achievement, memory, visual-spatial skills, sustained attention, and higher order language skills. • Higher than expected proportion with scores >1SD below normative values in executive functions (e.g., planning, cognitive flexibility).
Calderon et al. (24)	*n* = 21, 7 years, D-TGA	– Columbia Mental Maturity Scale, – Animal Stroop test, – Statue subtest from the NEPSY, – Tower of London, – Digit span, – Corsi block-tapping task, – False belief tasks (1st and 2nd order).	• Patients' mean IQ scores within the normal range. • Compared to a control group, patients with D-TGA had lower scores in executive functions (i.e., inhibition, working memory, planning) and social cognition (i.e., theory of mind).
Calderon et al. (25)	*n* = 45, 5/7 years, D-TGA	– Columbia Mental Maturity Scale, – Comprehension subtest from the NEPSY, – Digit span, – Spatial span, – The hand game, – Hearts and flowers incongruent and mixed conditions, – Day and night, – Animal Stroop test, – Dimensional change card sorting test.	• Patients' mean scores lower than controls' mean scores in receptive language, attention, and executive functions (i.e., inhibition, cognitive flexibility). • Persistent impairments in cognitive inhibition and cognitive flexibility from ages 5 to 7.
Freed et al. (8)	*n* = 82, 1.5–2 years, D-TGA	BSID II	• Most patients with scores > 1SD below normative values in cognitive, motor, and language function.
Hicks et al. (11)	*n* = 91, 2 years, D-TGA	BSID III	• Higher than expected proportion of patients with scores >1SD or >2SD below normative values in language function.
Hövels-Gürich et al. (32)	*n* = 77, 3–9 years, D-TGA	– K-ABC, – Vocabulary subtest of the K-ABC, – Kiphard and Schilling body coordination test, – Denver developmental screening test, – Frostig developmental test of visual perception.	• Patients' mean IQ scores within the normal range. • Lower than expected scores in motor function, vocabulary, and acquired abilities.
Hövels-Gürich et al. (17)	*n* = 60, 7–14 years, D-TGA	– K-ABC, – Kiphard and Schilling body coordination test, – Oral and speech motor control test, – Mayo tests of speech and oral apraxia, – Illinois test of psycholinguistic abilities, – Test of auditory analysis skills.	• Speech, motor, and developmental impairments more frequent compared to the general population. • Lower than expected scores in acquired abilities and language.

(*Continued*)

TABLE 1 | **Continued**

Reference	*n*, age (years), diagnosis	Neurocognitive or psychiatric assessment	Main results
Hövels-Gürich et al. (42)	*n* = 60, 7–14 years, D-TGA	Achenbach child behavior checklist	• Parent-reported psychosocial maladjustment more frequent than in the general population on all domains (i.e., internalizing, externalizing, social, and attention problems, and competences).
Karl et al. (19)	*n* = 74, 4–14 years, D-TGA	– WPPSI, – WISC III, – Movement Assessment Battery, – Achenbach child development checklist, – Achenbach teacher report form.	• Patients' mean IQ scores within the normal range. • Lower scores in motor function. • Parent- and teacher-reported psychosocial maladjustment more frequent than in a control group on domains including behavioral, speech, language, and learning ability problems.
McGrath et al. (16)	*n* = 135, 1/8 years, D-TGA	*Evaluation at 1 year* – BSID, – Fagan test of infant intelligence. *Evaluation at 8 years* – WISC III, – WIAT.	• Most 1-year test scores were statistically but modestly associated with 8-year test scores. • The majority of patients with scores >1SD below normative values at 8 years had displayed scores >1SD at 1 year.
Adolescents			
Bellinger et al. (14)	*n* = 139, 16 years, D-TGA	– WIAT II, – General Memory Index of the Children's Memory Scale, – Test of visual–perceptual skills, – Rey–Osterrieth complex figure, – Delis–Kaplan executive function system, – Behavior rating inventory of executive function (child, parent, and teacher versions), – Connors attention-deficit and hyperactivity disorder (parent version), – Reading the mind in the eyes test, revised.	• Lower than expected scores on academic skills, visuo-spatial skills, memory, executive functions, and social cognition. • Higher than expected proportion of patients with scores >1SD or >2SD below normative values in academic skills, memory and visuo-spatial skills. • By parent reports, about 1 in 5 had attention or executive impairments in daily life.
Cassidy et al. (22)	*n* = 139, 8/16 years, D-TGA	– WISC III, – WIAT II, – Trail making test, – Test of variables of attention.	• Processing speed associated with executive functions (i.e., working memory, inhibition, and shifting) and academic skills at 8 and 16 years.
DeMaso et al. (45)	*n* = 139, 16 years, D-TGA	– Schedule for affective disorders and schizophrenia for school-aged children, – Children's Global Assessment Scale, – Brief Psychiatric Rating Scale for Children, – Children's Depression Inventory, – Revised Children's Manifest Anxiety Scale, – Child stress disorders checklist, – Posttraumatic Stress Diagnostic Scale, – Conners' attention-deficit/hyperactivity disorder rating scales, – Conduct Disorder Scale.	• Patients were more likely than controls to meet criteria for a lifetime psychiatric diagnosis. • Higher lifetime and current prevalence of attention-deficit/hyperactivity disorder. • Psychosocial functioning was within a pathological range for 15% of patients. • Parent- and self-reports identified high depressive, anxiety, and posttraumatic stress symptoms.
Heinrichs et al. (31)	*n* = 60, 14–21 years, D-TGA	– Hamburg-Wechsler intelligence test, – Analytical thinking subtests of the Leistungsprüfsytem nach Horn, – Mannheimer Rechtschreib test.	• Patients' mean IQ scores within the normal range. • Higher than expected proportion of patients with IQ scores ≥2. • Lower than expected scores on orthography.
Adults			
Klouda et al. (53)	Total mixed cohort, *n* = 48, 18–49 years • *n* = 24, moderate CHD, • *n* = 24, complex CHD (including D-TGA, *n* = 9).	CNS vital signs	• Patients with critical CHD had lower than expected scores on multiple domains: psychomotor speed, processing speed, sustained and executive attention, and on the overall, neurocognitive index.

