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# **Social cognition and behavioral outcomes in congenital heart disease: profiles and neuropsychiatric comorbidities**

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## **KEYWORDS**

Autism traits; social cognition; congenital heart disease; executive functions; anxiety symptoms

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## Abbreviation

Attention deficit/hyperactivity disorder (ADHD), Autism Spectrum Rating Scale (ASRS), Behavior Rating Inventory of Executive Functions for school-aged children, 2nd Edition (BRIEF-2), cardiopulmonary bypass (CPB), congenital heart disease (CHD), Empathy/Systematizing Quotient Child Version (ESQ-C), Multidimensional Anxiety Scale for Children, 2nd Edition (MASC-2), Social Responsiveness Scale (School-age form), 2nd Edition (SRS-2), theory of mind (ToM), Theory of Mind Task Battery (ToM-TB), Wechsler Intelligence Scale for Children, 5th edition (WISC-V)

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## ABSTRACT

Autism spectrum disorders are more prevalent in children with congenital heart disease (CHD) than in the general population. Children with CHD without diagnosed autism are also at increased risk for neurodevelopmental and psychiatric impairments. We characterized social and behavioral outcomes in children with CHD and examined neurodevelopmental and psychiatric comorbidities. Children without diagnosed autism who underwent infant open-heart surgery were eligible. Parent-reports assessed social communication, unusual behaviors, self-regulation, anxiety, and executive function (EF). Neuropsychological tests assessing theory of mind (ToM), working memory, and verbal comprehension were administered. Outcomes were compared to normative data. Linear regressions were estimated with parent-reported scores and ToM abilities as outcomes. Predictors were anxiety symptoms, parent-reported EF, and working memory scores. Covariates were age, parental education, ADHD diagnosis, and verbal comprehension. Clinically relevant comorbidities were identified ( $N$  children scoring  $\geq 1SD$  below the norm). Fifty-six children ( $10.8 \pm 1.8$  years) participated virtually. Compared to norms, children with CHD had impaired ToM, more unusual behaviors ( $p = .002$ ), and less self-regulation ( $p = .018$ ), but better social communication ( $p = .014$ ). “Autism-like” traits were positively associated with anxiety symptoms ( $\beta(95\% \text{ CI}) = 0.28(0.08-0.49)$ ,  $p = .008$ ) and worse working memory ( $\beta(95\% \text{ CI}) = -0.36(-0.59-0.13)$ ,  $p = .003$ ). Twenty-one out of 22 children who displayed clinically relevant social and behavioral scores also showed anxiety symptoms ( $n = 4$ ), impaired EF ( $n = 7$ ), or both ( $n = 10$ ). Children with CHD without diagnosed autism have elevated unusual behaviors, lower self-regulation, and impaired ToM. There is a high risk of co-existing anxiety and impaired EF which may increase disease burden. Targeted therapeutic interventions are needed to reduce long-term psychosocial risks in these children.

Congenital heart disease (CHD) is the most common congenital malformation, affecting about 8 in 1000 live newborns (Bernier et al., 2010). With progress in surgical and medical management, the survival rate into adulthood for individuals with complex CHD has improved to approximately 90% (Marelli et al., 2007). Nevertheless, patients with CHD face an increased risk for long-term neurodevelopmental and mental health issues that may occur across different domains including executive functioning (Calderon et al., 2010; Cassidy et al., 2015; Feldmann et al., 2021; Jackson et al., 2021) and elevated psychiatric symptoms, predominantly anxiety (Calderon et al., 2016; DeMaso et al., 2017; Freitas et al., 2013; Pike et al., 2018). Studies have also reported increased prevalence of social difficulties (Abda et al., 2019).

While the prevalence of autism spectrum disorders is higher in CHD compared to the general population (Bean Jaworski et al., 2017; Razzaghi et al., 2015; Sigmon et al., 2019; Tsao et al., 2017), social interaction difficulties, unusual behaviors, and impaired theory of mind (ToM) can also appear in the absence of a formal autism diagnosis (Calderon et al., 2019). During early childhood, patients with CHD are at increased risk for difficulties with social interaction and communication (Clancy et al., 2020). In school-age, several studies in children with transposition of the great arteries (d-TGA) (Bellinger et al., 2011; Calderon et al., 2010, 2012, 2014), univentricular CHD (Bellinger et al., 2015), and corrected atrial septal defect (Sarrechia et al., 2015) have demonstrated impairments in social cognition, assessed by ToM and emotion recognition tasks. Importantly, social and behavioral difficulties are evident in daily life, as parents report more social interaction problems and autistic features (Werninger et al., 2020) and overall lower social competences in school-aged children with CHD compared to healthy peers (Abda et al., 2019). Bellinger and colleagues further demonstrated in different cohorts of patients with CHD more “autism-like” symptoms compared to healthy peers measured with the Autism Spectrum Quotient (Bellinger et al., 2011, 2015). Furthermore, patients with CHD continue to be at increased risk for social communication difficulties, unusual behaviors, and impaired theory of mind in adulthood. Chiavarino et al. (2015) found lower ToM performance in adults with different types of complex CHD. Asschenfeldt et al. (2020) demonstrated impaired emotion recognition and more self- and proxy-reported social interaction problems and autistic features in young adults with repaired atrial or ventricular septal defect (Asschenfeldt et al., 2020; Chiavarino et al., 2015).

To date, most studies have investigated only certain aspects of social and behavioral difficulties, and, thus, the broader phenotypic profile of these issues in patients with CHD remains unclear. A better understanding of the nature and extent of these impairments is needed to better define the neurodevelopmental burden of patients with CHD and to inform research, clinicians, and families accordingly. It is unknown whether patients with CHD with social communication difficulties, unusual behaviors, and impaired ToM are at increased risk for other comorbid neurodevelopmental and psychiatric impairments. Co-existing neurodevelopmental and psychiatric impairments may developmentally interact with social and behavioral difficulties and may eventually lead to an increased disease burden. This might affect academic achievement and quality of life of these patients in the long term. Importantly, neurodevelopmental and psychiatric comorbidities are common in individuals without CHD: Children with diagnosed autism spectrum disorder or attention

deficit/hyperactivity disorder (ADHD) frequently display co-existing impaired social cognition and executive dysfunction (Miranda et al., 2017; Oerlemans et al., 2013), which seem to be directly associated with each other (Fong & Iarocci, 2020; Pineda-Alhucema et al., 2018) and may share underlying neuronal correlates (Miranda et al., 2017). Furthermore, patients with diagnosed autism or ADHD are at increased risk for anxiety symptoms (Bishop et al., 2019; van Steensel et al., 2011). In ADHD, more social difficulties have been associated with elevated anxiety (Bishop et al., 2019).

