Perioperative Course and Socioeconomic Status Predict Long-Term Neurodevelopment Better Than Perioperative Conventional Neuroimaging in Children with Congenital Heart Disease

Astrid Neukomm, MMed[1,2], Melanie Ehrler, PhD[1,2,3], Maria Feldmann, MD, PhD[1,2], Aziz Chaouch, MSc[4], Walter Knirsch, MD[2,3,5], Cornelia Hagmann, MD, PhD[2,6], Andras Jakab, MD, PhD[2,7], and Beatrice Latal, MD, MPH[1,2,3]

Objective The objective of the study was to compare the use of neonatal conventional brain magnetic resonance imaging (MRI) with that of clinical factors and socioeconomic status (SES) to predict long-term neurodevelopment in children with severe congenital heart disease (CHD).

Study design In this prospective cohort study, perioperative MRIs were acquired in 57 term-born infants with CHD undergoing cardiopulmonary bypass surgery during their first year of life. Total brain volume (TBV) was measured using an automated method. Brain injury severity (BIS) was assessed by an established scoring system. The neurodevelopmental outcome was assessed at 6 years using standardized test batteries. A multiple linear regression model was used for cognitive and motor outcomes with postoperative TBV, perioperative BIS, CHD complexity, length of hospital stay, and SES as covariates.

Results CHD diagnoses included univentricular heart defect (n = 15), transposition of the great arteries (n = 33), and acyanotic CHD (n = 9). Perioperative moderate-to-severe brain injury was detected in 15 (26%) patients. The total IQ was similar to test norms ($P = .11$), whereas the total motor score ($P < .001$) was lower. Neither postoperative TBV nor perioperative BIS predicted the total IQ, but SES ($P < .001$) and longer hospital stay ($P = .004$) did. No factor predicted the motor outcome.

Conclusion Although the predictive value of neonatal conventional MRIs for long-term neurodevelopment is low, duration of hospital stay and SES better predict the outcome in this CHD sample. These findings should be considered in initiating early therapeutic support. *(J Pediatr 2022;251:140-8)*.

The incidence of severe congenital heart disease (CHD) requiring immediate treatment after birth is about 0.3% of all live births.[1] In recent decades, the survival rate has increased to 85% to 90% due to improved surgical and perioperative management.[2-4] However, patients with CHD are at risk of delayed neurodevelopment, affecting cognition, language, motor function,[5-8] and executive function[8,9] during childhood and into adolescence[5-9] and adulthood.[10] Evidence is increasing that brain immaturity,[11] smaller brain volumes,[12-15] and perioperative brain injury[12,16-18] are related to altered neurobehavior during the neonatal period[14,15] and delayed neurodevelopment during early childhood.[12,13,15] Data are limited on the impact of perioperative magnetic resonance imaging (MRI) alterations on the long-term neurodevelopmental outcome. To date, only one study with a small sample of patients with aortic arch obstructions and high brain injury loads correlated MRI alterations with neurodevelopment at 6 years.[12] That study found significant associations of smaller postoperative regional brain volumes with IQ below 85, moderate-to-severe white matter injury (WMI) with a lower IQ, and WMI in the posterior part of the internal capsule with worse motor scores.[12] Nevertheless, clinical factors have not reliably predicted the neurodevelopmental outcome.[12,13,16,19] It is important to consider socioeconomic status (SES) when identifying patients with CHD at risk for impairments.[20,21] Our aim was to determine the predictive value of neonatal conventional brain MRI alterations, clinical factors, and SES for the long-term cognitive and motor outcome in children with severe CHD. We hypothesized that lower postoperative total brain volume (TBV), more severe perioperative brain injury, more complex CHD, longer hospital stay, and

Beery	Beery-Buktenica Developmental Test of Visual-Motor Integration—sixth edition
BIS	Brain injury severity
CHD	Congenital heart defects
SES	Socioeconomic status
SON-R	Snijders-Oomen Non-Verbal Intelligence Tests 2-8—Revision
SR	Super-resolution
TBV	Total brain volume
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence—third edition
ZNA	Zurich Neuromotor Assessment

From the [1]Child Development Center and [2]Children's Research Center, University Children's Hospital Zurich, Zurich, Switzerland; [3]University of Zurich, Zurich, Switzerland; [4]Division of Biostatistics, Center of Primary Care and Public Health (Unisanté) Lausanne, Lausanne, Switzerland; [5]Pediatric Cardiology, Department of Surgery, Pediatric Heart Center, [6]Department of Neonatology, and [7]Center for MR Research, University Children's Hospital Zurich, Zurich, Switzerland

This research was funded by the Mäxi Foundation and the Anna Müller Grocholski Foundation. The authors declare no conflicts of interest.

0022-3476/© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

https://doi.org/10.1016/j.jpeds.2022.07.032

lower SES all predict a poorer cognitive and motor outcome at 6 years of age in children with CHD.

Methods

This work was conducted as part of a prospective, longitudinal cohort study at the University Children's Hospital Zurich. Neonates born between October 2009 and March 2020 who required cardiopulmonary bypass surgery were recruited from the pediatric cardiac intensive care or neonatal care unit. Patients with gestational age <36 weeks at birth or a suspected genetic syndrome or confirmed genetic disorder were excluded.[13,17] Brain MRI was performed perioperatively. Clinical data were collected prospectively from the clinical records of patients. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland. Written informed consent was obtained from all parents or legal guardians.

A total of 128 patients were recruited. Three patients died during their first year of life. Of 125 surviving patients, 69 had reached preschool age by the time of this analysis, of whom 8 patients were excluded for methodologic reasons and 4 patients were lost to follow-up (follow-up rate = 93%). Therefore, 57 patients were available for analysis (**Figure 1**; available at www.jpeds.com). The 57 patients included did not differ from the 12 patients excluded or lost to follow-up in CHD complexity ($P = .11$) or SES ($P = .54$), but they had a significantly higher median Bayley cognitive composite score at 1 year of age (included patients: median = 110, IQR = [97.5, 115], excluded or lost-to-follow-up patients: median = 95, IQR = [90, 95], $P = .004$).

Brain MRI, Image Processing, and Injury Scoring

Perioperative cerebral MRI was acquired in natural sleep from all patients who were in clinically and hemodynamically stable condition with a 3.0 T MRI scanner with an 8-channel head coil (GE Signa MR750). For volumetric analysis, 2-dimensional fast spin-echo T2-weighted sequences were acquired in axial, sagittal, and coronal planes. The sequence measures for the conventional MRIs were identical to those reported in a previous study.[13] For postprocessing, first, a brain mask was created with a semiautomated atlas-based custom MeVisLab (MeVis Medical Solutions AG) module.[22,23] A super-resolution (SR) reconstruction algorithm implemented in the SVRTK toolbox was then applied to the 3 orthogonally acquired 2-dimensional fast spin-echo image stacks, creating a 3-dimensional SR volume of brain morphology with an isotropic resolution of $0.5 \times 0.5 \times 0.5$ mm^3.[24] The 3-dimensional SR images were segmented into tissue compartments using the Developing Human Connectome Project structural pipeline.[25] Tissue types were segmented, and the TBV was calculated with the FSLstats command in FSL software. Postoperative MRIs could not be obtained for 8 patients (**Figure 2**; available at www.jpeds.com). Preoperative MRIs were available for all these 8 patients. These patients were not excluded from the analysis, but instead the 8 missing postoperative TBVs were estimated by the chained equation involving one imputation and 50 iterations with the "mice" package in R.[26] To estimate the missing values, preoperative TBV, baseline characteristics, and outcome measures were used as predictors. To avoid multiple testing but to answer hypothesis-driven questions, we examined only the predictive value of postoperative brain volumes. In addition, we supposed that the postoperative TBV would be clinically more relevant for the long-term neurodevelopmental outcome. In 8 (14%) of our patients, new WMI appeared postoperatively. The WMI load has been shown to affect network strength and integration.[27] Neonatal surgery and the perioperative period, thus, represent an additional insult to brain development. Therefore, the postoperative TBV most likely captures the cumulative impact of perioperative adverse events.