(*Continued*)

TABLE 1 | **Continued**

Reference	*n*, age (years), diagnosis	Neurocognitive or psychiatric assessment	Main results
Tyagi et al. (54)	Total mixed cohort, *n* = 310, 18–76 years • *n* = 80, D-TGA, • *n* = 81, TOF, • *n* = 65, SV anatomy, • *n* = 84, mild CHD.	– Controlled oral word association test, – Grooved pegboard, – Rey auditory verbal learning test, – Stroop test, – Symbol digit modalities test, – Trail making test, – Wisconsin card sorting test, – Wechsler Adult Intelligence Scale.	• D-TGA patients scored worse than those with mild CHD on an overall neuropsychological index. • Proportion with scores >1.5 SD below normative values on at least 3 tests was higher in the D-TGA group compared to both the mild CHD group and the expected frequency in the general population.
van Rijen et al. (56)	Total mixed cohort, *n* = 349, 20–46 years, • *n* = 55, D-TGA, • *n* = 72, TOF, • *n* = 37 pulmonary stenosis, • *n* = 185, mild CHD.	– Young adult self-report, – Young adult behavior checklist.	• Diagnosis of D-TGA was associated with higher risks of behavioral problems, particularly externalizing problems (e.g., intrusive and aggressive behavior).

BSID, Bayley Scales of Infant Development; CHD, congenital heart defects; D-TGA, dextro-transposition of the great arteries; IQ, intelligence quotient; K-ABC, Kaufman assessment battery for children; SV, single ventricle; TOF, tetralogy of Fallot; WIAT, Wechsler individual achievement test; WISC, Wechsler intelligence scale for children; WPPSI, Wechsler preschool and primary scale of intelligence.

more complex, making decoding them difficult to individuals with D-TGA. These and other cognitive deficits may "derail" the developmental trajectory in the mental health domain. Of note, executive function deficits increase the risk of psychosocial and psychiatric morbidities in adolescents with D-TGA. In BCAS, worse psychosocial outcomes and poorer QoL of 16-year olds were strongly predicted by executive dysfunction, suggesting a robust association between these higher order processes and self-perception and psychosocial adaptation (45).

Finally, it is possible that accumulating cognitive deficits, particularly in organization, flexibility, and self-control, along with poor social interactions trigger a lower threshold for stress, predisposing individuals to anxiety and depression. This hypothesis is, however, speculative and more research is needed.

