



**HAL**  
open science

## Fetal Brain Volume Predicts Neurodevelopment in Congenital Heart Disease

Anjali Sadhwani, David Wypij, Valerie Rofeberg, Ali Gholipour, Maggie Mittleman, Julia Rohde, Clemente Velasco-Annis, Johanna Calderon, Kevin Friedman, Wayne Tworetzky, et al.

► **To cite this version:**

Anjali Sadhwani, David Wypij, Valerie Rofeberg, Ali Gholipour, Maggie Mittleman, et al.. Fetal Brain Volume Predicts Neurodevelopment in Congenital Heart Disease. *Circulation*, 2022, 145 (15), pp.1108-1119. 10.1161/CIRCULATIONAHA.121.056305 . hal-03566513

**HAL Id: hal-03566513**

**<https://hal.science/hal-03566513>**

Submitted on 15 Jun 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Fetal Brain Volume Predicts Neurodevelopment in Congenital Heart Disease

Anjali Sadhwani, PhD , David Wypij, PhD, Valerie Rofeberg, MS, Ali Gholipour, PhD , Maggie Mittleman, BS, Julia Rohde, BA, Clemente Velasco-Annis, BS, Johanna Calderon, PhD , Kevin G. Friedman, MD, Wayne Tworetzky, MD, P. Ellen Grant, MD , Janet S. Soul, MDCM , Simon K. Warfield, PhD , Jane W. Newburger, MD, MPH , Cynthia M. Ortinau, MD\*, and Caitlin K. Rollins, MD, SM

Department of Psychiatry and Behavioral Sciences (A.S., J.C.),

Boston Children's Hospital, MA. Department of Cardiology (D.W., V.R., K.G.F., W.T., J.W.N.),

Boston Children's Hospital, MA. Department of Radiology (A.G., C.V.-A., P.E.G., S.K.W.),

Boston Children's Hospital, MA. Department of Neurology (M.M., J.R., J.S.S., C.K.R.),

Boston Children's Hospital, MA. Department of Psychiatry (A.S., J.C.),

Harvard Medical School, Boston, MA. Department of Radiology (A.G., P.E.G., S.K.W.),

Harvard Medical School, Boston, MA. Department of Pediatrics (D.W., K.G.F., W.T., J.W.N.),

Harvard Medical School, Boston, MA. Department of Neurology (J.S.S., C.K.R.),

Harvard Medical School, Boston, MA. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA (D.W.).

Department of Pediatrics, Washington University in St Louis, MO (C.M.O.).

## Key Words:

brain ■ heart defects, congenital ■ magnetic resonance imaging

\* C.M. Ortinau and C.K. Rollins contributed equally.

## Correspondence

Correspondence to: Caitlin K. Rollins, MD, SM, 300 Longwood Avenue, Boston, MA 02115.  
Email [caitlin.rollins@childrens.harvard.edu](mailto:caitlin.rollins@childrens.harvard.edu)

## **Background:**

Neurodevelopmental impairment is common in children with congenital heart disease (CHD), but postnatal variables explain only 30% of the variance in outcomes. To explore whether the antecedents for neurodevelopmental disabilities might begin in utero, we analyzed whether fetal brain volume predicted subsequent neurodevelopmental outcome in children with CHD.

## **Methods:**

Fetuses with isolated CHD and sociodemographically comparable healthy control fetuses underwent fetal brain magnetic resonance imaging and 2-year neurodevelopmental evaluation with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) and the Adaptive Behavior Assessment System, Third Edition (ABAS-3). Hierarchical regression evaluated potential predictors of Bayley-III and ABAS-3 outcomes in the CHD group, including fetal total brain volume adjusted for gestational age and sex, sociodemographic characteristics, birth measures, and medical history.

## **Results:**

The CHD group (n=52) had lower Bayley-III cognitive, language, and motor scores than the control group (n=26), but fetal brain volumes were similar. Within the CHD group, larger fetal total brain volume correlated with higher Bayley-III cognitive, language, and motor scores and ABAS-3 adaptive functioning scores ( $r=0.32-0.47$ ; all  $P<0.05$ ), but this was not noted in the control group. Fetal brain volume predicted 10% to 21% of the variance in neurodevelopmental outcome measures in univariate analyses. Multivariable models that also included social class and postnatal factors explained 18% to 45% of the variance in outcome, depending on developmental domain. Moreover, in final multivariable models, fetal brain volume was the most consistent predictor of neurodevelopmental outcome across domains.