A trained neonatologist with experience in neonatal MRI scored all lesions of preoperative and postoperative MRI scans. The brain lesions were classified using the brain injury severity (BIS) score (**Figure 3**; available at www.jpeds.com).[16,28] The maximal BIS score from preoperative and postoperative MRI was taken into account as the cumulative BIS score.[16] For the 13 patients for whom only one MRI, either preoperative or postoperative, was available, we used the BIS score of the single available MRI instead of a cumulative BIS score. Due to the sample size and distribution of lesions (**Figure 4**; available at www.jpeds.com), the BIS score was dichotomized: 0 = no lesion, mild WMI, or intraventricular hemorrhage grade 1 or 2 and 1 = stroke or moderate-to-severe WMI.

Neurodevelopmental Assessment at 6 Years of Age

The children in our study underwent neurodevelopmental testing at 1, 2, 4, and 6 years of age. At 6 years, cognitive function was assessed with the third edition of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III).[29] For 3 children with delayed language development, the Snijders-Oomen Non-Verbal Intelligence Tests 2-8—Revision (SON-R) was performed.[30] Motor function was assessed with the Zurich Neuromotor Assessment (ZNA).[31] Visual motor function was assessed with the sixth edition of the Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery).[32] Trained developmental pediatricians conducted the assessments. They were not blinded to the clinical course or to major MRI alterations because the assessments were conducted within a routine clinical follow-up program. The WPPSI-III assesses total IQ, verbal IQ, performance IQ, and processing speed. The SON-R assesses a nonverbal IQ and was considered equivalent to a total IQ score in the WPPSI-III within this study. The assessed IQs have a mean of 100 and an SD of 15. The ZNA assesses 4 domains: pure motor function, adaptive fine motor function, adaptive gross motor function, and static balance. The time needed to solve the ZNA tasks was transformed to z-scores from normative values. A total motor score was calculated in accordance with literature.[33] The Beery test assesses 3 domains: visual-motor integration, visual perception, and motor coordination. The composite scores have a mean of 100 and an SD of 15. SES was calculated from maternal education and

paternal occupation. The score ranged from 2 to 12, with higher scores indicating higher SES.[34] This measure of SES has been used in healthy and other at-risk Swiss populations such as preterm born children.[21,35,36]

Data Analyses

The neurodevelopmental outcome of cognitive, motor, and visual motor function at 6 years of age was compared with the respective normative means using 1-sample *t* tests for normal data and Mann-Whitney U tests for non-normal data. Hypotheses were tested by calculating multivariable linear regression models for the primary outcomes: total IQ and total motor score. Post hoc, two additional models were calculated for 2 outcomes, processing speed (WPPSI-III) and motor coordination (Beery), because patients performed significantly worse than the normative samples for these domains (Table II). Distributions of residuals were checked for normality. For non-normal outcome variables, ordinal logistic regression models were calculated to confirm results. All models included the following predictors: postoperative TBV, cumulative BIS score (no/mild brain injury vs moderate/severe brain injury), CHD complexity, length of hospital stay, and SES. To test CHD complexity, we created an ordinal variable classifying acyanotic heart disease as mild complexity, dextro-transposition of the great arteries as medium complexity, and single ventricle physiology as high complexity. Because we only had 7 patients with hypoplastic left heart syndrome, we did not perform subgroup analysis for hypoplastic left heart syndrome. The length of hospital stay was log-transformed due to skewed data distribution. The models were corrected for gestational age at MRI and MRI batch (ie, before and after scanner update). To correct for multiple testing, *P* values were corrected for the false discovery rate according to the Benjamini-Hochberg procedure.[37] All analyses were conducted using R, version 4.1.0, statistical software developed by the R Core Team.[38] The STROBE guidelines for reporting observational studies were followed.[39]

Results

Sample Descriptive and MRI Characteristics

Neonatal demographic, clinical, and MRI characteristics of the patients with CHD are displayed in Table I. Perioperative moderate-to-severe brain injury was detected in 15 (26.3%) patients. The postoperative TBV did not differ between the BIS categories (mean TBV for BIS 0 and 1 = 374.03 mL [SD = 39.79 mL]; mean TBV for BIS 2 and 3 = 367.94 mL [SD = 35.83 mL]; $P = .62$).

Neurodevelopmental Assessment at 6 Years of Age

Neurodevelopmental assessment was performed at a median age of 6.0 years (youngest participant: 4 years and 1 month, oldest participant: 7 years). At follow-up, 12 patients (21.8%) were receiving cardiac medication and 15 patients (27.3%) were attending regular therapy, mostly speech therapy (9 patients; 16.4%). Neurodevelopmental outcomes were compared with the respective normative means and are presented in Table II. The total, verbal, and performance IQ of the CHD cohort did not differ significantly from the normative test means. Nine (15.8 %) patients had a total IQ below 85, which is closely in line with the normal distribution (15.87%).[41] The processing speed score of the CHD cohort was significantly lower than the normative mean. The total motor score and all the ZNA component z-scores were also significantly lower. Beery visual motor integration of the CHD cohort did not differ significantly from the normative mean. Beery visual perception was significantly better in the CHD population than the normative mean, but Beery motor coordination was significantly worse.

Table I. Neonatal demographic, clinical, and MRI characteristics of patients with CHD

Number of patients = 57	Median [IQR], mean (SD), n {%}
Gestational age at birth, weeks	39.6 (1.3)
Weight at birth, g	3336.9 (463.8)
Head circumference at birth, cm*	34.5 (1.3)
Male sex	41 {71.9}
Socioeconomic status	9.0 [7.0, 11.0]
Cardiac diagnosis	
Acyanotic	9 {15.8}
Single ventricle physiology	15 {26.3}
Hypoplastic left heart syndrome	7 {12.2}
D-Transposition of the great arteries	33 {57.9}
Preoperative lowest O2 saturation, %*	62.0 [47.0, 79.0]
Preoperative resuscitation	1 {1.8}
Balloon atrial septostomy	25 {43.9}
CPB surgery at neonatal age (≤30 days of life)[19]	47 {82.5}
Age at first CPB surgery, days	12.0 [9.0, 22.0]
Duration of intraoperative CPB, min*	180.4 (57.2)
Postoperative resuscitation	1 {1.8}
Postoperative seizures	0 {0}
Postoperative ECMO	0 {0}
Hospital stay, days	33.0 [26.0, 42.0]
Gestational age at preoperative MRI, weeks	40.5 (1.4)
Age at preoperative MRI, days	7.0 [5.8, 9.0]
Gestational age at postoperative MRI, weeks	43.2 (1.8)
Age at postoperative MRI, days	25.0 [20.0, 32.0]
Total brain volume on postoperative MRI, cm^3*	372.3 (38.4)
Cumulative BIS score	
BIS 0—No brain injury	38 {66.7}
BIS 1—Mild WMI or IVH grade 1 or 2	4 {7.0}
BIS 2—Stroke without moderate/severe WMI	1 {1.8}
BIS 3—Moderate/severe WMI	14 {24.6}

CPB, cardiopulmonary bypass; *ECMO*, extracorporeal membrane oxygenation; *IVH*, intraventricular hemorrhage.
Data are reported as mean and SD for normal data and as median and IQR for non-normal data. Categorical data are reported as numbers and proportions. Mild WMI: 1-3 lesions, each lesion <2 mm in diameter. Moderate/severe WMI: >3 lesions or any lesion >2 mm in diameter.[16] IVH was scored according to Papile et al.[40] The cumulative BIS score considers the more severe lesion of the preoperative and postoperative MRI.[16] Preoperatively, one patient had a stroke affecting the right anterior cerebral artery, one patient had a stroke affecting the left posterior cerebral artery, and one patient had a stroke affecting the right middle cerebral artery.
*>10% of data are missing.