In individuals with CHD, the prevalence of executive function deficits is high, with more than 70% of the children exhibiting some degree of executive dysfunction (e.g., lower working memory, inhibitory control and cognitive flexibility) (Cassidy et al., 2015), which can interfere with their ability to read social cues. In addition, youth with CHD present with elevated psychiatric symptoms, predominantly anxiety disorders (DeMaso et al., 2017; Freitas et al., 2013; Pike et al., 2018) that might, in turn, hinder their capacity to process social information. Calderon et al. (2010) provided the first evidence that lower scores on inhibitory control are associated with lower ToM skills (i.e., first and second order false belief understanding) in children with d-TGA (Calderon et al., 2010). Further evidence suggests that a computer-based working memory training (i.e., Cogmed) may improve “autism-like” symptoms in children with CHD. However, the authors only found an improvement at the 3-month follow-up but not at post-intervention (Calderon et al., 2020). Moreover, Werninger suggested that there is a substantial prevalence of comorbid ADHD-related symptoms and “autism-like” symptoms in children with CHD (Werninger et al., 2020). However, to date, the co-existence and the potential interplay of executive functions in everyday life, anxiety, social and behavioral difficulties in children CHD have not been examined.

The aim of this study is to provide additional characterization of the profile of social communication difficulties, unusual behaviors, and impaired theory of mind in school-aged children with complex CHD using a comprehensive set of standardized measures and to quantify the cumulative burden of neurodevelopmental and psychiatric sequelae by assessing potential comorbidities. First, we characterized parent-reported social and behavioral symptoms as measured by autism symptom scales, children’s ToM abilities, and parent-reported empathy skills in children with CHD who underwent cardiac surgery in infancy and did not have a formal autism diagnosis. We hypothesized that, compared to the general population, children with CHD will display worse outcomes in areas such as social communication and higher-order ToM. We also predicted that children with ToM impairments will have social communication difficulties and restricted repetitive behaviors in everyday life, as reported by their parents. Second, we examined potential comorbidities of social and behavioral difficulties, particularly problems in executive function and anxiety symptoms. We predicted that more social and behavioral difficulties will be associated with worse outcomes in executive functions and with greater anxiety symptoms.

# Materials and methods

## *Study sample*

This cross-sectional single-center cohort study was conducted at Boston Children's Hospital between 2019 and 2020. Eligibility criteria included a diagnosis of CHD requiring cardiopulmonary bypass (CPB) surgery within the first year, age between 7 years 0 months and 12 years 11 months, fluency in English, no chromosomal or genetic syndrome, no severe physical or sensory impairments (hearing, visual or psycho-motor), and absence of a confirmed autism diagnosis (based on medical records and parent interviews). We also screened for intellectual or developmental impairment in the medical record and during parent interview, and we excluded children who had severe intellectual or developmental impairment (e.g., severe language or motor delay) that would prevent completion of the planned study assessment.

The clinical database for all patients treated at Boston Children's Hospital was reviewed to identify eligible children. In total, 377 children met the inclusion criteria and were contacted by e-mail or postal mail. Of those, 294 families did not respond and could not be reached by phone and 6 families refused participation. Of the 77 families who were contacted, a screening interview was completed by telephone. Seven children did not meet the inclusion criteria due to confirmed autism diagnosis or other severe neurodevelopmental impairment, and 14 families did not consent to participate. A total of 56 families (15% of all initially contacted patients; 80% of all patients contacted by telephone and proved to be eligible) agreed to participate. Neuropsychological assessment was conducted remotely by a pediatric research neuropsychologist (JC), and questionnaires were filled out online by the child's primary caregiver. Remote assessment was conducted due to the ongoing COVID-19 pandemic. While research on the validity of remote neuropsychological evaluations remains sparse, it has been suggested that remote assessment of several neuropsychological tests is feasible (e.g., subtests of the WISC-V, Cox et al., 2022). All assessments were conducted using a laptop, computer, or tablet (no cellphone screen was used). Families who did not have a proper device were sent a tablet to complete the assessment remotely. The examiner conducted all assessment in an office and the families were at home. Verbal responses were recorded where pointing was not possible. Children completed the assessments without parental assistance.

The study was approved by the hospital's Institutional Review Board. Primary caregivers of all participants gave written informed consent prior to participation.

## *Outcome measures*

### *Primary outcomes*

Primary outcomes for this study were the *Autism Spectrum Rating Scale (ASRS)* (Goldstein & Naglieri, 2009) and the *Theory of Mind Task Battery (ToM-TB)* (Hutchins & Prelock, 2010; Hutchins et al., 2008).

Parent-reported autism symptoms were assessed with the full-length *ASRS* (6–18 years) (Goldstein & Naglieri, 2009). The *ASRS* is a validated 71-item questionnaire to measure autism characteristics according to DSM-5 diagnostic criteria. The total score and the three *ASRS* subscales were used for the current study. The *social/communication* subscale assesses the use of verbal and non-verbal social communication skills in social interactions. The *unusual behavior* subscale assesses the level of tolerance for changes in routine, engagement in apparently purposeless or stereotypical behaviors, and overreaction to certain sensory inputs. The *self-regulation* subscale assesses how well the child can control behavior and thoughts, maintain focus, and resist distraction. Raw scores were transformed into *T*-scores ( $Mean = 50$ ,  $SD = 10$ ) based on representative US norms including children with and without clinical conditions. Cronbach's alpha ranges from 0.92 to 0.97 indicating excellent internal consistency. Higher *ASRS* scores indicate more “autism-like” symptoms.

ToM was assessed using the *ToM-TB* (Hutchins et al., 2008) as part of the virtual neuropsychological assessment. The *ToM-TB* consists of 15 test questions within 9 tasks. Tasks are presented in a storybook format via short visual vignettes depicting social situations of increasing complexity. The *ToM-TB* provides a total score (0–15) with higher scores indicating better ToM abilities and three subscales corresponding to the three developmental stages of ToM (i.e., early, basic, and advanced). The *early ToM* subscale evaluates basic emotion recognition, which emerges in typically developing children between 1 and 3 years of age. Patients were classified as having “fully developed” *early ToM* if they correctly passed all subtests. The *basic ToM* subscale measures social cognition typically emerging between 3.5 and 5 years of age and include visual perceptual-taking and first-order false belief tasks (i.e., the ability to infer somebody's false belief). Patients were classified as “fully developed” *basic ToM* if they correctly passed all subtests. The *advanced ToM* subscale evaluates second-order theory of mind including emotional and false belief tasks typically mastered between 5.5 and 8 years of age. Second-order emotion and false belief tasks assess the ability to infer what one person thinks about another person's mental or emotional states. For example, saying that Paul thinks Mary is upset, when in reality, she is not. Patients were classified as “fully developed” *advanced ToM* if they correctly passed at least one subtest of each task (in accordance with the technical manual (Hutchins & Prelock, 2010) the *ToM-TB* subtest *Second-Order False Belief task* was only administered to children > 8 years of age). Cronbach's alpha ranges from 0.91 to 0.94 indicating excellent internal consistency.