## **Conclusions:**

Small fetal brain volume is a strong independent predictor of 2-year neurodevelopmental outcomes and may be an important imaging biomarker of future neurodevelopmental risk in CHD. Future studies are needed to support this hypothesis. Our findings support inclusion of fetal brain volume in risk stratification models and as a possible outcome in fetal neuroprotective intervention studies.

--

## Nonstandard Abbreviations and Acronyms

<b>ABAS-3</b>	Adaptive Behavior Assessment System, Third Edition
<b>Bayley-III</b>	Bayley Scales of Infant and Toddler Development, Third Edition
<b>CHD</b>	congenital heart disease
<b>MRI</b>	magnetic resonance imaging

## Clinical Perspective

### What Is New?

- In children with congenital heart disease, smaller total brain volume on fetal magnetic resonance imaging correlated with worse neurodevelopmental outcome at 2 years of age across all domains of development and adaptive functioning.
- A predictive model including total brain volume along with sociodemographic and medical data accounted for up to 45% of the variance in neurodevelopmental outcome within the congenital heart disease group.
- Fetal brain volume was the most consistent predictor of outcomes across neurodevelopmental domains compared with other sociodemographic and medical or surgical variables examined.

### What Are the Clinical Implications?

- These findings suggest that small fetal brain volume may be an important imaging biomarker of future neurodevelopmental risk in congenital heart disease.
- Our hypothesis-generating results support testing the effectiveness of fetal interventions to protect the brain and improve the developmental trajectory for children with congenital heart disease.

Neurodevelopmental impairment is common in children with congenital heart disease (CHD). Young children with CHD are at greater risk for impaired cognitive, language, or motor development; school-aged children often present with deficits in executive functioning, attention, visual-spatial skills, and social cognition.<sup>1–5</sup> Given the high prevalence and impact of developmental disabilities, in 2012 the American Heart Association issued a statement recommending neurodevelopmental evaluation of all children who have undergone open heart surgery in infancy.<sup>6</sup>

Early identification of children with CHD at highest risk of neurodevelopmental impairment may improve outcome.<sup>7–9</sup> However, predictive models from large prospective cohorts with comprehensive data collection, including the Boston Circulatory Arrest Trial and Single Ventricle Reconstruction Trial, have shown that sociodemographic, genetic, and medical factors measured after birth predict only 27% to 30% of the variance in outcome.<sup>1,2,10</sup> Moreover, intervention studies concentrating on changing surgical methods have revealed only modest improvements in clinical outcome.<sup>1</sup>

Magnetic resonance imaging (MRI) studies of neonates and fetuses with CHD indicate altered brain development before cardiac surgery<sup>11,12</sup> and small brain volumes in utero.<sup>13–16</sup> Because postnatal neuroimaging abnormalities have been associated with adverse neurodevelopmental outcome,<sup>17,18</sup> it is possible that abnormal prenatal brain MRI findings reflecting disrupted fetal brain development may also relate to subsequent neurodevelopment. Establishing an association between fetal brain development and neurodevelopmental outcome would provide initial evidence for fetal brain disturbances as a mechanism of neurodevelopmental impairment.

We performed the first longitudinal study investigating the relationship between fetal brain MRI and postnatal neurodevelopment in CHD. In this hypothesis-generating study, we prospectively enrolled fetuses with and without CHD to evaluate the association between fetal brain volumes and 2-year neurodevelopment. We hypothesized that fetal brain volumes would explain a significant portion of the variance in neurodevelopmental outcome in the CHD group.