Risk Factor Analysis of Neurodevelopment at 6 Years of Age

Test statistics of the linear regression models are presented in Table III for the primary outcomes, IQ, and total motor

Table II. Six-year neurodevelopmental outcome of patients with CHD

Outcome variables	Mean (SD) or median [IQR]	95% CI of median or mean	Cohen's D	*P*	Corrected *P**
Total IQ†	98.0 [92.0, 105.0]	94.0-101.0	0.21	.11	.11
Verbal IQ	95.4 (17.5)	90.6-100.1	0.27	.06	.08
Performance IQ	103.3 (12.9)	99.8-106.8	0.26	.07	.08
Processing speed	93.8 (12.1)	90.5-97.2	0.51	<.001***	.001**
Total motor score	−1.0 [−1.8, −0.3]	−1.6 to −0.8	0.82	<.001***	<.001***
Pure motor function	−0.5 (1.3)	−0.9 to −0.1	0.38	.02*	.04*
Adaptive fine motor	−1.2 (1.5)	−1.7 to −0.8	0.84	<.001***	<.001***
Adaptive gross motor	−0.6 [−1.2, 0.3]	−0.8 to −0.1	0.35	.02*	.04*
Static balance	−0.9 (1.1)	−1.3 to −0.6	0.86	<.001***	<.001***
Visual motor integration	97.7 (9.5)	94.8-100.6	0.24	.11	.11
Visual perception	107.0 (12.2)	103.4-110.7	0.58	<.001***	.001**
Motor coordination	95.8 (9.9)	92.8-98.8	0.43	.007**	.001**

Neurodevelopmental outcome variables were compared with the standardized test mean using 1-sample *t* tests and Mann-Whitney U tests as appropriate for the sample distributions. Data on motor (ZNA) and visual motor (Beery) outcome were missing for 9 patients and 14 patients, respectively. Patients with missing motor and visual motor outcome had similar total IQ to those who completed motor and visual motor assessment (motor: $P = .09$; visual motor: $P = .16$). *P* value < .05*, <.01**, <.001***.
*Benjamini-Hochberg correction for the number of outcome comparisons.[37]
†The total IQ includes IQ of 54 WPPSI-III and 3 SON-R tests. Significance and direction of effects did not differ when the 3 subjects with SON-R were excluded from analysis.

score and **Table IV** (available at www.jpeds.com) for the post hoc analyses of processing speed and motor coordination. The total IQ at 6 years of age was significantly predicted by the length of hospital stay during the first surgery and by SES but not by conventional MRI alterations or CHD complexity. Visual examination found no threshold for the length of hospitalization above which the outcome would be significantly worse. Furthermore, we did not identify any conventional MRI variable, clinical factor, or SES as a predictor for total motor outcome, motor coordination, or processing speed. There was a trend for the postoperative TBV to correlate with the 6-year motor outcome ($P = .09$); however, this relationship did not survive false discovery rate correction ($P = .44$). Due to non-normal total IQ and total motor outcome variables, ordinal regression models were additionally calculated to support the initial findings. These models provided comparable directions and significance of effects (**Table V**; available at www.jpeds.com). We also performed an analysis with a different categorization of BIS (no brain injury vs any brain injury). This different dichotomization did not change significance of the results (total IQ: postoperative TBV: B = −0.04, $P = .34$, cumulative BIS: B = −0.09, $P = .98$, CHD complexity: B = −4.72, $P = .07$, hospital stay: B = −10.02, $P = .002$, SES: B = 3.02, $P < .001$; total motor score: postoperative TBV: B = 0.01, $P = .11$, cumulative BIS: B = −0.08, $P = .88$, CHD complexity: B = 0.03, $P = .93$, hospital stay: B = −0.27, $P = .68$, SES: B = −0.06, $P = .58$).

Discussion

This prospective cohort study was designed to determine the value of perioperative conventional MRI changes, clinical factors such as CHD complexity and length of hospitalization, and SES to predict long-term cognitive and motor outcomes in children with severe CHD. We showed that postoperative TBV and cumulative BIS did not predict 6-year outcome, whereas the duration of hospital stay and SES independently predicted the cognitive outcome but not the motor outcome. A previous study, conducted in the same cohort as presented here, found an association, albeit weak, between postoperative TBV and 1-year cognitive and language outcomes.[13] This finding suggests that the

Table III. Predictors of the IQ in patients with CHD at preschool age, multiple linear regression model

Dependent variables	Independent variables	B	SE B	β	t	*P*	Corrected *P**	Adjusted R^2	*P* of the whole model
Total IQ†	Postoperative TBV	−0.04	0.04	−0.10	−0.92	.36	.46	0.41	<.001***
	Cumulative BIS score	2.12	3.66	0.06	0.58	.57	.57		
	CHD complexity	−4.36	2.53	−0.19	−1.72	.09	.15		
	Hospital stay (log)	−10.30	3.08	−0.36	−3.34	.002**	.004**		
	SES	2.99	0.70	0.46	4.24	<.001***	<.001***		
Total motor score	Postoperative TBV	0.01	0.01	0.27	1.75	.09	.44	−0.04	.62
	Cumulative BIS score	0.44	0.58	0.13	0.76	.45	.68		
	CHD complexity	0.06	0.39	0.02	0.15	.88	.88		
	Hospital stay (log)	−0.40	0.65	−0.09	−0.62	.54	.68		
	SES	−0.08	0.11	−0.11	−0.71	.48	.68		

B, unstandardized beta; *β*, standardized beta; *SE B*, SE of unstandardized beta.
All models were controlled for MRI batch and gestational age at MRI. *P* values < .05*, <.01**, <.001***.
*Benjamini-Hochberg correction for the number of included predictors.[37]
†The total IQ includes IQ of 54 WPPSI-III and 3 SON-R tests. Significance and direction of effects did not differ when the 3 subjects with SON-R were excluded from analysis.

predictive strength of perioperative conventional MRI changes decreases with longer interval until follow-up assessment. In accordance with our findings, Claessens et al investigated patients with aortic arch obstruction at school age and found no significant difference in postoperative TBV between children with an IQ above 85 vs below 85 or any association between the neonatal TBV and motor scores.[12] However, they found associations between regional brain volumes (basal ganglia, thalamus, brain stem) and an IQ above 85 vs IQ below 85.[12] Interestingly, other studies on children with CHD in early childhood have also found significant associations. Stegeman et al described neonatal cortical gray matter and cerebellar volume but not unmyelinated white matter being associated with fine motor scores at 9 and 18 months of age.[42] Again, these effects were small.[42] Bonthrone et al reported a significant association between a neonatal atypicality index, representing the deviation of brain volumes from typical neonatal brain development, and the Bayley cognitive composite scores at 22 months of age.[43] Sadwani et al reported that fetal total and regional brain volumes explained 10%-21% of variance in cognitive, language, and motor development at 2 years of age.[44] One potential reason for the conflicting results might be the different intervals between neuroimaging and neurodevelopmental assessment. Thus, other factors may have a greater impact on the long-term neurodevelopmental outcome than neonatal brain volumes. However, results are contradictory even between studies performing brain MRI and functional assessments at the same age. A significant association between the TBV and motor development was found when assessed simultaneously at 1 and 3 years of age.[45] Another study showed that the TBV correlated with language performance when examined at one year of age.[46] In contrast, other studies did not show any association between the TBV and neurodevelopment when both were assessed in early childhood.[47,48] Interestingly, significant associations have been found between the TBV and IQ, executive, and motor outcomes for school-age children, adolescents, and adults.[49-52] One reason that the TBV is possibly associated with the outcome in cross-sectional studies but not in longitudinal studies might be that no additional factors accumulating over time contribute to the variance in the outcome.