Interventions to Improve Outcomes

As a result of progress in understanding the challenges patients with CHD face, interventions to prevent, mitigate, or palliate morbidities are emerging (**Figure 1**). Many hospital-based Cardiac Neurodevelopmental Programs are providing early screening and treatment recommendations. Nevertheless, there is urgent need for well-designed randomized controlled trials evaluating the efficacy of neurocognitive and psychological interventions in this population. McCusker et al. (79) conducted a study evaluating the efficacy of interventions focused on maternal and family functioning, individualized psycho-education, and outreach to community health-care providers. Although maternal mental health and family functioning improved, few benefits were seen on children's behavioral outcomes and school achievement.

One major concern in the D-TGA population relates to executive dysfunction, and thus, a proof-of-concept for evidence-based interventions is needed (20). Many behavioral interventions may be implemented from early childhood and throughout the lifespan. Intensive computerized training targeting attention and working memory has improved executive skills and behavioral outcomes in children with ADHD (80) and children born with low birth weight (81). If these programs prove effective, reduction of executive function morbidities could reduce the likelihood that psychiatric disorders emerge (82, 83). Research is ongoing to determine the short- and long-term effects of such structured interventions in youth with CHD.

As recommended by several Associations (39, 84), many transitional and educational programs for patients with CHD are being developed. It may be useful to integrate psychologists into these medico-social programs. Their intervention, within the framework of individual or group support, could prevent subclinical disorders from evolving into depression or anxiety disorders. These interventions could focus on the emotional expression and management, and the development of effective coping strategies. Interventions aiming to optimize the "sense of coherence" (85), that is, the understanding of events, the confidence in one's power and resources, and the ability to give sense to events, could also improve the psychosocial outcomes of patients with CHD.

Finally, several mental health treatments, including pharmacotherapy and psychotherapy, are available and could be tested in this population. Cognitive behavioral therapy, targeting the modification of maladaptive thought patterns and behaviors, has proven to be effective in treating anxiety and depression disorders (86). Mindfulness and relaxation techniques may also be beneficial. Mindfulness training is associated with substantial reduction in stress-related (82), depressive (83) and ADHD symptoms (87).

CONCLUSION

Over the last two decades, dramatic progress was made in the understanding of neuropsychological and psychiatric outcomes of individuals with D-TGA (for a summary of main studies, please refer to **Table 1**). The cardiac neurodevelopmental and mental health field is moving from a descriptive approach of challenges

to an in-depth understanding of neurobiological and psychological mechanisms of impairment. Novel hypotheses will be critical to improve outcomes and QoL for individuals with D-TGA.

AUTHOR CONTRIBUTIONS

LK and JC conducted the literature search, drafted this manuscript, and revised it critically for important intellectual content. DB, MM, DK, NG and DCB made substantial contributions to the conception of this review and revised it critically for important intellectual content. All the authors (LK, DB, MM, DK, NG, DCB, and JC) approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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METHODS
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Development of an Online, Evidence-Based Patient Information Portal for Congenital Heart Disease: A Pilot Study

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Objectives: In response to an increased need for patient information on congenital heart disease in the Netherlands, we initiated a nationwide initiative to develop an online, evidence-based patient information portal, starting with a pilot project aimed at the subgroup of patients with congenital aortic and pulmonary valve disease.

Methods and results: We developed an information portal that aims to (1) improve patient knowledge and involvement and to subsequently reduce anxiety and decisional conflict and improve mental quality of life and (2) to support physicians in informing and communicating with their patients. The information portal was developed according to the systematic International Patient Decision Aid Standards development process employing Delphi techniques by a multidisciplinary workgroup of pediatric and adult congenital cardiologists, a congenital cardiothoracic surgeon, a psychologist, an epidemiologist, a patient representative, and web and industrial design experts. First, patients and physicians were surveyed and interviewed to assess the current state of patient information and explore their preferences and needs to determine the focus for the development of the information portal. We found that patient knowledge and numeracy are limited, reliable information is scarce, physicians inform patients selectively and patient involvement is suboptimal, and there is a need for more reliable, tailored, and multi-faceted information. Based on the findings of these surveys and interviews, a patient-tailored information portal was designed that presents evidence-based disease- and age-specific medical and psychosocial information about diagnosis, treatment, prognosis, and impact on daily life in a manner that is comprehensible and digestible for patients and that meets the needs expressed by both patients and physicians. The effect of the website on patient outcome is currently being assessed in a multicenter stepped-wedge implementation trial.