## Methods

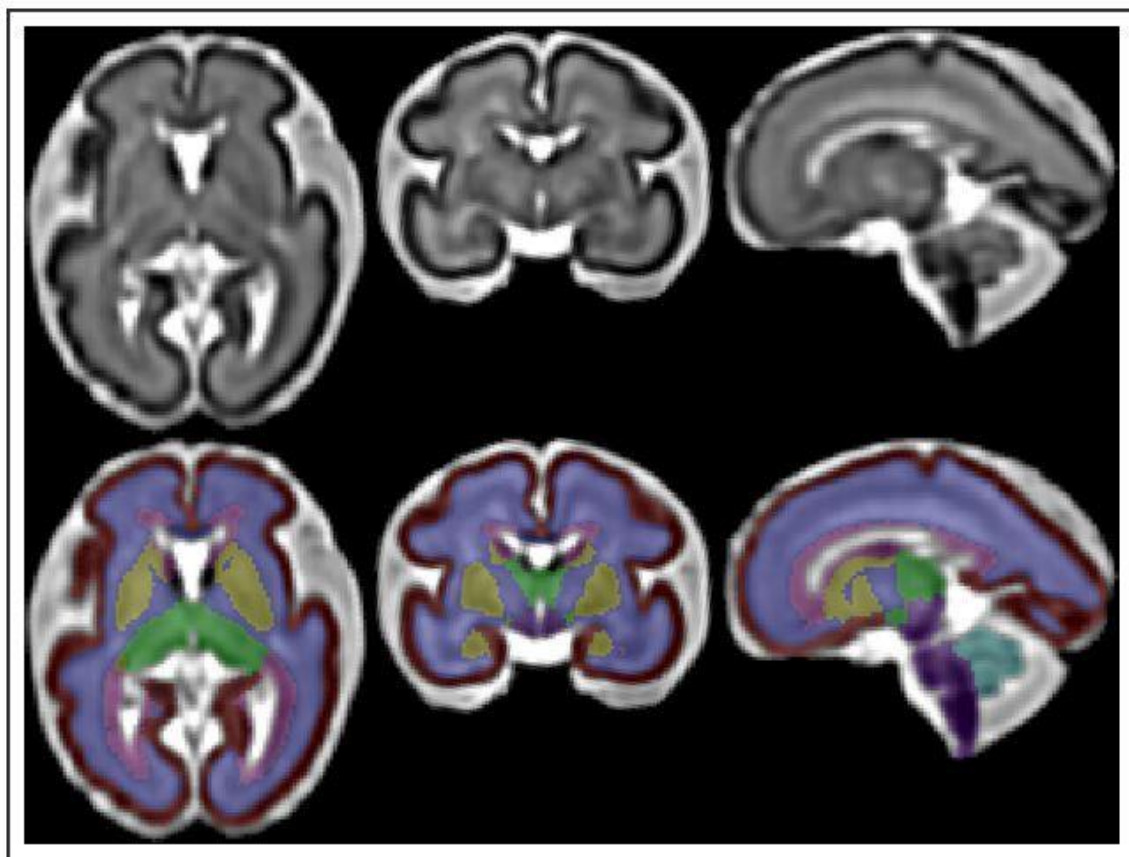
### Study Design and Participants

We analyzed data from a prospective, longitudinal fetal brain MRI and neurodevelopment study. Eligibility criteria and methods for the fetal MRI portion were published previously.<sup>15</sup> Briefly, fetuses with isolated CHD and healthy control fetuses with a family history of CHD participated. Inclusion criteria for enrollment were maternal age during pregnancy of 18 to 45 years and fetal gestational age of 18 to 30 weeks. Exclusion criteria encompassed both maternal and fetal factors. Maternal exclusion criteria were multiple gestation pregnancy, maternal CHD, MRI contraindication, or clinician deemed inappropriate (eg, considering termination). Fetal exclusion criteria were trivial/mild CHD as defined by Hoffman and Kaplan,<sup>19</sup> extracardiac anomaly, brain malformation, known genetic abnormality, or clinically detected congenital infection. To be eligible for the neurodevelopment study, a participant also had to have available data from at least 1 fetal brain MRI (ie, a fetus with only motion-corrupted scans was not eligible), and the child must have undergone either in-person or questionnaire-based neurodevelopmental assessment. Participants were excluded from the analysis if they were diagnosed with a genetic abnormality after birth before their

neurodevelopmental evaluation. Enrollment in the study ended in March 2020 owing to safety concerns and the unknown effects of personal protective equipment on test interpretation in the setting of COVID-19. The Boston Children's Hospital Institutional Review Board approved the study and parents provided written informed consent. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure from the corresponding author on request.

### **MRI Acquisition and Processing**

Whereas the longitudinal study included multiple fetal brain MRIs, for the current study, we analyzed the first fetal brain MRI from which usable data were obtained. We acquired multiplanar repeated T2-weighted single-shot fast spin echo sequences on a 3-Tesla Siemens MRI scanner and processed images with our in-house built software for super-resolution volume reconstruction and semiautomated atlas-based segmentation to calculate regional and total brain volumes; details have been described previously (Figure 1).<sup>15,20,21</sup> Total brain volume included all parenchymal brain tissue and excluded cerebrospinal fluid.<sup>15</sup> MRIs were reviewed for incidental findings.