Our results suggest that mild brain lesions are not associated with the 6-year outcome. Although the total number of patients within the BIS categories 2 and 3 in our cohort is low (n = 15, 26%), the prevalence of any perioperative brain injury is 33%, which lies within the range of 19%-52% described in literature.[53,54] Many studies have shown that the prevalence of brain injury increases with CHD complexity.[11,53,55] Because we scanned only hemodynamically stable patients in natural sleep, a recruitment bias toward patients with less severe CHD may have arisen. Results are contradictory regarding the association of brain injury with the neurodevelopmental outcome.[54] In contrast to our results, studies with higher prevalence and severity of neonatal brain injuries found an association of brain injury with cognitive,[12,18] language,[56] and motor[12,16] development in patients with CHD at early childhood[16,18,56] and school age.[12] In a study by Claessens et al, 62% of patients had moderate-to-severe WMI in the postoperative MRI.[12] Children with moderate-to-severe WMI had a worse IQ at 2 and 6 years of age.[12] If neonatal brain injury were detected in the posterior limb of the internal capsule, patients showed lower motor scores at school age.[12] However, in agreement with our results, Bonthrone et al found no association between preoperative brain injury and the cognitive outcome at 22 months of age in a CHD population with a prevalence of moderate-to-severe brain injury of 16.4%.[57] Similarly, despite a prevalence of 42% of new postoperative WMI in their sample, but with 67% of them being mild, Beca et al found that new postoperative WMI was unrelated to 2-year neurodevelopment, whereas brain immaturity was.[11] Kuhn et al also could not find an association between the brain injury score and the outcome up to 2 years of age in a group with a rate of 53% preoperative lesions and 57% new postoperative lesions but with a low median BIS at both time points.[58] Future studies are needed to explore the role of more advanced MRI analyses such as regional volumes, morphometrics, and diffusion tensor imaging on long-term neurodevelopment. The latest studies on diffusion tensor imaging have shown extensive persisting white matter changes[27,59,60] to be associated with the neurodevelopmental outcome up to 30 months of age.[59]

We were unable to replicate the finding of a large meta-analysis[8] demonstrating that more severe CHD complexity was associated with a poorer neurodevelopmental outcome. However, this is most likely due to the small sample size of our cohort and the relatively few patients with single ventricle physiology. In accordance with the large body of evidence, the length of postnatal hospital stay, which is a marker of disease severity,[6,61] significantly predicted the 6-year cognitive outcome with a moderate effect size (**Figure 5**). The management of cardiac patients during prolonged hospital stay has been shown to be improved by cardiac ICU developmental team meetings,[62] neonatal individualized developmental care, and family-centered developmental care.[62-64]

In our study, SES was an important predictor of cognitive development with a moderate effect size. In CHD, lower SES is associated with multiple medical disadvantages during fetal and perioperative care. These include lower fetal detection rates[65] resulting in higher neonatal mortality,[66] longer time until surgery,[67,68] fewer interventions with extracorporeal membrane oxygenation,[69] fewer catheterizations,[68] and poorer adherence to cardiologic and neurodevelopmental follow-up appointments.[70-73] Further, SES emerges repeatedly as an important factor in short- and long-term cognitive development in patients with CHD[20,21,68,74-76] and its impact on the cognitive outcome increases with advancing age.[21] Family SES is also an important factor in child health–related quality of life.[77,78] Maternal mental health and anxiety as well as parenting style are associated with behavioral and cognitive outcomes in young CHD children.[79,80] It is likely that a higher SES is associated with a more stimulating home environment, which in turn promotes cognitive

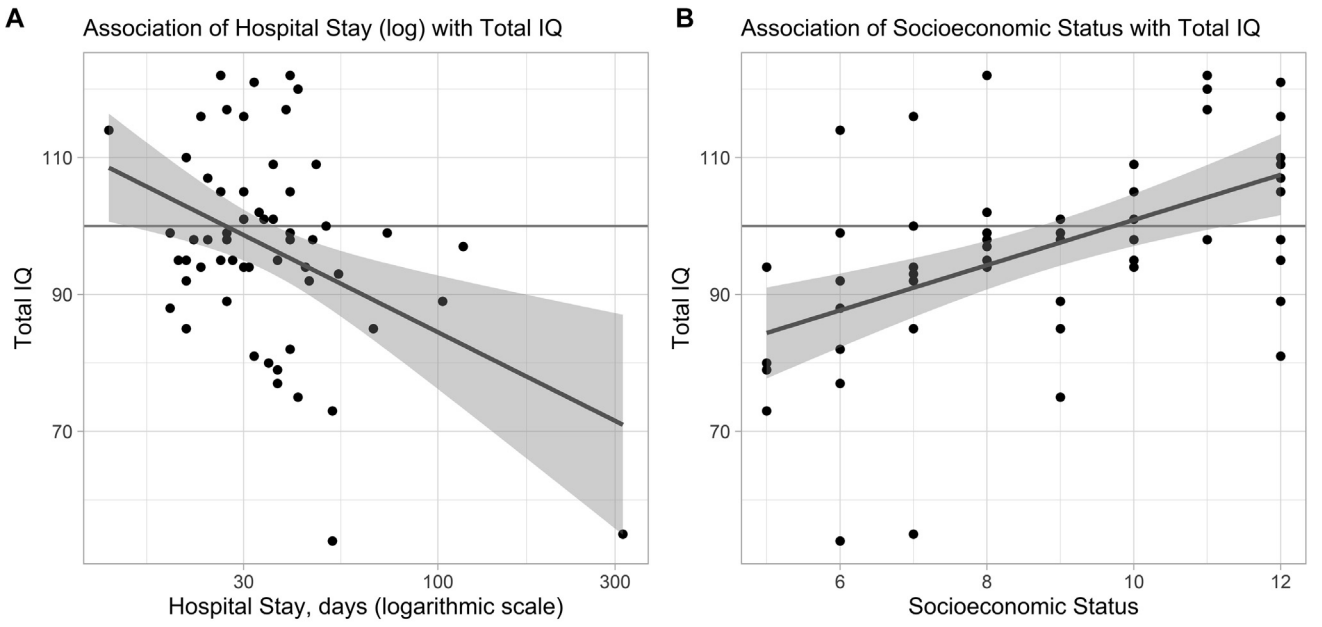

Figure 5. **A,** Association of perioperative hospital stay on a logarithmic scale (log) with a 6-year total IQ in patients with CHD. **B,** Association of SES with a 6-year total IQ in patients with CHD. Scatter plots of linear regression models. *Dots* indicate the total IQ of each patient in relation to its hospital stay and SES. The *line* indicates the linear regression estimate, and the *gray band* indicates the 95% CI of the linear regression estimate.

development. The latter has been shown in a recent study of children with CHD.[57] In line with this finding are the results from studies demonstrating that psychoeducational and parenting skills training supports the parent-infant/child interaction, resulting in improved mental Bayley scales at 6 months of age,[81] improved child behavior at the ages of 3-8 years,[82] less maternal anxiety,[81] and better parenting confidence.[82] Accordingly, the Cardiac Neurodevelopmental Outcome Collaborative published guidelines on early risk identification, family-centered approaches, and community-based services.[83] We draw the following clinical implications from our findings. First, cardiac intensive care units should provide individualized family-centered developmental care.[62-64] Second, health care professionals should place a particular focus on families with a lower SES already during the fetal and neonatal period. In addition, those families benefit particularly from interventions such as early psychoeducation and parenting skills training.[84,85] Third, families should be supported by an interdisciplinary team of professionals in adherence to cardiological and neurodevelopmental follow-up appointments.[86] Surveillance of eligible patients during hospital stay by the developmental team and educating parents about the need for follow-up visits result in significantly higher follow-up rates.[87] Before hospital discharge, socioeconomic barriers to these screenings need to be identified.[88,89] Cardiology and neurodevelopmental appointments could be clustered to reduce barriers like travel distance, transportation costs, and absence from work.[90] Telehealth care is a new opportunity that has gained importance during the COVID-19 pandemic which may improve assessment, follow-up, and interventions for this population.[91]