### ***Secondary outcomes***

The *Social Responsiveness Scale (School-age form), 2nd Edition (SRS-2)* (Constantino, 2012) and the *Empathy/Systemizing Quotient Child Version (ESQ-C)* (Auyeung et al., 2009) were used to investigate social impairments beyond the two primary outcomes (i.e., *ASRS* and *ToM-TB*).

The *SRS-2* (Constantino, 2012) measures social skills and autistic mannerisms. *T*-scores ( $Mean = 50$ ,  $SD = 10$ ) were calculated based on representative US norms for the total score and the DSM-5 subscales (*Social Communication Impairments, Restricted Repetitive Behavior*). Higher *SRS-2* scores indicate more “autism-like” symptoms. The *ESQ-C* (Auyeung et al., 2009) measures the child's ability to feel empathy and relate to other people's feelings in everyday situations. Sex-specific *T*-scores ( $Mean = 50$ ,  $SD = 10$ ) were calculated for the *Child Empathy Quotient* using sex-specific means and standard deviations

of typically developing children reported by Auyeung et al. (2009). Higher *Child Empathy Quotient* scores imply better empathy skills.

Table 1. Sample characteristics.

Characteristic (N = 56)		
Sociodemographic	Age in years (Mean [SD])	10.8 (1.8)
	Female sex (N [%])	26 (46.4)
	Race (N [%])	
	African American	2 (3.6)
	Asian	2 (3.6)
	Caucasian	46 (82.1)
	Unknown	6 (10.7)
	Primary caregiver's highest education (N [%])	
	High school	3 (5.4)
	Partial college or special training	10 (17.9)
	Undergraduate	18 (32.1)
	Graduate	24 (42.9)
	Unknown	1 (1.8%)
Clinical and neonatal	Number of siblings (Median [IQR])	2.0 (2.0, 3.0)
	Birth weight in kg (M [SD])	3.0 (0.7)
	Gestational age at birth in weeks (M [SD])	38.1 (2.4)
	Prenatal diagnosis (N [%])	31 (55.4)
Cardiac	CHD Class (N [%])	
	Biventricular without CoA	40 (71.4)
	Biventricular with CoA	7 (12.5)
	Univentricular without CoA	8 (14.3)
	Univentricular with CoA	1 (1.8)
	Number of CPB surgeries (Median [IQR])	1.0 (1.0, 2.0)
	Total length of hospitalization for 1st CPB surgery (Median [IQR])	14 (7–24)
	DHCA time in minutes (M [SD])	5.5 (12.2)
	Age at first surgery in days (Median [IQR])	27 (4–126)
	Heart transplant (N [%])	1 (1.8)
	No. of cardiac medications (N [%])	
	0	40 (71.4)
	1	9 (16.1)
≥2	7 (12.5)	
Educational and psychiatric	Major clinical events at any given time (N [%])	
	Cardiac arrest	4 (7.1)
	ECMO	4 (7.1)
	Seizure	2 (3.6)
	Stroke	3 (5.4)
	Tutoring in school (N [%])	
	Enrichment	5 (8.9)
	Academic challenges	7 (12.5)
	Individualized education program (IEP) (N [%])	19 (33.9)
	Special education (N [%])	6 (10.7)
	Therapeutic interventions (N [%])	
	Early intervention	36 (64.3)
	Speech therapy	14 (25.0)
Occupational therapy	26 (46.4)	
Physical therapy	20 (35.7)	
Psychotherapy	19 (33.9)	
ADHD diagnosis* (N [%])	9 (16.1)	
ADHD medication (N [%])	4 (7.1)	
Other psychiatric diagnosis** (N [%])	6 (10.7)	
Other psychotropic medication (N [%])	0 (0)	
Learning disability (N [%])	1 (1.8)	

CPB, cardiopulmonary bypass; ADHD, attention deficit/hyperactivity disorder.

\*History of an ADHD diagnosis was gathered from parent reports and patient charts.

\*\*Formal diagnosis of anxiety, depression, or other psychiatric disorder.

The *Behavior Rating Inventory of Executive Function, 2nd Edition (BRIEF-2)* (Gioia et al., 2015) and the *Multidimensional Anxiety Scale for Children, 2nd Edition (MASC-2)* (March, 2012) were used to investigate comorbidities of social impairments. The *BRIEF-2* (Gioia et al., 2015) measures executive functions in everyday situations. *T*-scores (*Mean* = 50, *SD* = 10) were calculated based on representative US norms for the total score and the three index



scales: *Behavioral Regulation*, *Emotional Regulation*, and *Cognitive Regulation*. Higher *BRIEF-2* scores imply more executive dysfunction. The *MASC-2* (March, 2012) is a comprehensive assessment of anxiety dimensions in children and adolescents. T-scores (*Mean* = 50, *SD* = 10) were calculated based on representative US norms for the total score and the six subscales: *Separation Anxiety/Phobia*, *Generalized Anxiety Disorder Index*, *Social Anxiety*, *Obsessions and Compulsions*, *Physical Symptoms*, and *Harm Avoidance*. Higher *MASC-2* scores imply more anxiety symptoms.

The *Conners-3* (Conners, 1997), subtests of the *Wechsler Intelligence Scale for Children, 5th edition (WISC-V)* (Wechsler, 2015) and primary caregiver's highest education were considered as descriptive variables and/or covariates. The *Conners-3* (Conners, 1997) assesses ADHD-related behaviors in children. T-scores (*Mean* = 50, *SD* = 10) were calculated based on representative US norms for the total score. Higher *Conners-3* scores imply more ADHD-related symptoms. The following *WISC-V* subtests were administered *Matrix Reasoning*, *Digit Span*, *Similarities*, and *Vocabulary*. Age-normed scaled scores were calculated for all subtests (*Mean* = 10, *SD* = 3). An age-normed *Verbal Comprehension Index* score (*Mean* = 100, *SD* = 15) was calculated from the scores on two subtests, *Similarities* and *Vocabulary*. Higher scores indicate better verbal comprehension. For all of the questionnaires used, Cronbach's alpha scores indicate good to excellent internal consistency (Auyeung et al., 2009; Conners, 1997; Constantino, 2012; Gioia et al., 2015; March, 2012).