Conclusion: The present pilot project succeeded in developing an online, evidence-based information portal that is supported by both patients and physicians. The information portal will be further developed and expanded to include all other major forms of congenital heart disease, translations into other languages, and a public information portal to serve patients' relatives and the general public at large.

Keywords: patient information, shared decision-making, congenital heart disease, patient education tools, patient information portal, multidisciplinary approach, International Patient Decision Aid Standards development process, Delphi technique

INTRODUCTION

Congenital heart disease is the most common congenital birth defect with an incidence of approximately 1% of all live births (1, 2). Due to major advances in the treatment of congenital heart disease over the past decades, approximately 90% of these patients now reach adulthood (3). This has, however, made congenital heart disease a chronic illness with, for example, an estimated 2.4 million people currently living with a congenital heart defect in the United States of America alone and an estimated 65,000 in the Netherlands.

The consequences of congenital heart disease for the individual patient are complex, time varying, and heavily dependent on the specific defect(s), individual patient-related factors, and treatment options and decisions. These consequences may have a significant impact on many facets of the patients' lives, both clinical and personal. Therefore, informing patients and their relatives in a complete, objective, and understandable manner is essential in optimizing patient quality of life, lifestyle, health behavior, treatment adherence, and patient involvement in treatment decisions (4–16).

In response to an increased need for patient information in congenital heart disease in the Netherlands, we therefore initiated a nationwide initiative to improve patient information, starting with a pilot project aimed at a subgroup of congenital heart disease patients with aortic or pulmonary valve disease, including Tetralogy of Fallot (13–15, 17–21).

The objective of this pilot project was to develop an online information portal that aims to (1) improve patient knowledge and involvement and to subsequently reduce anxiety, depression, and decisional conflict and improve mental quality of life and (2) to support physicians in informing and communicating with their patients.

METHODS AND RESULTS

The present pilot study comprises a complete comprehensive development process for a target subgroup restricted to patients with congenital aortic and/or pulmonary valve disease and/or Tetralogy of Fallot as a proof of concept. The subsequent full-scale project will entail expansion to all other major forms of congenital heart disease, building on this proof of concept.

The focus of this pilot project was to develop a nationwide patient-tailored, evidence-based patient information tool to be incorporated into specialist congenital cardiac care developed by and for patients, caregivers, and physicians, based on both patient/caregiver and physician preferences.

First, we evaluated the current state of patient information in congenital heart disease in the Netherlands to determine key focus points for development. Next, we developed the information portal in a multidisciplinary national working group (**Table 1**) according to the systematic International Patient Decision Aid Standards (IPDAS) development process, employing Delphi techniques (22, 23). Finally, we designed and are currently conducting a stepped-wedge cluster randomized implementation trial. All three steps are described below.

EVALUATION OF THE CURRENT STATE OF PATIENT INFORMATION

The first crucial step in the development of the portal was a thorough evaluation of the current state of patient information and information needs in congenital heart disease in the Netherlands. The results of this phase would define the key focus points for the development of the information portal and, thus, represent the primary input for the next phase of the project.

We carried out this phase by conducting comprehensive surveys and interviews among patients ($N = 63$), caregivers of

TABLE 1 | Working group members.

Role	Center	Appointed by
Clinical		
Patient representative[a]	–	Dutch Patient Association for Congenital Heart Disease
Pediatric cardiologist	LUMC, Leiden	Dutch Association for Pediatrics
Adult congenital cardiologist	Radboudumc, Nijmegen	Dutch Association for Cardiology
Congenital cardiac surgeon	AMC, Amsterdam	Dutch Association for Cardiothoracic Surgery
Clinical psychologist	Erasmus MC, Rotterdam	–
Methodological		
Epidemiologists	Erasmus MC, Rotterdam	Dutch Heart Foundation
Web and industrial design firm[b]	–	–

[a]Chairman of the Dutch Patient Association for Congenital Heart Disease.
[b]Specialized in the development and implementation of patient information portals and decision aids.
–, not applicable; LUMC, Leiden University Medical Center; Radboudumc, Radboud University Medical Center; AMC, Academic Medical Center; Erasmus MC, Erasmus University Medical Center.

pediatric patients ($N = 10$), and physicians ($N = 32$). A detailed report of these surveys will be published separately, but the main findings included the following:

- *Patient/caregiver knowledge is limited:* although patients/caregivers *think* they are adequately informed, actual disease-specific knowledge was objectively sufficient in only half of the respondents, which is in line with previous findings (13, 14, 17–21).
- *Reliable information is scarce:* only 62% of patient/caregiver respondents agreed that reliable information was readily available to them. Subsequently, patients rely heavily on their physicians for information as evidenced by a mere 13% of patients citing sources other than their cardiologist or cardiac surgeon as one of their main sources of information.
- *Patient/caregiver numeracy is limited:* only 46% of respondents were able to successfully complete a 3-question basic numeracy test adapted from the Numeracy Scale (24, 25).
- *Patient/caregiver involvement is suboptimal:* both physicians and patients/caregivers agree that patients/caregivers are insufficiently involved. Physicians agree that most difficulty they experience in involving patients/caregivers is due to limited patient knowledge and comprehension.
- *Physicians inform patients/caregivers selectively:* as self-reported by physicians, the information they convey is mostly based on their own judgment of what is important and comprehensible to each patient/caregiver. This may not always correspond with what patients/caregivers themselves think is important.
- *Patient information preferences and needs:* in line with previous findings (26), the most important preferences and needs with regard to patient information expressed by *patients/caregivers* were as follows:
  - More (reliable) information on:
    - Implications for personal life (education, career, pregnancy, insurance, etc.)
    - Health behavior and lifestyle recommendations
    - Prognosis
    - Psychosocial aspects
    - Pros and cons of various treatment options
    - Recovery after surgery
  - Disease-specific information
  - Age-specific information
  - Non-contradictory information.

  Whereas *physicians* expressed a strong need for:
  - A single, trusted, evidence-based source of reliable patient information to which they can refer their patients
  - Tools to aid communication with patients/caregivers.

DEVELOPMENT OF INFORMATION PORTAL

Based on the findings of the surveys and interviews and in response to the needs expressed by both patients and physicians therein, a first prototype of an information portal was drafted according to the IPDAS development process and employing Delphi techniques. This prototype was then internally reviewed and revised by all members of the working group in live meetings until a consensus was reached on all topics (**Table 1**) (alpha-testing). The resulting second prototype was then again extensively reviewed by independent adult patients ($n = 2$), caregivers of pediatric patients ($n = 2$), physicians ($n = 6$; two pediatric cardiologists, two adult congenital cardiologists and two congenital cardiac surgeons), and clinical psychologists ($n = 2$) from outside the working group, sampled from clinical practice (beta-testing). All testers were given specific instructions to focus on all aspects of the information portal, including information content, language, illustrations, design, and usability. Additionally, the patients/caregivers were also observed as they navigated the portal. The feedback from this beta-testing was the input for the final review and revision by the working group.

The product of this development process is a comprehensive patient information tool that corresponds with the preferences and needs expressed by patients and physicians and addresses the shortcomings identified in the surveys and interviews.

The implementation of the patient information portal in clinical care will take place as follows. Patients/caregivers that present to the cardiologist are invited to use the online information portal by the cardiologist who hands out a sketchpad during the consultation (**Figure 1**). This sketchpad offers a template for the cardiologist to provide a clear graphical representation of the patient's heart defect as well as any other relevant notes for the patient/caregiver. On the sketchpad, the cardiologist also indicates which of the predefined diagnoses are applicable to the patient. The patients/caregivers can then take their sketch sheet home and review the cardiologist's notes and drawings and visit the information portal using the link and personal private account details listed on the sketch sheet. When they do so, they enter a private information portal (**Figure 2**) with the following key characteristics.

Disease- and Age-Specific Information

All information on the portal is compiled and presented specifically and separately for each congenital heart defect and target group (teenagers, adults, or parents/caregivers) with regard to both content and language.

Upon their first visit to the website, users are prompted to select their target group and diagnosis (two simple multiple choice prompts). Based on the combination of these inputs, a tailored personal subportal is custom built for each user. Their personal subportal contains only the information that is relevant to them. In case of multiple congenital heart defects, all relevant information is automatically combined into a single tailored subportal for that unique combination of inputs.