Our study has several strengths. Preoperative and postoperative MRIs could be obtained from most patients. Brain regions were segmented with the automated Developing Human Connectome Project pipeline. Neurodevelopmental assessment was performed with an extensive, standardized developmental test battery. The follow-up rate at 6 years of age was 93%. Some limitations must also be considered. This study sample is heterogenous in severity of clinical course and CHD complexity, with a small ratio of patients with single ventricle physiology and a high ratio of patients with dextro-transposition of the great arteries. The rather small sample size limits the power of the analyses performed and precludes subgroup analysis of CHD diagnoses. The postoperative imaging time point in our study was rather late compared with other studies.[12,18] Over time, WMI lesions may resolve on T1-weighted MRI.[92] Therefore, in this cohort, the number of brain injuries may have been underestimated. Importantly, studies that performed postoperative MRIs at an earlier time point also found an association between brain injury and the neurodevelopmental outcome only in populations with a high brain injury load.[12,16,18,56] More sophisticated imaging techniques, such as diffusion tensor imaging, may capture white matter changes for a longer time span and, therefore, may constitute a better biomarker for later neurodevelopmental outcomes.[59] The BIS scoring system is rather crude, with little differentiation between the type and location of lesions. Replacing the missing cumulative BIS scores with the available

single–time point BIS scores might have led to an additional underestimation of BIS for the affected individuals. We did not have a control group for the 6-year neurodevelopmental assessment and thus could only compare results to test norms. Children being followed had higher cognitive composite scores on the 1-year Bayley than those excluded or lost to follow-up ($P = .004$), indicating the presence of an ascertainment bias. The study sample is a high-performing group with an IQ within the normal range, which may be a reason for the lack of relationship between conventional MRI alterations and the 6-year outcome. Finally, the MRI software was updated during the study. Although the pulse sequence remained identical, the upgrade could potentially affect the MRI contrast and, thus, the segmentation of the MRI volumes.[13] However, analyses were corrected for the MRI batch.

In conclusion, in our cohort of well-performing children with a low brain injury load, the postoperative TBV and perioperative BIS did not predict the neurodevelopmental outcome. In contrast, longer postnatal hospital stay, which is a marker of disease severity, and lower SES remain the most important predictors for cognitive development. These findings underline the importance of early therapeutic support for children with low SES and long hospital stay. ■

Submitted for publication Feb 18, 2022; last revision received Jul 17, 2022; accepted Jul 23, 2022.

References

1. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-900.
2. GBD 2017 Congenital Heart Disease Collaborators. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc Health 2020;4:185-200.
3. Wernovsky G. The paradigm shift toward surgical intervention for neonates with hypoplastic left heart syndrome. Arch Pediatr Adolesc Med 2008;162:849-54.
4. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. Circulation 2010;122:2254-63.
5. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, et al. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. Pediatrics 2010;125:e818-27.
6. Huisenga D, La Bastide-Van Gemert S, Van Bergen A, Sweeney J, Hadders-Algra M. Developmental outcomes after early surgery for complex congenital heart disease: a systematic review and meta-analysis. Dev Med Child Neurol 2020;63:29-46.
7. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. J Pediatr Psychol 2007;32:527-41.
8. Feldmann M, Bataillard C, Ehrler M, Ullrich C, Knirsch W, Gosteli-Peter MA, et al. Cognitive and executive function in congenital heart disease: a meta-analysis. Pediatrics 2021;148:e2021050875.
9. Jackson WM, Davis N, Calderon J, Lee JJ, Feirsen N, Bellinger DC, et al. Executive functions in children with heart disease: a systematic review and meta-analysis. Cardiol Young 2021;31:1914-22.
10. Schlosser L, Kessler N, Feldmann M, Wehrle F, Rometsch S, Greutmann M, et al. Neurocognitive functioning in young adults with congenital heart disease: insights from a case-control study. Cardiol Young 2022;32:694-701.
11. Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, et al. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. Circulation 2013;127:971-9.
12. Claessens NHP, Algra SO, Ouwehand TL, Jansen NJG, Schappin R, Haas F, et al. Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. Dev Med Child Neurol 2018;60:1052-8.
13. Meuwly E, Feldmann M, Knirsch W, von Rhein M, Payette K, Dave H, et al. Postoperative brain volumes are associated with one-year neurodevelopmental outcome in children with severe congenital heart disease. Sci Rep 2019;9:10885.
14. Owen M, Shevell M, Donofrio M, Majnemer A, McCarter R, Vezina G, et al. Brain volume and neurobehavior in newborns with complex congenital heart defects. J Pediatr 2014;164:1121-7.e1.
15. Bonthrone AF, Kelly CJ, Ng IHX, Counsell SJ. MRI studies of brain size and growth in individuals with congenital heart disease. Transl Pediatr 2021;10:2171-81.
16. Peyvandi S, Chau V, Guo T, Xu D, Glass HC, Synnes A, et al. Neonatal brain injury and timing of neurodevelopmental assessment in patients with congenital heart disease. J Am Coll Cardiol 2018;71:1986-96.
17. Bertholdt S, Latal B, Liamlahi R, Pretre R, Scheer I, Goetti R, et al. Cerebral lesions on magnetic resonance imaging correlate with preoperative neurological status in neonates undergoing cardiopulmonary bypass surgery. Eur J Cardiothorac Surg 2014;45:625-32.
18. Andropoulos DB, Ahmad HB, Haq T, Brady K, Stayer SA, Meador MR, et al. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. Paediatr Anaesth 2014;24:266-74.
19. International Cardiac Collaborative on Neurodevelopment I. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. Ann Thorac Surg 2016;102:843-9.
20. Ryberg C, Sunnegårdh J, Thorson M, Broberg M. Intellectual functioning in children with congenital heart defects treated with surgery or by catheter interventions. Front Pediatr 2016;4:113.
21. Naef N, Wehrle F, Rousson V, Latal B. Cohort and individual neurodevelopmental stability between 1 and 6 years of age in children with congenital heart disease. J Pediatr 2019;215:83-9.e2.
22. Tourbier S, Bresson X, Hagmann P, Thiran JP, Meuli R, Cuadra MB. An efficient total variation algorithm for super-resolution in fetal brain MRI with adaptive regularization. Neuroimage 2015;118:584-97.
23. Deman P, Tourbier S, Meuli R, Bach Cuadra M. meribach/mevislabFetalMRI: MEVISLAB MIAL Super-Resolution Reconstruction of Fetal Brain MRI v1.0. Zenodo; 2020.
24. Kuklisova-Murgasova M, Quaghebeur G, Rutherford MA, Hajnal JV, Schnabel JA. Reconstruction of fetal brain MRI with intensity matching and complete outlier removal. Med Image Anal 2012;16:1550-64.
25. Makropoulos A, Robinson EC, Schuh A, Wright R, Fitzgibbon S, Bozek J, et al. The developing human connectome project: a minimal processing pipeline for neonatal cortical surface reconstruction. Neuroimage 2018;173:88-112.
26. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1-67.
27. Feldmann M, Guo T, Miller SP, Knirsch W, Kottke R, Hagmann C, et al. Delayed maturation of the structural brain connectome in neonates with congenital heart disease. Brain Commun 2020;2:fcaa209.
28. Dimitropoulos A, McQuillen PS, Sethi V, Moosa A, Chau V, Xu D, et al. Brain injury and development in newborns with critical congenital heart disease. Neurology 2013;81:241-8.
29. Wechsler D. Wechsler Preschool and Primary Scale of Intelligence – III (WPPSI-III). the Psychological Corporation; 2002.
30. Tellegen PJ, Laros JA, Petermann F. SON-R 2-8. Non-verbaler Intelligenztest; 2018.
31. Largo R, Fischer J. Zürcher Neuromotorik. AWE-Verlag; 2007.
32. Beery N, Buktenica N, al e. Beery-Buktenica Developmental Test of Visual-Motor Integration. Pearson; 2010.
33. Teixeira J, Caflisch J, Chaouch A, Beck I, Feldmann M, Polentarutti S, et al. Motor and visuomotor function in 10-year-old children with