**Figure 1. Reconstructed fetal brain magnetic resonance imaging at 28 weeks.** Reconstructed fetal brain magnetic resonance imaging at 28 weeks in axial (**left**), coronal (**middle**), and sagittal (**right**) planes with brain structures segmented in the bottom row (red, fetal cortex; indigo, white matter; yellow, subcortical gray matter; green, diencephalon; purple, brainstem; turquoise, cerebellum).



## Two-Year Neurodevelopmental Evaluation

Children underwent neurodevelopmental assessment at 18 to 24 months of age. An intake questionnaire ascertained patient and family demographic characteristics. The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III),<sup>22</sup> a standardized measure of development, was administered by a licensed clinical psychologist (A.S.). When possible, the psychologist was blind to the child's health status. However, in some cases, the parents disclosed their child's heart condition or it was revealed as part of clinical care (33% of the CHD group). Composite scores (mean±SD, 100±15) and subscale scores (10±3) for the cognitive, language, and motor domains were calculated. Parents completed the Adaptive Behavior Assessment System, Third Edition (ABAS-3),<sup>23</sup> a standardized questionnaire assessing observed adaptive functioning at home, from which we calculated the composite score for overall adaptive functioning (General Adaptive Composite). To evaluate clinical factors that may be associated with neurodevelopmental outcome, birth measures (eg, birth weight), cardiac anatomy, and neurologic data (eg, stroke/seizure) were extracted through chart review.

## Statistical Analyses

To account for dramatic growth in the fetal brain that occurs over gestation<sup>15</sup> and varying gestational age at MRI, as well as sex differences in brain structure that emerge in utero,<sup>24</sup> total brain volumes were adjusted for sex and linear and quadratic gestational age at MRI. The residual total brain volume reflects the difference between the individual's total brain volume and the expected value on the basis of the linear regression equation. A patient whose brain size was smaller than predicted by linear regression for a given gestational age and sex would have a negative residual total brain volume, whereas a fetus whose brain size was larger than expected on the basis of the regression equation would have a positive residual. These residual total brain volumes were used throughout all analyses and are subsequently referred to as total brain volume for simplicity.<sup>15</sup> Correlations and interaction models assessed potential effect modification of total brain volume on neurodevelopmental outcomes by group (CHD vs control).

For our regression models, we considered several potential clinical predictors of neurodevelopmental outcome on the basis of previous research: primary caregiver education, White race, male sex, single ventricle anatomy, diagnosis of hypoplastic left heart syndrome or transposition of the great arteries, cardiac class on the basis of cardiac anatomy (2-ventricle vs single ventricle physiology, with or without arch obstruction),<sup>25</sup> birth weight, gestational age at birth, length of stay at first hospitalization, stroke, seizure, total support duration during cardiopulmonary bypass, extracorporeal membrane oxygenation, and age at first surgery >30 days (vs ≤30 days). When predictors demonstrated a high degree of collinearity, 1 factor was chosen to consider in regression modeling. For example, birth weight was chosen for inclusion rather than gestational age because of limited variability in gestational age in this cohort, the likelihood that birth weight provided additional information reflective of maternal environment, and data from the Single Ventricle Reconstruction Trial suggesting that birth weight may have a greater association with neurodevelopmental outcome.<sup>26</sup> Cardiac class was chosen as a single variable to classify cardiac anatomy because of its capture of both ventricular status and systemic outflow tract obstruction and known association with neurodevelopmental outcomes.<sup>1</sup>

For the primary hierarchical regression models for the CHD group, we started with fetal total brain volume, as this was the variable of major interest, then considered additional candidate variables separated into stages to reflect the order in which data become available. Stage 1 included fetal total brain volume, stage 2 included demographic characteristics (primary caregiver education, race, and fetal sex), stage 3 included cardiac class, stage 4 included birth weight, and stage 5 included postnatal medical variables (age at first surgery, total support time, stroke or seizure, extracorporeal membrane oxygenation, and length of stay). To enter the model, candidate variables at each stage were required to improve the Akaike information criterion and have a positive partial  $R^2$ . Variables that entered the model for a given stage were retained in later stages. To display the hierarchical regression results graphically, we calculated the relative contribution of each variable to the total adjusted  $R^2$  by dividing the adjusted partial  $R^2$  by the sum of the positive adjusted partial  $R^2$ s, then scaling by the total adjusted  $R^2$  of the model.