Clinical and sociodemographic factors were collected from patient charts and by means of a standardized questionnaire filled out by the primary caregiver.

### *Statistical analysis*

Clinical and sociodemographic characteristics were reported. Number and probabilities were reported for nominal data, median and interquartile range (*IQR*) for ordinal-scaled data, and mean and standard deviation (*SD*) for continuous data. Total scores and subscales of the parent-reported social functioning questionnaires (i.e., *ASRS*, *SRS-2*, *ESQ-C*) were compared to normative data with one-sampled *t*-tests (Reference *Mean* = 50, *SD* = 10). Numbers and proportions of children scoring outside the normal range (*ASRS*, *SRS-2*:  $T \geq 60$ , *ESQ-C*:  $T \leq 40$ ) were reported and compared to normative data with Chi-square tests (Reference proportion = 16%). To describe ToM abilities, number and proportion of children with "not fully developed" ToM stages (i.e., subscales *early*, *basic*, and *advanced ToM* of the *ToM-TB*) were reported. In order to explore the profile of social and behavioral difficulties, the proportions of children with significant parent-reported outcomes and/or impaired ToM were displayed in a Venn Diagram. For this purpose, numbers and proportions of children who scored  $\geq 1SD$  above the mean indicating worse outcomes in the *ASRS* subscales ( $T \geq 60$ ) and who have "not fully developed" *advanced ToM (ToM-TB)* were considered.

To investigate potential comorbidities (i.e., lower executive function and more anxiety) of social and behavioral difficulties, two separate regression models were calculated. For parent-reported outcomes, a linear regression model was calculated with the *ASRS total score* as the dependent variable. For ToM impairments, an ordinal regression model was calculated with the *ToM-TB total score* as the dependent variable. *MASC-2 total score*, *BRIEF-2 total score*, and *Digit Span scaled score* were included as independent variables and age, primary caregiver's education, having an ADHD diagnosis, and *WISC-V Verbal Comprehension Index*

were included as covariates. *Conners-3 total score* was not considered as a covariate due to its high collinearity with the *BRIEF-2 total score* (Pearson's  $r = 0.85$ ). Instead, the presence of an ADHD diagnosis (derived from patient charts and parent reports) was included as covariate. For the linear regression model, standardized  $\beta$  coefficients with 95% confidence intervals (95-CI) and adjusted  $R^2$  were reported. For the ordinal regression model, odds ratio (OR) and Mc Fadden  $R^2$  (McFadden, 1974) were reported. Values between 0.2 and 0.4 in McFadden  $R^2$  indicate a very good model fit (Cameron & Windmeijer, 1997). Missing values of independent variables and covariates were imputed with the R package *MICE* (imputations:  $N = 1$ , iterations:  $N = 5$ ) (van Buuren & Groothuis-Oudshoorn, 2011). All variables assessed within the study were considered as potential predictors for missing data estimation.

With a sample size of 56 patients, using two-sided Type I error rate of  $\alpha = 5\%$ , we had 80% power to detect a correlation of  $r = 0.36$  (small to moderate effect size) between a continuous measure of parent-reported outcomes (*ASRS total score*) and anxiety/executive function outcomes (*MASC-2 total score*, *BRIEF-2 total score*, and *Digit Span scaled score*).  $p$ -Values  $< .05$  were considered statistically significant. Analyses were hypothesis-driven and were not corrected for multiple comparisons. Statistical analyses were performed with R (R Core Team, 2020). The STROBE guidelines for reporting observational studies were followed.

Table 2. Total scores and subscales of parent-reported questionnaires measuring autism spectrum traits and comparison to the normative population.

Questionnaire	Scale	Mean (SD)	t(df), 95% CI	p-Value*
ASRS	Total score	52.0 (8.1)	1.9(55), 49.8 to 54.2 Proportion with $T \geq 60$ : 7(12.5%)	.069 <sup>+</sup> .475 <sup>++</sup>
	Social communication	47.5 (7.5)	-2.5(55), 45.5 to 49.5 Proportion with $T \geq 60$ : 3(5.4%)	<b>.014<sup>+</sup></b> .030 <sup>++</sup>
	Unusual behavior	53.7 (8.6)	3.2(55), 51.4 to 56.0 Proportion with $T \geq 60$ : 15(26.8%)	<b>.002<sup>+</sup></b> .028 <sup>++</sup>
	Self-regulation	53.2 (9.9)	2.4(55), 50.6 to 55.9 Proportion with $T \geq 60$ : 17(30.4%)	<b>.018<sup>+</sup></b> .003 <sup>++</sup>
SRS-2	Total score	52.0 (10.5)	1.4(54), 49.1 to 54.8 Proportion with $T \geq 60$ : 11(20.0%)	.169 <sup>+</sup> .418 <sup>++</sup>
	Social communication impairment	51.4 (10.5)	1.0(54), 48.6 to 54.2 Proportion with $T \geq 60$ : 10(18.2%)	.332 <sup>+</sup> .659 <sup>++</sup>
	Restricted repetitive behavior	54.0 (10.7)	2.8(54), 51.1 to 56.8 Proportion with $T \geq 60$ : 14(25.5%)	<b>.008<sup>+</sup></b> .056 <sup>++</sup>
ESQ-C	Child empathy quotient	48.0 (10.1)	-1.4(51), 45.2 to 50.9 Proportion with $T \geq 60$ : 6 (11.8%) <sup>+</sup>	.169 <sup>+</sup> .380 <sup>++</sup>

95% CI refers to mean.

<sup>+</sup>One-sampled t-test with normative reference  $T = 50$ .

<sup>++</sup>one-sampled chi-square test with normative reference  $T \geq 60 = 16\%$ , + ESQ-C was missing in four participants. Significant  $p$ -values are displayed in bold.

## Results

Fifty-six children ( $n = 56$ , 46% female) with different types of complex CHD (16% univentricular CHD) participated in the study. Children were between 7 and 12 years of age (Mean age:  $10.8 \pm 1.8$  years). Seventy-five percent of the children's primary caregivers had at least a college degree. Patient characteristics are summarized in Table 1. A full list of CHD diagnoses is displayed in Table S1. Participating patients did not significantly differ from nonparticipating patients (eligible and initially contacted,  $n = 321$ ) regarding sex ( $p = .6$ ) and cardiac physiology (univentricular vs. biventricular CHD,  $p = .8$ ). There was a higher proportion of Caucasian patients in the group of participants (82%) compared to non-

participants (61%,  $p = .004$ ). Patients who refused to participate at any time point ( $n = 20$ ) did not differ from participating patients regarding sex ( $p = .7$ ), cardiac physiology ( $p = .9$ ), or race ( $p = .7$ ).