Multi-Faceted Information Based on Patient/Caregiver Preferences

As patients/caregivers indicated a discrepancy between their own information needs and the information generally

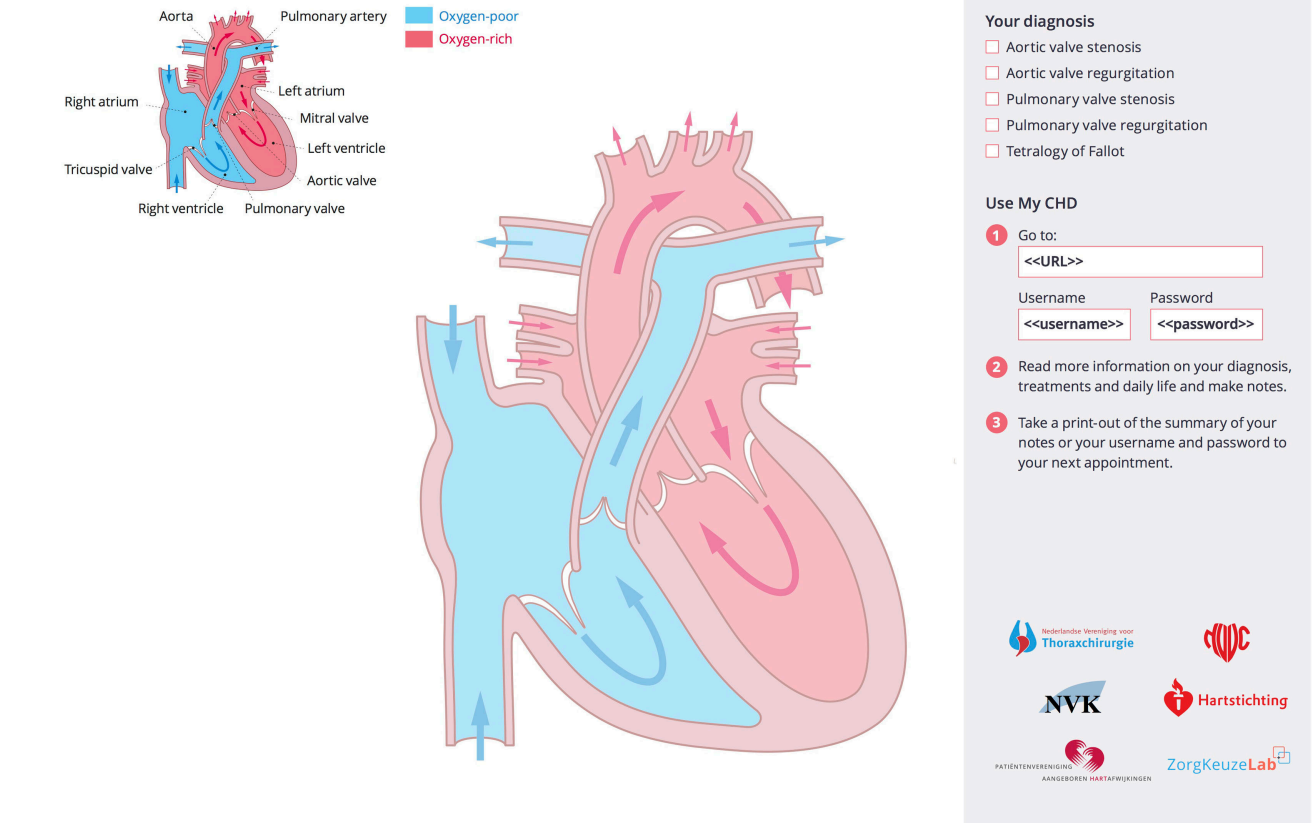

FIGURE 1 | **Sketchpad**.

provided by physicians and other sources, the information provided by the portal is not based solely on what physicians think is important but rather represents both the clinical and the patient perspectives. Therefore, the information portal contains information on all aspects of disease that were found to be important to patients/caregivers and physicians in the surveys and interviews, such as diagnosis, treatment, prognosis, psychosocial aspects, and implications for daily life and future life planning.

Format That Is Comprehensible and Digestible

To maximize digestibility and comprehensibility, the information is fragmented into various frequently asked questions that correspond with the topics that patients/caregivers and physicians indicated to be important in the surveys and interviews. Comprehension is further enhanced by the liberal use of custom illustrations, designed to the specifications of the multidisciplinary working group by a professional medical illustrator. Additionally, a professional medical text writer was contracted to optimize the linguistics of the textual content for each target group separately to maximize comprehensibility, digestibility and attractiveness for users of all ages and education levels. Furthermore, to address the limited numeracy among the target audience, all numerical risks on the information portal are supported by risk visualizations, such as icon arrays.