We also used 2 alternative regression analysis approaches to address the possibility that the primary analysis approach could amplify the predictive value of fetal brain MRI because of its early introduction to the model and retention by design in subsequent stages. For the first alternative approach, alternative hierarchical regression, we based the introduction of all variables on the order in which data would become clinically available: stage 1: demographic characteristics; stage 2: cardiac class; stage 3: fetal total brain volume; stage 4: birth weight; and stage 5: postnatal medical variables. For the second alternative approach, stepwise forward selection, we applied stepwise forward selection regression models on the basis of significant improvement in the Akaike information criterion with no restriction on the ordering of which variables to include.

## Results

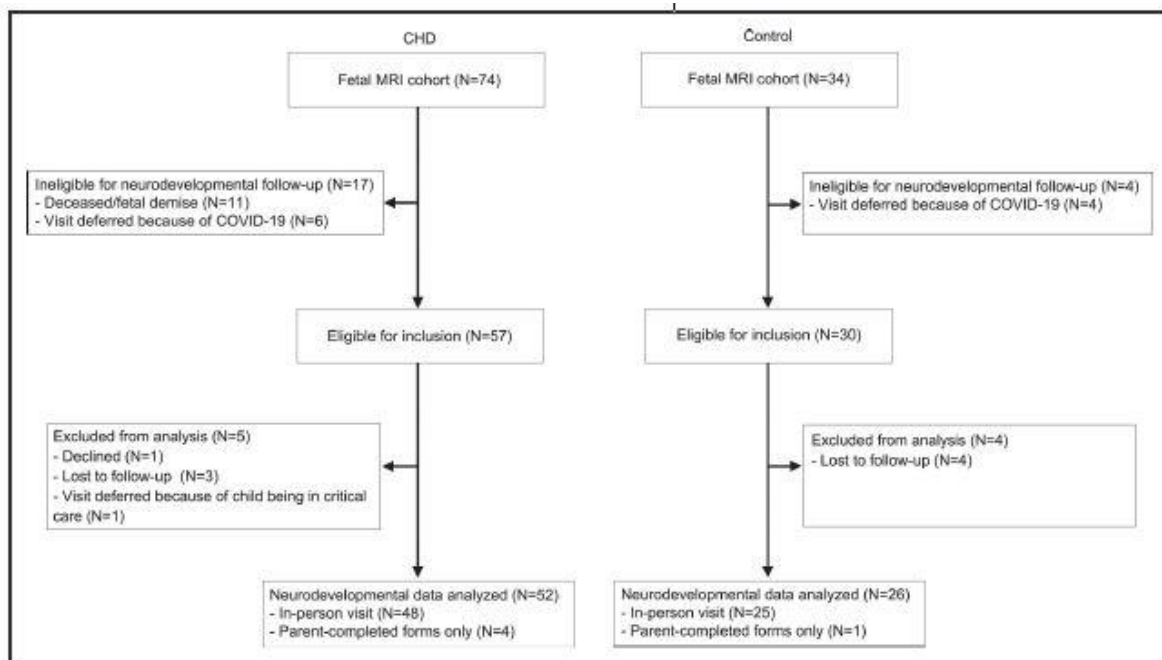
### Demographic and Medical Characteristics

Of 90 participants eligible for neurodevelopmental follow-up, 78 (52 CHD, 26 control) completed the assessment (retention rate, 87%; [Figure 2](#)). In the CHD group, patients who returned for follow-up had higher gestational age at birth compared with those who did not ( $38.6 \pm 1.6$  vs  $37.1 \pm 2.4$  weeks;  $P=0.04$ ). In the control group, participants who returned had older mothers ( $32.5 \pm 4.1$  vs  $26.5 \pm 3.0$  years;  $P=0.01$ ) who were more likely to be college educated (69% vs 0%;  $P=0.01$ ) than those who did not. Other fetal and maternal characteristics and brain volumes were comparable between those who did and did not return.