**Table 3.** Regression models predicting autism spectrum traits.

Regression model	Dependent variables	Independent variables and covariates <sup>+</sup>	Standardized estimate (95% CI)	p-Value	Model fit
Linear regression	ASRS total score	MASC-2 Total Score	0.281 (0.077 to 0.485)	<b>.008</b>	Adjusted $R^2$ = 0.579
		BRIEF-2 Total Score	0.169 (-0.082 to 0.419)	.182	
		Digit Span scaled score	-0.364 (-0.594 to -0.133)	<b>.003</b>	
		Age <sup>+</sup>	-0.080 (-0.276 to 0.116)	.417	
		Primary caregiver's education <sup>+</sup>	-0.065 (-0.265 to 0.135)	.514	
		ADHD diagnosis <sup>+</sup>	0.368 (0.179 to 0.556)	<b>&lt;.001</b>	
		Verbal Comprehension Index <sup>+</sup>	-0.008 (-0.232 to 0.217)	.944	
Ordinal regression	ToM-TB total score	MASC-2 Total Score	0.969 (0.924 to 1.014)	.170	McFadden $R^2$ = 0.089
		BRIEF-2 Total Score	1.034 (0.985 to 1.088)	.180	
		Digit Span scaled score	1.235 (1.032 to 1.494)	<b>.021</b>	
		Age <sup>+</sup>	1.534 (1.124 to 2.113)	<b>.007</b>	
		Primary caregiver's education <sup>+</sup>	1.655 (0.920 to 3.011)	.093	
		ADHD diagnosis <sup>+</sup>	0.567 (0.138 to 2.269)	.421	
		Verbal comprehension <sup>+</sup>	0.974 (0.922 to 1.030)	.358	

MASC-2 total score, BRIEF-2 total score, and Digit Span scaled score were included as independent variables and age, primary caregiver's education, having an ADHD diagnosis, WISC-V Verbal Comprehension Index, and Digit Span scaled score were included as <sup>+</sup>covariates. For linear regression, standardized estimates were expressed by  $\beta$  (measured in units of SD). For ordinal regression, standardized estimates were expressed by odds ratio (OR). Significant p-values are displayed in bold. Number of missing data: BRIEF-2 total score ( $N = 3$ ), MASC-2 total score ( $N = 1$ ), primary caregiver's education ( $N = 1$ ), WISC-V Verbal Comprehension Index ( $N = 1$ ). Missing data was imputed (see section 2.3 for details) in order to maintain power.

### ***Social cognition and behavioral profiles in children with CHD***

In comparison to the normative population, children with CHD displayed significantly more unusual behavior ( $p = .002$ ) and self-regulation difficulties ( $p = .02$ ) as measured by the ASRS parent-report (Table 2). A higher-than-expected proportion of children with CHD displayed clinically elevated scores ( $T \geq 60$ ) in those subscales (unusual behavior:  $p = .03$ ; self-regulation difficulties:  $p = .003$ ) compared to the norm. ASRS total score did not differ from the norm ( $p = .07$ ). Social communication abilities were significantly better than the norm ( $p = .01$ ). See Figure 1 and Table 2 for details. Similar findings were found on the SRS-2: children with CHD displayed more *Restricted Repetitive Behaviors* ( $p = .01$ ) in comparison to the normative population, while *Social Communication and Interaction* abilities ( $p = .33$ ) and *SRS-2 total score* ( $p = .17$ ) did not significantly differ from the norm. Parent-reported empathy skills measured with the *ESQ-C* did not differ from the norm ( $p = .17$ ) (Table 2).

On the *ToM-TB*, all children had “fully developed” *early ToM* (i.e., emotion recognition). *Basic ToM* was “not-fully developed” in 49%. *Advanced ToM* was “not fully developed” in 73% of the children. One-third failed a task that mainly requires visual perception abilities to understand what others see depending on their position (i.e., *Line of Sight* task of the subscale *basic ToM*) and 13% failed the *first order false belief* task of the subscale *basic ToM* (see list of all subtests in Table S2). One child did not complete the *ToM-TB* due to fatigue and was therefore excluded from further analyses investigating *ToM* outcomes.

Figure 2 displays the profile of social and behavioral difficulties in children with CHD. Twelve children (22%) had no social and behavioral difficulties (i.e.,  $T < 60$  in all *ASRS* subscales and “fully developed” *advanced ToM*). Three children (5%) showed parent-reported difficulties ( $T \geq 60$  in at least one *ASRS* subscale) but had “fully developed” *ToM*. Twenty-one children (38%) had “not fully developed” *advanced ToM* but no parent-reported difficulties. Nineteen children (35%) had both parent-reported difficulties ( $T \geq 60$  in at least one *ASRS* subscale) and “not fully developed” *advanced ToM*. Based on this test’s norm expectations, typically-developing children between 5.5 and 8 years of age master *advanced ToM* abilities (Hutchins & Prelock, 2010).

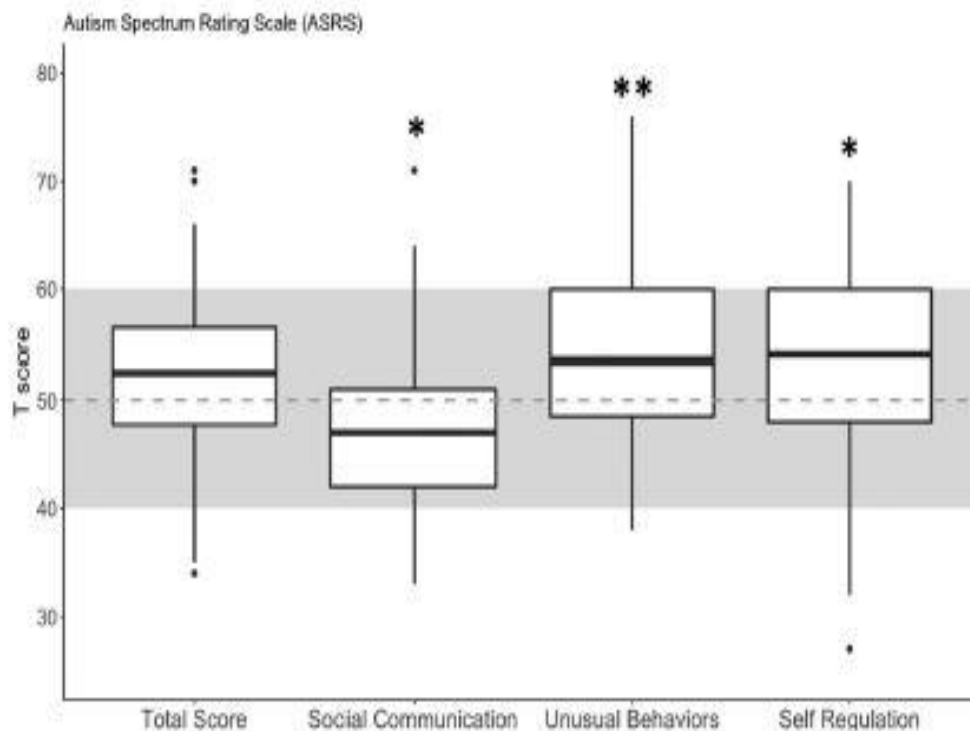


Figure 1. Boxplot displaying Autism Spectrum Rating Scale (ASRS) total scores and subscales. Note: The lower/upper border of the box represent the first/third quartile. The line within the box corresponds to the median. Dots represent outliers (>1.5 IQR below/above the first/third quartile). Higher scores indicate worse outcomes. Significance level: \* $p < 0.05$ , \*\* $p < 0.01$ .