Support Patient/Caregiver–Physician Communication

Patients/caregivers indicated that they are often unsure about which topics should be discussed with the physician. Throughout the information portal, we therefore provide numerous suggestions for important topics that should be discussed, as indicated by both physicians and patients/caregivers. Furthermore, there is a comment box on each page of the information portal in which patients/caregivers are encouraged to note any questions they may have about the information on that page. These questions are then saved in their personal account. Users can view, edit, and/or print a summary of their questions and optionally discuss this with their physicians.

Physicians and other involved health-care providers are also provided with their own personal accounts for the information portal, so that they can use the information portal to aid in

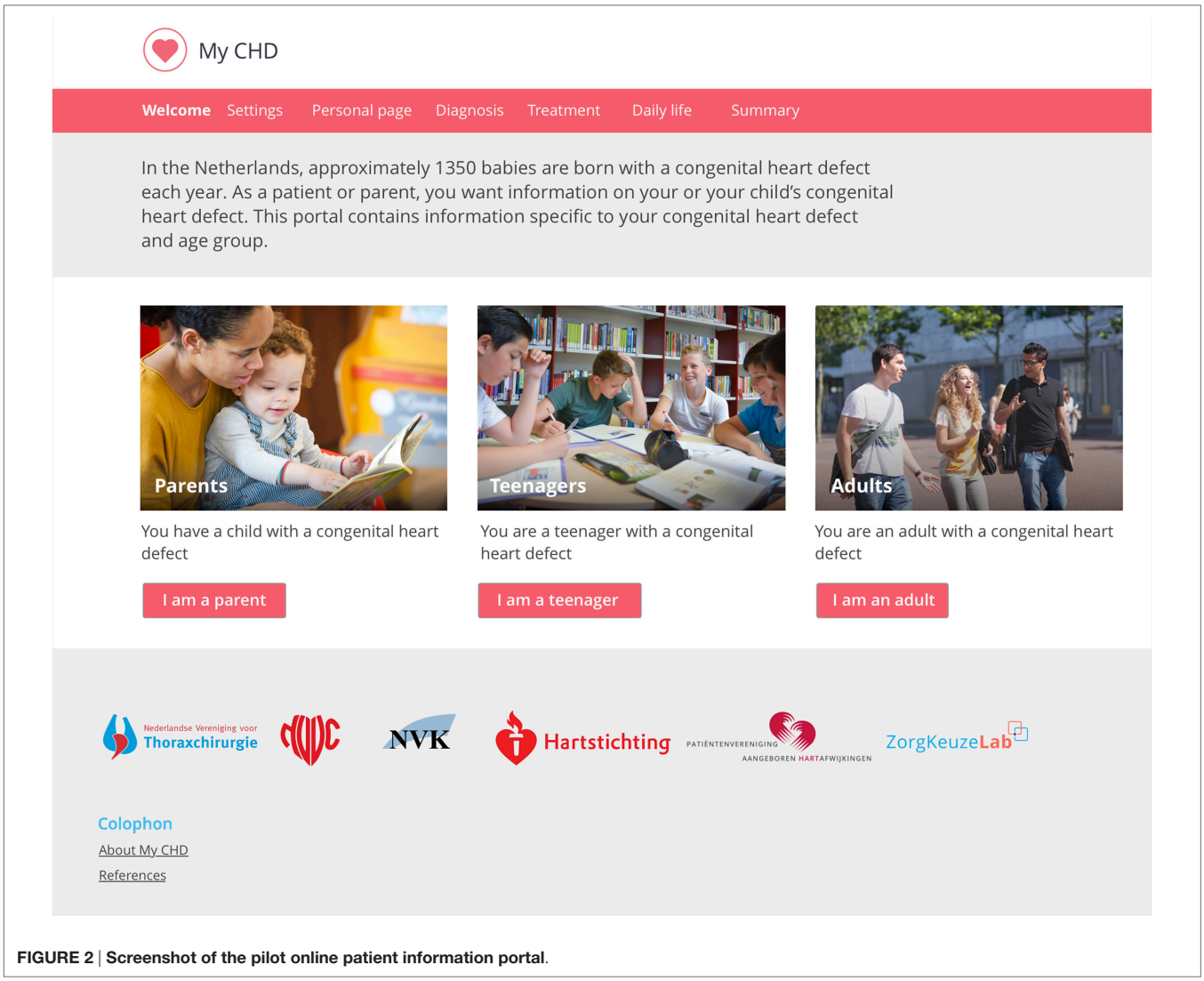

FIGURE 2 | Screenshot of the pilot online patient information portal.

explaining or illustrating disease-related information to patients/caregivers in the consulting room. Moreover, the sketchpad, as described above, is intended to further facilitate communication in the consulting room.