congenital heart disease: association with behaviour. Cardiol Young 2021:1-6.
34. Largo RH, Pfister D, Molinari L, Kundu S, Lipp A, Duc G. Significance of prenatal, perinatal and postnatal factors in the development of AGA preterm infants at five to seven years. Dev Med Child Neurol 1989;31:440-56.
35. Bartal T, Adams M, Natalucci G, Borradori-Tolsa C, Latal B, Swiss Neonatal Network and Follow-up Group[Corporate Author]. Behavioral problems in very preterm children at five years of age using the Strengths and Difficulties Questionnaire: A multicenter cohort study. Early Hum Dev 2020;151:105200.
36. Pittet-Metrailler MP, Mürner-Lavanchy I, Adams M, Bickle-Graz M, Pfister RE, Natalucci G, et al. Neurodevelopmental outcome at early school age in a Swiss national cohort of very preterm children. Swiss Med Wkly 2019;149:w20084.
37. Benjamini Y, Hochberg Y. Controlling the false discovery rate - a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57:289-300.
38. R Core Team. R. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2021.
39. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806-8.
40. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
41. Lenhard W, Lenhard A. Normwertrechner. Bibergau: Psychometrica. 2020. Accessed October 15, 2021. https://www.psychometrica.de/normwertrechner.html
42. Stegeman R, Sprong MCA, JMPJ Breur, Groenendaal F, de Vries LS, Haas F, et al. Early motor outcomes in infants with critical congenital heart disease are related to neonatal brain development and brain injury. Dev Med Child Neurol 2022;64:192-9.
43. Bonthrone AF, Dimitrova R, Chew A, Kelly CJ, Cordero-Grande L, Carney O, et al. Individualized brain development and cognitive outcome in infants with congenital heart disease. Brain Commun 2021;3:fcab046.
44. Sadhwani A, Wypij D, Rofeberg V, Gholipour A, Mittleman M, Rohde J, et al. Fetal brain volume predicts neurodevelopment in congenital heart disease. Circulation 2022;145:1108-19.
45. Ibuki K, Watanabe K, Yoshimura N, Kakimoto T, Matsui M, Yoshida T, et al. The improvement of hypoxia correlates with neuroanatomic and developmental outcomes: comparison of midterm outcomes in infants with transposition of the great arteries or single-ventricle physiology. J Thorac Cardiovasc Surg 2012;143:1077-85.
46. Rollins CK, Asaro LA, Akhondi-Asl A, Kussman BD, Rivkin MJ, Bellinger DC, et al. White matter volume predicts language development in congenital heart disease. J Pediatr 2017;181:42-8.e2.
47. Watanabe K, Matsui M, Matsuzawa J, Tanaka C, Noguchi K, Yoshimura N, et al. Impaired neuroanatomic development in infants with congenital heart disease. J Thorac Cardiovasc Surg 2009;137:146-53.
48. Heye KN, Knirsch W, Latal B, Scheer I, Wetterling K, Hahn A, et al. Reduction of brain volumes after neonatal cardiopulmonary bypass surgery in single-ventricle congenital heart disease before Fontan completion. Pediatr Res 2018;83:63-70.
49. von Rhein M, Buchmann A, Hagmann C, Huber R, Klaver P, Knirsch W, et al. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. Brain 2014;137:268-76.
50. Hiraiwa A, Kawasaki Y, Ibuki K, Hirono K, Matsui M, Yoshimura N, et al. Brain development of children with single ventricle physiology or transposition of the great arteries: a longitudinal observation study. Semin Thorac Cardiovasc Surg 2020;32:936-44.
51. Heinrichs AK, Holschen A, Krings T, Messmer BJ, Schnitker R, Minkenberg R, et al. Neurologic and psycho-intellectual outcome related to structural brain imaging in adolescents and young adults after neonatal arterial switch operation for transposition of the great arteries. J Thorac Cardiovasc Surg 2014;148:2190-9.
52. Naef N, Schlosser L, Brugger P, Greutmann M, Oxenius A, Wehrle F, et al. Brain volumes in adults with congenital heart disease correlate with executive function abilities. Brain Imaging Behav 2021;15:2308-16.
53. Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2014;43:14-24.
54. Mebius MJ, Kooi EMW, Bilardo CM, Bos AF. Brain injury and neurodevelopmental outcome in congenital heart disease: a systematic review. Pediatrics 2017;140:e20164055.
55. Peyvandi S, Kim H, Lau J, Barkovich AJ, Campbell A, Miller S, et al. The association between cardiac physiology, acquired brain injury, and postnatal brain growth in critical congenital heart disease. J Thorac Cardiovasc Surg 2018;155:291-300.e3.
56. Andropoulos DB, Easley RB, Brady K, McKenzie ED, Heinle JS, Dickerson HA, et al. Changing expectations for neurological outcomes after the neonatal arterial switch operation. Ann Thorac Surg 2012;94:1250-5. discussion 5-6.
57. Bonthrone AF, Chew A, Kelly CJ, Almedom L, Simpson J, Victor S, et al. Cognitive function in toddlers with congenital heart disease: The impact of a stimulating home environment. Infancy 2021;26:184-99.
58. Kuhn VA, Carpenter JL, Zurakowski D, Reitz JG, Tague L, Donofrio MT, et al. Determinants of neurological outcome in neonates with congenital heart disease following heart surgery. Pediatr Res 2021;89:1283-90.
59. Ramirez A, Peyvandi S, Cox S, Gano D, Xu D, Tymofiyeva O, et al. Neonatal brain injury influences structural connectivity and childhood functional outcomes. PLoS One 2022;17:e0262310.
60. Claessens NHP, JMPJ Breur, Groenendaal F, Wösten-van Asperen RM, Stegeman R, Haas F, et al. Brain microstructural development in neonates with critical congenital heart disease: an atlas-based diffusion tensor imaging study. Neuroimage Clin 2019;21:101672.
61. von Rhein M, Dimitropoulos A, Valsangiacomo Buechel ER, Landolt MA, Latal B. Risk factors for neurodevelopmental impairments in school-age children after cardiac surgery with full-flow cardiopulmonary bypass. J Thorac Cardiovasc Surg 2012;144:577-83.
62. Butler SC, Huyler K, Kaza A, Rachwal C. Filling a significant gap in the cardiac ICU: implementation of individualised developmental care. Cardiol Young 2017;27:1797-806.
63. Lisanti AJ, Vittner D, Medoff-Cooper B, Fogel J, Wernovsky G, Butler S. Individualized family-centered developmental care: an essential model to address the unique needs of infants with congenital heart disease. J Cardiovasc Nurs 2019;34:85-93.
64. Kasparian NA, Kan JM, Sood E, Wray J, Pincus HA, Newburger JW. Mental health care for parents of babies with congenital heart disease during intensive care unit admission: systematic review and statement of best practice. Early Hum Dev 2019;139:104837.
65. Krishnan A, Jacobs MB, Morris SA, Peyvandi S, Bhat AH, Chelliah A, et al. Impact of socioeconomic status, race and ethnicity, and geography on prenatal detection of hypoplastic left heart syndrome and transposition of the great arteries. Circulation 2021;143:2049-60.
66. Li YF, Zhou KY, Fang J, Wang C, Hua YM, Mu DZ. Efficacy of prenatal diagnosis of major congenital heart disease on perinatal management and perioperative mortality: a meta-analysis. World J Pediatr 2016;12:298-307.
67. Milazzo AS, Sanders SP, Armstrong BE, Li JS. Racial and geographic disparities in timing of bidirectional Glenn and Fontan stages of single-ventricle palliation. J Natl Med Assoc 2002;94:873-8.
68. Bucholz EM, Sleeper LA, Goldberg CS, Pasquali SK, Anderson BR, Gaynor JW, et al. Socioeconomic status and long-term outcomes in single ventricle heart disease. Pediatrics 2020;146:e20201240.
69. Chan T, Barrett CS, Tjoeng YL, Wilkes J, Bratton SL, Thiagarajan RR. Racial variations in extracorporeal membrane oxygenation use following congenital heart surgery. J Thorac Cardiovasc Surg 2018;156:306-15.
70. Demianczyk AC, Behere SP, Thacker D, Noeder M, Delaplane EA, Pizarro C, et al. Social risk factors impact hospital readmission and outpatient appointment adherence for children with congenital heart disease. J Pediatr 2019;205:35-40.e1.