## *Comorbidities of social and behavioral difficulties in children with CHD*

Regression analyses were conducted to identify comorbidities of autism spectrum traits (Table 3). Results showed that higher scores for anxiety ( $p = 0.01$ ) and lower working memory ( $p = .003$ ) were significantly associated with more parent-reported social and behavioral difficulties on the ASRS. Executive function measured with the *BRIEF-2* total score was not significantly associated with parent-reported social and behavioral difficulties ( $p = .182$ ). However, when the variable *Digit Span* was excluded from the model, higher *BRIEF-2* total scores were significantly associated with more parent-reported difficulties. The *Digit Span* measures attention and working memory, a core executive function, which was moderately correlated with the *BRIEF-2* total score (Pearson's  $r = -0.515$ ,  $p < .001$ ) and may have resulted in collinearity in the model. There was no association between ToM impairments and anxiety ( $p = .17$ ) or parent-reported executive function ( $p = .18$ ). This remained the case when the *Digit Span* was excluded from the model. Lower *Digit Span* scores were significantly associated with more difficulties in ToM ( $p = .02$ ). Summary measures are presented in Table S3.

Post hoc, separate regression models were calculated with the subscales of the *MASC-2* (i.e., *Separation Anxiety/Phobia*, *Generalized Anxiety Disorder Index*, *Social Anxiety*, *Obsessions and Compulsions*, *Physical Symptoms*, and *Harm Avoidance*) and the *BRIEF-2* (i.e., *Emotion Regulation*, *Behavioral Regulation*, *Cognitive Regulation*) as independent variables to investigate whether results were driven by a specific subscale. We further investigated associations with the *BRIEF-2* working memory subscale as a parent-reported measure for working memory (supplementing the performance-based measure *digit span*). All subscales of the *BRIEF-2* and the *MASC-2*, except for the *BRIEF-2* working memory subscale (FDR corrected  $p = .08$ ) and the *MASC-2* subscales *Social Anxiety* (FDR corrected associated with the *ASRS* total score (all others  $p < .04$ )). No subscale was significantly associated with *ToM-TB* total score (all  $p > .1$ ). Model estimates are displayed in Table S4.

Figure 3 displays comorbidities of social and behavioral difficulties in children with CHD. Of 56 children, 22 (39%) had clinically elevated scores ( $T \geq 60$ ) in at least one *ASRS* subscale (*Social Communication*, *Unusual Behaviors*, *Self-Regulation*). Of those 22 children, 21 (95%) also had clinically elevated scores in the *BRIEF-2* total score and/or the *MASC-2* total score indicating clinically relevant comorbidity.

## **Discussion**

Children with complex CHD are at increased risk for social and behavioral difficulties even in the absence of a formal autism diagnosis. This study aimed to characterize the profile of social and behavioral difficulties in school-aged children with CHD and to examine the co-existence of potential cognitive and mental health impairments. We showed that despite not having an autism diagnosis, children did have more unusual behaviors and relative deficits in self-regulation and ToM (e.g., first- and second-order false belief) in comparison to the normative population. Social communication and empathy skills were normal. One in three children had combined clinically relevant parent-reported difficulties and compromised ToM. More parent-reported difficulties were associated with more anxiety symptoms, worse

working memory and to some extent also with parent-reported executive functions in everyday life. Of particular importance is that among those children with clinically relevant social and behavioral difficulties, the vast majority (i.e., 21 of 22 children) also presented with clinically relevant executive function impairments and/or anxiety symptoms.

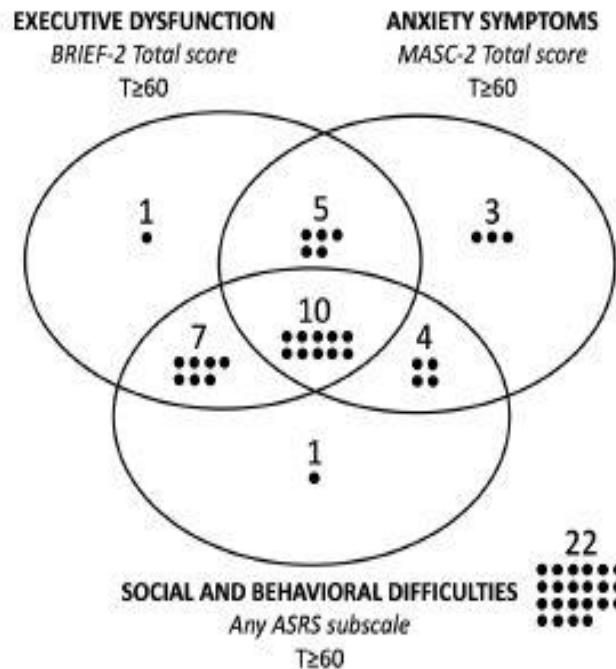


Figure 3. Venn Diagram displaying comorbidities of social and behavioral difficulties in children with CHD. Note. Questionnaires were missing in three patients and they were thus excluded from this diagram. Twenty-two patients (displayed in the lower right corner) had normal scores in all three questionnaires ( $T < 60$  in the BRIEF-2 total score, MASC-2 total score and all ASRS subscales).