Evidence-Based Information

All information on the information portal is based on international guidelines and peer-reviewed published evidence where possible. Furthermore, all four centers for congenital cardiac surgery in the Netherlands have combined their prospective databases of early outcome after all congenital cardiac surgery performed in these centers in the past 10 years to allow conveyance of reliable, nationwide data on risks and recovery after contemporary cardiac surgery to patients/caregivers.

IMPLEMENTATION TRIAL

As the last phase of this pilot project, we are conducting a stepped-wedge cluster randomized (27, 28) implementation trial of the information portal in four large congenital cardiac centers in the Netherlands, which is ongoing as of writing.

The aim of this last phase of the pilot project is twofold:

- To gain insight into both the practical and cultural intricacies at each of the eight participating departments (departments of both adult and pediatric cardiology at each of the four participating centers) that need to be taken into account for effective implementation of the information portal and to subsequently develop individual implementation plans tailored to each of these departments and
- To evaluate the effect of the implementation of the information portal on patients and caregivers with regard to:
  - Disease-specific knowledge
  - Anxiety and depression
  - Mental quality of life
  - Patient/caregiver involvement and autonomy
  - Experiences with and views on patient information
  - Views on participation in decision-making
  - Decisional conflict.

Adult patients and caregivers of pediatric patients with congenital aortic and/or pulmonary valve disease and/or Tetralogy of Fallot that visit the outpatient clinic at one of the four participating centers are prospectively included. In total, at least 250 respondents will be included, 125 in the control group (no access to the information portal) and 125 in the intervention group (access to the information portal), all of whom will complete an online survey on the above topics 1 month after their visit to the outpatient clinic.

DISCUSSION AND FURTHER DEVELOPMENT

The present pilot project succeeded in developing and implementing a nationwide online, evidence-based, disease- and age-specific information portal for (caregivers of) patients with congenital heart disease, based on extensive input from all parties involved in congenital cardiac care in the Netherlands and addressing both patient and physician needs. Our extensive and meticulous nationwide multidisciplinary development process ensures broad nationwide acceptance into clinical practice by both patients/caregivers and health-care providers.

In various disease states, more informed and activated patients have been previously found to be associated not only with improved quality of life, treatment adherence, health behavior, and clinical outcome but also with more efficient health-care utilization and lower health-care costs (4–16). The implementation trial, the final phase of the current pilot project, will shed light on the effect of the implementation of our pilot information portal on short-term psychosocial patient outcome. In the further development of the information portal, we will also focus specifically on clinical and long-term psychosocial effects as well as physician, implementation, and health-care service outcomes.

We are currently planning the further refinement and expansion of this information portal to all major forms of congenital heart disease, in which we aim to cover >90% of all cases of congenital heart disease. This full-scale project will build on all the knowledge, expertise, methods, framework, and infrastructure gained in the pilot project and will also be carried out in a multidisciplinary fashion. Additionally, focus groups with specific expertise will be employed when beneficial. This full-scale project will also include translations into other common languages, first and foremost English. We are also exploring innovative and interactive methods for improving patient participation, particularly in teenagers and adolescents.

Besides the further development of the current patient-tailored information portal, the full-scale project will also include the parallel development of a public information portal suited for broader use by patients and caregivers before a definitive diagnosis has been made, as well as their relatives and friends and the general public at large.

In the interest of sustainability, all relevant Dutch physician associations and patient associations have committed to a long-term partnership in this initiative. A multidisciplinary national working group in which each of these partners is represented will remain instated to oversee continuous review, updating, enhancement, and expansion of the information portal to ensure that we continue to provide up-to-date, evidence-based patient information of the highest standard.

Future partnerships and (conceptual) dissemination beyond the field of congenital heart disease and internationally may provide unique opportunities for further enhancing quality, expertise, and sustainability in this initiative.

ETHICS STATEMENT

This study was approved by the institutional review board (MEC-2015-099), and all subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR NOTE

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AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors (JE, AD, JK, RB, EU, EG, RT, AB, and JT).

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