71. Jackson JL, Morack J, Harris M, DeSalvo J, Daniels CJ, Chisolm DJ. Racial disparities in clinic follow-up early in life among survivors of congenital heart disease. Congenit Heart Dis 2019;14:305-10.
72. Mackie AS, Rempel GR, Rankin KN, Nicholas D, Magill-Evans J. Risk factors for loss to follow-up among children and young adults with congenital heart disease. Cardiol Young 2012;22:307-15.
73. Loccoh EC, Yu S, Donohue J, Lowery R, Butcher J, Pasquali SK, et al. Prevalence and risk factors associated with non-attendance in neurodevelopmental follow-up clinic among infants with CHD. Cardiol Young 2018;28:554-60.
74. Ramanan S, Sundaram S, Gopalakrishnan A, Anija DV, Sandhya P, Jose DS, et al. Intermediate-term neurodevelopmental outcomes and quality of life after arterial switch operation beyond early neonatal period. Eur J Cardiothorac Surg 2021;60:1428-36.
75. Majeed A, Rofeberg V, Bellinger DC, Wypij D, Newburger JW. Machine learning to predict executive function in adolescents with repaired d-transposition of the great arteries, tetralogy of fallot, and fontan palliation. J Pediatr 2022;246:145-53.
76. Majnemer A, Limperopoulos C, Shevell M, Rohlicek C, Rosenblatt B, Tchervenkov C. Developmental and functional outcomes at school entry in children with congenital heart defects. J Pediatr 2008;153:55-60.
77. Xiang L, Su Z, Liu Y, Huang Y, Zhang X, Li S, et al. Impact of family socioeconomic status on health-related quality of life in children with critical congenital heart disease. J Am Heart Assoc 2019;8:e010616.
78. Drakouli M, Petsios K, Giannakopoulou M, Patiraki E, Voutoufianaki I, Matziou V. Determinants of quality of life in children and adolescents with CHD: a systematic review. Cardiol Young 2015;25:1027-36.
79. McCusker CG, Doherty NN, Molloy B, Casey F, Rooney N, Mulholland C, et al. Determinants of neuropsychological and behavioural outcomes in early childhood survivors of congenital heart disease. Arch Dis Child 2007;92:137-41.
80. Wu Y, Espinosa KM, Barnett SD, Kapse A, Quistorff JL, Lopez C, et al. Association of elevated maternal psychological distress, aAltered fetal brain, and offspring cognitive and social-emotional outcomes at 18 months. JAMA Netw Open 2022;5:e229244.
81. McCusker CG, Doherty NN, Molloy B, Rooney N, Mulholland C, Sands A, et al. A controlled trial of early interventions to promote maternal adjustment and development in infants born with severe congenital heart disease. Child Care Health Dev 2010;36:110-7.
82. Burek B, Ford MK, Hooper M, Green R, Kohut SA, Andrade BF, et al. Transdiagnostic feasibility trial of internet-based parenting intervention to reduce child behavioural difficulties associated with congenital and neonatal neurodevelopmental risk: introducing I-InTERACT-North. Clin Neuropsychol 2021;35:1030-52.
83. Ware J, Butcher JL, Latal B, Sadhwani A, Rollins CK, Brosig Soto CL, et al. Neurodevelopmental evaluation strategies for children with congenital heart disease aged birth through 5 years: recommendations from the cardiac neurodevelopmental outcome collaborative. Cardiol Young 2020;30:1609-22.
84. Wallis KE, Davis Rivera LB, Guthrie W, Bennett AE, Mandell DS, Miller JS. Provider responses to positive developmental screening: disparities in referral practices? J Dev Behav Pediatr 2021;42:23-31.
85. Werner H, Latal B, Valsangiacomo Buechel E, Beck I, Landolt MA. The impact of an infant's severe congenital heart disease on the family: a prospective cohort study. Congenit Heart Dis 2014;9:203-10.
86. Fourdain S, Caron-Desrochers L, Simard MN, Provost S, Doussau A, Gagnon K, et al. Impacts of an interdisciplinary developmental follow-up program on neurodevelopment in congenital heart disease: the CINC study. Front Pediatr 2020;8:539451.
87. Michael M, Scharf R, Letzkus L, Vergales J. Improving neurodevelopmental surveillance and follow-up in infants with congenital heart disease. Congenit Heart Dis 2016;11:183-8.
88. Lopez KN, Morris SA, Sexson Tejtel SK, Espaillat A, Salemi JL. US mortality attributable to congenital heart disease across the lifespan from 1999 through 2017 exposes persistent racial/ethnic disparities. Circulation 2020;142:1132-47.
89. Nashed LM, O'Neil J. The impact of socioeconomic status and race on the outcomes of congenital heart disease. Curr Opin Cardiol 2022;37:86-90.
90. Kaltman JR, Burns KM, Pearson GD, Goff DC, Evans F. Disparities in congenital heart disease mortality based on proximity to a specialized pediatric cardiac center. Circulation 2020;141:1034-6.
91. Cox SM, Butcher JL, Sadhwani A, Sananes R, Sanz JH, Blumenfeld E, et al. Integrating telehealth into neurodevelopmental assessment: a model fFrom the Cardiac Neurodevelopmental Outcome Collaborative. J Pediatr Psychol 2022;47:707-13.
92. Mahle WT, Tavani F, Zimmerman RA, Nicolson SC, Galli KK, Gaynor JW, et al. An MRI study of neurological injury before and after congenital heart surgery. Circulation 2002;106:I109-14.