### Profile of social and behavioral difficulties in children with CHD

Findings from the current study are in line with previous studies in children with CHD (Bellinger et al., 2011; Calderon et al., 2010, 2012, 2014; Sarrechia et al., 2015; Werninger et al., 2020). However, an unexpected finding was that the children showed significantly better social communication compared to the norm when measured with the *ASRS* questionnaire and normal functioning when measured with the *SRS-2* questionnaire. Consequently, also the *ASRS* and *SRS-2* total scores did not significantly differ from the norm. Similar to our findings, a previous study in preschoolers with CHD did also not find a significant difference in the *SRS* between test norms and patients with CHD without a genetic comorbidity (i.e., similar to the inclusion criteria in this study) (Brosig et al., 2017). In contrast, several other studies suggested compromised social communication and interaction skills in children with CHD. A systematic review by Clancy et al. (2020) showed that impaired social functioning is already present in early life. Infants with CHD are at increased risk for social withdrawal, socio-emotional delay and social interaction difficulties (Clancy et al., 2020). A study in school-aged children with different types of CHD found more social communication difficulties measured with the parent-reported *SRS* in patients compared to normative data (Werninger et al., 2020). It is possible that differences in the type of measurement or the developmental timing across studies but also differences in access to neurodevelopmental follow-up programs and early intervention services add to the variability of findings. Further,

we excluded children with a formal autism diagnosis and therefore group differences may become smaller. In addition, this study was conducted during the COVID-19 pandemic which may have influenced the parental rating of their child's social functioning due to limited social interactions. Nevertheless, studies are needed to further investigate the risk for social communication and interaction impairments in children with CHD using measurement tools other than parent reports, such as teacher reports, clinician rating, and standardized autism diagnostic assessments (e.g., *ADOS*).

Basic ToM (e.g., visual perspective taking and first-order false belief task) and advanced ToM (e.g., second-order emotion and false belief tasks) were compromised in a high proportion of patients participating in this study. Previous studies in younger children with d-TGA also found delayed development of ToM measured with first- and second-order false belief tasks (Calderon et al., 2010, 2012, 2014). The current study shows that these impairments seem to persist throughout elementary school. In typically developing children, ToM usually develops sequentially, starting in early childhood and advanced ToM is expected to be fully developed between 5 and 8 years of age (Hutchins & Prelock, 2010). In our study, 3 out of 4 children failed one or more of the advanced ToM tasks at a mean age of 11 years. Thus, our findings suggest substantial ToM impairments in this cohort. Advanced ToM is crucial for inferring other people's intentions, beliefs, and emotions in order to successfully participate in social interactions. This significant delay in children with CHD may put them at a high risk for compromised socio-emotional development in the long term. Further, the extensive ToM test battery used in this study allowed for more in-depth investigation of ToM difficulties in these children: Half of the children also failed one or more of the basic ToM tasks. Basic ToM is expected to consolidate between 4 and 5 years of age in typically developing children. This includes visual perception taking and first-order false belief tasks. Interestingly, many 8–12-year-old children with CHD failed a basic ToM task which required visual perception taking. It has been reported that visual-spatial abilities are also vulnerable in individuals with complex CHD (Bean Jaworski et al., 2018; Bellinger et al., 2003, 2011). Potentially, visuo-spatial impairments in these children may have contributed to children's failure at some of the basic ToM tasks. However, the majority of ToM-TB tasks did not require any visuo-spatial abilities and thus, the observed ToM difficulties are not solely driven by visuo-spatial problems. In addition, ToM performance was correlated with working memory. This association is in line with previous studies in typically developing children showing that working memory capacity is associated with ToM (Lecce et al., 2017; Mutter et al., 2006) and may even predict the success of ToM trainings (Lecce & Bianco, 2018). Based on these findings, we suggest that working memory impairments should be considered a red flag for potential theory of mind difficulties.

Similar findings have been described previously in adults with CHD. A study in adults with repaired septal defect had more self- and proxy-reported social and behavioral difficulties and lower ToM abilities compared to healthy controls (Asschenfeldt et al., 2020). Another study by Chiavarino et al. (2015) found more ToM impairments in a small sample of patients with different types of CHD compared to healthy controls when assessed with a semi-structured interview (Chiavarino et al., 2015). These findings provide first evidence that social and

behavioral difficulties may persist across life and thus indicate substantial long-term sequelae which may lead to mental health difficulties and compromised well-being.

The underlying etiological pathways leading to the described profile of social and behavioral difficulties in patients with CHD remain unclear. Previous studies found genetic variants that contribute to both CHD and autism (e.g., Jin et al., 2017; Rosenthal et al., 2021). Indeed, Rosenthal et al. (2021) showed that these shared risk genes are linked to a molecular network of disrupted ion channels, which may play a key role in both heart and brain development (Rosenthal et al., 2021). However, as these studies only investigated patients with a formal diagnosis, it is unclear if genetic variants may also contribute to “autism-like” symptoms without a formal autism diagnosis. Furthermore, the underlying neuronal correlates of social and behavioral difficulties in CHD remain unknown. Importantly, neuroimaging studies in patients with CHD have elucidated macro- and microscopic alterations, which become evident during the fetal and neonatal period (e.g., Dimitropoulos et al., 2013; Khalil et al., 2016; Mebius et al., 2017). Persisting brain alterations in adolescents and young adults with CHD have further been linked to neurodevelopmental impairments including worse executive functions (Ehrler et al., 2021; Naef et al., 2021; Rollins et al., 2014; Semmel et al., 2018). However, future studies are needed to determine the link between social and behavioral difficulties and brain structural and functional alterations in youth with CHD and to elaborate potential interactions between different neurodevelopmental functions. Further, in order to gain additional insights into the underlying etiology of social and behavioral impairments in CHD and the degree of symptom severity, future studies should consider comparing patients with and without a formal autism diagnosis.

### **Neurodevelopmental and psychiatric comorbidities of social and behavioral difficulties in children with CHD**

Our study found that more parent-reported social and behavioral difficulties in children with CHD were associated with worse executive function skills and more anxiety symptoms. Post hoc analyses of the different *BRIEF-2* and *MASC-2* subscales showed that the associations with social and behavioral difficulties were not driven by any specific subscale. Indeed, worse scores on all three indexes of the *BRIEF-2* (i.e., cognitive, behavior, and emotion regulation) and most subscales of the *MASC-2* (i.e., Separation Anxiety/Phobia, Generalized Anxiety, Obsessions and Compulsions, Physical Symptoms) were associated with more difficulties. Moreover, when considering those patients with clinically relevant difficulties ( $\geq 1$  *SD* outside the normal range), we found a substantial number of patients with co-occurring clinically relevant executive dysfunction and/or anxiety symptoms.