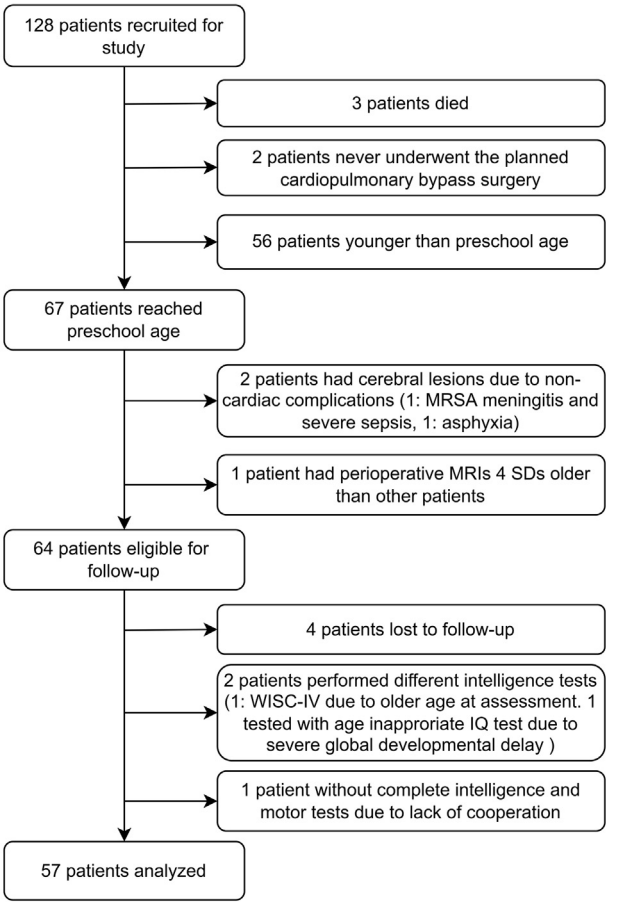

Figure 1. Flow chart of enrollment. *MRSA*, methicillin-resistant *Staphylococcus aureus*.

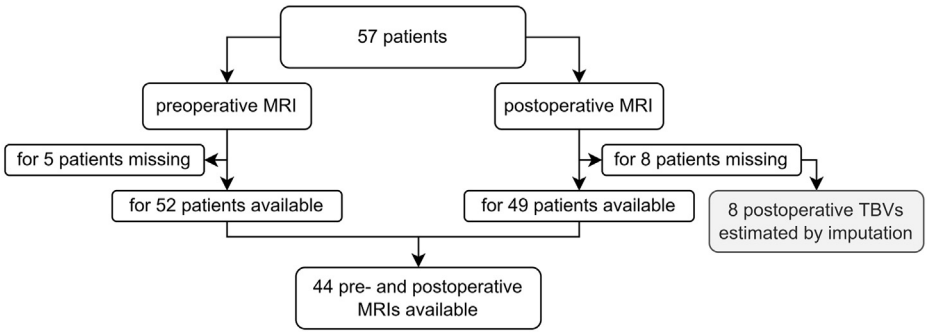

Figure 2. Availability of preoperative and postoperative MRIs.

Brain Injury Severity Score

BIS 0	BIS 1	BIS 2	BIS 3
No lesions	Mild WMI: 1-3 lesions, each <2mm in diameter IVH grade 1 or 2 according to Papile et al.: Grade 1 = Hemorrhage limited to germinal matrix, Grade 2 = Blood within the ventricular system without ventricle distention	Stroke of any size	Moderate to severe WMI: >3 lesions or any lesion >2mm in diameter

Figure 3. Brain lesions were classified using the BIS score.[16] In our cohort, intraventricular hemorrhage (IVH) grades 3 or 4 were seen on neither preoperative nor postoperative magnetic resonance images. (Grade 3 = blood in the ventricles with distension of the ventricles, grade 4 = intraventricular hemorrhage with parenchymal extension).[40]

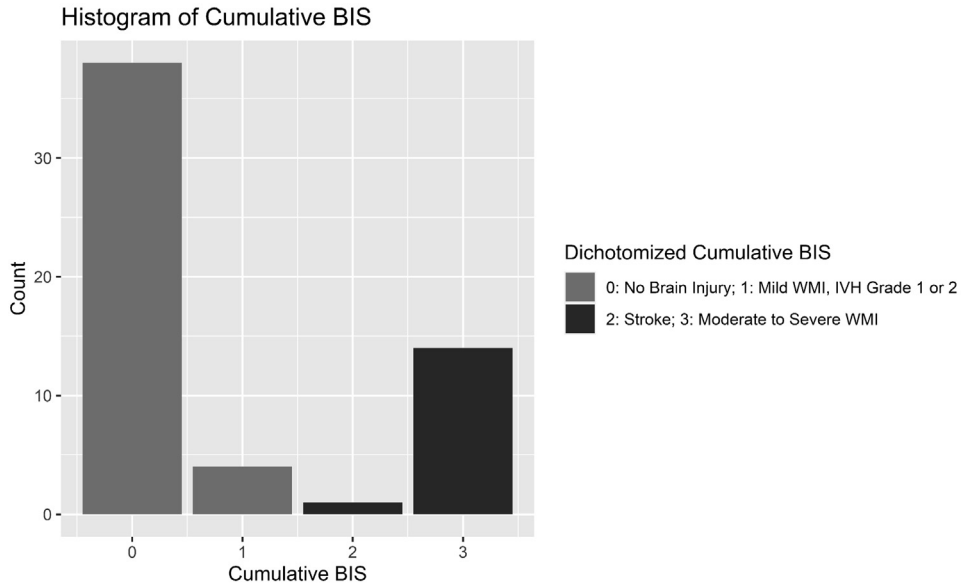

Figure 4. Histogram of the cumulative BIS score. *IVH*, intraventricular hemorrhage.

Table IV. Predictors of processing speed and motor coordination in patients with CHD at preschool age, multiple linear regression models

Dependent variables	Independent variables	B	SE B	β	t	*P*	Corrected *P**	Adjusted R^2	*P* of the whole model
Processing speed	Postoperative TBV	0.01	0.04	0.02	0.13	.90	.90	−0.03	.62
	Cumulative BIS score	7.38	4.28	0.27	1.73	.09	.46		
	CHD complexity	−1.65	2.91	−0.08	−0.57	.57	.90		
	Hospital stay (log)	1.23	4.42	0.04	0.28	.78	.90		
	SES	0.49	0.81	0.09	0.61	.55	.90		
Motor coordination	Postoperative TBV	−0.01	0.04	−0.02	−0.15	.88	.88	0.11	.13
	Cumulative BIS score	−1.53	3.54	−0.07	−0.43	.67	.83		
	CHD complexity	−3.57	2.36	−0.22	−1.52	.14	.28		
	Hospital stay (log)	−6.82	3.96	−0.26	−1.72	.09	.28		
	SES	0.93	0.67	0.21	1.40	.17	.28		

B, unstandardized beta; β, standardized beta; *SE B*, SE of unstandardized beta.
All models were controlled for MRI batch and gestational age at MRI. *P* value < .05*, <.01**, <.001***.
*Benjamini-Hochberg correction for the number of included predictors.[37]

Table V. Predictors of the IQ and total motor score in patients with CHD at preschool age, ordinal regression models for non-normal outcome variables

Dependent variables	Independent variables	B	SE B	OR	95-CI OR	*P*	Corrected *P**	Adjusted Mc Fadden's R^2
Total IQ†	Postoperative TBV	−0.01	0.01	0.99	0.98-1.00	.24	.30	0.09
	Cumulative BIS	0.22	0.56	1.25	0.41-3.80	.70	.70	
	CHD complexity	−0.69	0.38	0.50	0.22-1.10	.09	.14	
	Hospital stay (log)	−1.41	0.47	0.24	0.09-0.64	.004**	.01*	
	SES	0.56	0.13	1.75	1.37-2.28	<.001***	<.001***	
Total motor score	Postoperative TBV	0.01	0.01	1.01	1.00-1.03	.08	.39	0.01
	Cumulative BIS score	0.80	0.62	2.22	0.64-7.87	.21	.52	
	CHD complexity	0.02	0.42	1.03	0.41-2.49	.96	.96	
	Hospital stay (log)	−0.19	0.67	0.83	0.21-3.11	.78	.96	
	SES	−0.01	0.12	0.99	0.78-1.25	.91	.96	

All models were controlled for MRI batch and gestational age at MRI. *P* value < .05*, <.01**, <.001***.
*Benjamini-Hochberg correction for the number of included predictors.[37]
†The total IQ includes IQ of 54 WPPSI-III and 3 SON-R tests. Significance and direction of effects did not differ when the three subjects with SON-R were excluded from analysis.