Importantly, co-existing social and behavioral difficulties, anxiety symptoms and executive dysfunction are not unique to individuals with CHD. Executive dysfunction and anxiety are frequently observed in children with an autism diagnosis without CHD (Fong & Iarocci, 2020; Miranda et al., 2017; Oerlemans et al., 2013; van Steensel et al., 2011). Furthermore, social and behavioral difficulties often co-occur with executive dysfunction and anxiety in other clinical populations: in children with ADHD, impaired social cognition and executive dysfunction frequently co-exist and more social difficulties have been associated with elevated anxiety (Bishop et al., 2019; Miranda et al., 2017). Children born very preterm, a population with a developmental profile at least somewhat similar to that of children with



CHD (Easson et al., 2018), are also at increased risk for social and behavioral difficulties (Lavery et al., 2021), executive function difficulties (van Houdt et al., 2019), and anxiety (Fitzallen et al., 2021). A study by Korzeniewski et al. (2017) in 10-year-old preterm-born children found that those children who displayed clinically relevant social and behavioral difficulties were also more likely to report anxiety and executive function deficits (Korzeniewski et al., 2017). Regarding the frequent co-existence of social and behavioral difficulties, anxiety, and executive dysfunction across patient populations, it seems reasonable to hypothesize that these impairments may be developmentally linked to one another irrespective of the underlying disorder.

The etiological mechanisms of social and behavioral difficulties and anxiety has been discussed previously: In autism, anxiety has been associated with unusual behaviors (i.e., restricted and repetitive behaviors) in a number of studies (e.g., Joyce et al., 2017; Lidstone et al., 2014). Boulter et al. (2014) suggest that this association is mediated by intolerance of uncertainties – a finding that has also been reported in children without an autism diagnosis (Boulter et al., 2014). It has further been discussed that restricted and repetitive behaviors may serve as a coping response to reduce anxiety (e.g., Joyce et al., 2017; Rodgers et al., 2012). A better understanding of the developmental cascade linking CHD with autism and anxiety is needed to guide therapeutic interventions and improve counseling and care of these patients and their families.

Likewise, previous research has elaborated the causal relationship between ToM and executive function. Several longitudinal studies have suggested that early executive functions including self-monitoring and inhibition are required to develop ToM (Hughes & Ensor, 2007; Marcovitch et al., 2015; Müller et al., 2012). Further, neuroimaging studies suggest both shared and distinct underlying neuronal correlates of executive functions and ToM (Wade et al., 2018). Research investigating developmental associations between unusual behaviors (i.e., restricted and repetitive behaviors) and executive function is sparse. Longitudinal studies are lacking, but a large-scale meta-analysis found a robust correlation between unusual behaviors and executive functions both in children with an autism diagnosis and in typically developing children (Iversen & Lewis, 2021). For those most vulnerable, a better understanding of the social and behavioral profile, associated comorbidities, and underlying mechanisms can inform clinical practice and will be important in developing targeted therapeutic interventions by means of identifying meaningful endpoints to measure efficacy, by targeting comorbidities to mitigate some of these deficits, and by helping to guide the selection of profile-specific therapeutic tools.

## **Limitations**

The following limitations should be considered when interpreting the results. This single-center study did not include a control group of typically developing children. Instead, the scores of children with CHD who participated in this study were compared to representative US norms. In the case of ToM abilities, there were no age-adjusted normative scores provided by the manual, and thus ToM abilities were only presented descriptively (e.g., probabilities of fully developed and not fully developed ToM abilities). In addition, even though ToM tasks are informative in understanding cognitive and social development, there are limited standardized measures for clinical practice applications. As a result, ToM tasks are not always

considered for diagnostic purposes. Future larger studies are needed to investigate potential medical and demographic predictors of autism-like behaviors in children with CHD.

Patients with a formal autism diagnosis were excluded as the aim of this study was to investigate social and behavioral impairments in the absence of a formal diagnosis. However, autism diagnoses were obtained from medical records and parent interviews, but no formal autism evaluation has been conducted as part of the study. Thus, the sample may have included a few individuals with later childhood undiagnosed autism. Due to a clinical focus on the patients' heart condition or potential atypical/more subtle presentation of psychiatric symptoms, some individuals may be underdiagnosed. Future studies should therefore include formal evaluations of psychiatric disorders including autism when investigating neurodevelopmental comorbidities in patients with CHD.

Patients with a genetic syndrome and severe intellectual or developmental disabilities were excluded from this study, which limits the generalizability to forms of CHD with important associated anomalies. Further, most patients participating in this study were Caucasian and had a primary caregiver with a college degree. This sample is therefore not representative for the general US population, which limits the generalizability of the results.

Executive functions were assessed with the parent-reported *BRIEF-2* and the *digit span*, a neuropsychological test for working memory. The role of inhibition and flexibility was not examined in this study due to the lack of instruments adapted for remote administration. However, two recent meta-analyses have shown that patients with CHD perform worse in those domains compared to children without CHD (Feldmann et al., 2021; Jackson et al., 2021). A study in children with d-TGA showed an association between poorer inhibitory control and poor ToM outcomes (Calderon et al., 2010). Further, it has previously been suggested that cognitive flexibility plays an important role in ToM abilities (Bock et al., 2015) and in outcomes in patients with CHD more broadly (see Cassidy, 2020). Future studies should examine the role of flexibility and other executive functions in social and behavioral difficulties in children with CHD. In addition, “hot” executive functions, which refer to emotional regulatory skills, should be considered in future studies.

Neuropsychological tests were administered remotely due to the ongoing COVID-19 pandemic. The used tests were originally validated for in-person testing and were adapted for remote assessment for the current study. The normative reference data used for this study were obtained in-person and thus, comparability may be limited (van Patten, 2021). However, recent research suggests that remote WISC-V assessments are feasible (Cox et al., 2022) and comparable to in-person assessments (Hamner et al., 2021; Harder et al., 2020). Nevertheless, these studies only investigated subtests of the WISC-V and overall research validating remote neuropsychological assessments remains sparse. To date, no study has investigated the validity of remotely assessed ToM-TB. Although the developers of the ToM-TB validated the remote application of this test in their own practice and the graphic and picture-based nature of the tasks render the virtual administration possible via screen-share, it remains unclear if the remote setting may impact the child's attention and use of social cues and if potential visuospatial difficulties in patients with CHD may influence the performance in remote ToM tasks.

## Conclusion

Children with CHD are at an increased risk for more unusual behavior, less self-regulation and delayed ToM and co-occurring executive dysfunction and anxiety symptoms. Co-existing neurodevelopmental and psychiatric impairment leads to an increased disease burden and should be addressed with therapeutic interventions. Holistic therapeutic interventions for children with CHD, which target social and behavioral difficulties, executive dysfunction and anxiety, are needed to support and improve the long-term outcomes of patients with CHD. Moreover, future studies are needed to investigate the extent of unusual behaviors, less self-regulation and ToM impairments in adults with CHD to more fully appreciate the chronic burden experienced by these patients and to improve guidance and care in the long term.

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### Disclosure statement

No potential conflict of interest was reported by the author(s).

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