### Neurodevelopmental Assessment

Neurodevelopmental assessment occurred between June 2016 and March 2020 and all questionnaires were returned by May 2020. Mean age at assessment was comparable between groups (CHD,  $22.9 \pm 4.3$  months; control,  $24.1 \pm 4.2$ ;  $P=0.24$ ). On the Bayley-III, the CHD group had lower cognitive, language, and motor composite scores compared with the control group ( $d=-6.8, -12.9, -9.7$  points; all  $P<0.05$ ; [Table 2](#)). A greater proportion of the CHD group scored  $\geq 1$  SD below the normative mean than the control group in both the language and motor composites (CHD, 17%, 21%; control, 4%, 0%). Across all subscales (ie, expressive language, receptive language, gross motor, fine motor), the CHD group had significantly lower scores than the control group. The CHD group trended toward worse adaptive functioning (measured by the General Adaptive Composite) than the control group, although this difference did not reach statistical significance ( $P=0.06$ ).





**Figure 2. Recruitment and retention by group.** Recruitment, exclusions, and neurodevelopmental assessment by group. CHD indicates congenital heart disease; and MRI, magnetic resonance imaging.

### Relationship Between Fetal Brain MRI and Neurodevelopmental Outcome

We examined relationships between total brain volume and neurodevelopmental outcomes separately in the CHD and control groups and evaluated group interactions. Within the CHD group, larger total brain volume correlated with higher Bayley-III and ABAS-3 General Adaptive Composite scores ( $r=0.32-0.47$ ;  $P<0.05$ ; [Figure 3](#) and [Table 3](#)). In contrast, for the control group, total brain volume did not correlate with any outcome measure. Stronger associations of total brain volume with neurodevelopmental outcomes in the CHD group compared with the control group were especially evident for the Bayley-III gross motor and ABAS-3 General Adaptive Composite scores.

**Table 1.** Demographic and Medical Characteristics (Table view)

Characteristics	CHD (n=52)	Control (n=26)
<b>Maternal characteristics</b>		
Maternal age, y	31.9±4.7	32.5±4.1
<b>Race/ethnicity</b>		
White	42 (81)	22 (85)
Black/African American	3 (6)	2 (8)
Other/unknown*	7 (13)	2 (8)
Hispanic ethnicity	7 (13)	4 (15)
Education, college or greater	35 (67)	18 (69)
<b>Fetal characteristics</b>		
Male sex	33 (63)	15 (58)
Gestational age at MRI, wk	28.1±3.8	29.0±4.4
Total brain volume per mL†	-0.9±12.6	1.7±10.8
<b>Postnatal characteristics</b>		
Gestational age at birth, wk	38.6±1.6	39.2±1.4
Head circumference, cm	33.8±1.9	34.5±1.4
<b>Cardiac class</b>		
I	22 (42)	—
II	13 (25)	—
III	8 (15)	—
IV	9 (17)	—
Birth weight, kg	3.2±0.6	3.5±0.6
Age at first surgery, d	9 (3, 44)	—
Total support time, min	133 (75, 203)	—
Stroke or seizure	6 (12)	0
ECMO	2 (4)	—

Values are mean±SD, n (%), or median (interquartile range). CHD indicates congenital heart disease; ECMO, extracorporeal membrane oxygenation; and MRI, magnetic resonance imaging.

\*Other/Unknown includes Asian, multiracial, and patients who either did not self-identify with any of the listed options or preferred not to state.

† Total brain volume refers to residual after adjustment of fetal total brain volume for sex and gestational age (linear and quadratic terms).

Table 1 shows demographic and medical characteristics. Maternal hyperoxygenation was not administered to any participant. Within the CHD group, 32% had single ventricle heart disease, 8% had fetal cardiac intervention, and 63% underwent neonatal surgery. Table S1 reports the diagnosis and cardiac intervention for each participant. Median length of first hospital stay was 21 days. The CHD group had slightly lower birth weight than the control group, but otherwise the 2 groups had comparable maternal, fetal, and postnatal characteristics. The gestational age range at fetal brain MRI was 20 to 37 weeks. There were no group differences in total brain volume and no fetus had parenchymal brain injury on MRI.

**Table 2.** Neurodevelopmental Outcomes of Study Participants ([Table view](#))

Outcome	CHD	Control	Difference (95% CI)
Bayley-III	n=48	n=25	
Cognitive composite	99.4±9.9	106.2±14.6	-6.8 (-12.6, -1.1)
≤85	3 (6)	0	
Language composite	96.1±13.2	109.0±18.2	-12.9 (-20.3, -5.5)
≤85	8 (17)	1 (4)	
Receptive communication	9.8±2.6	12.2±3.5	-2.4 (-3.8, -0.9)
Expressive communication	8.8±2.4	10.8±3.1	-2.0 (-3.3, -0.7)
Motor composite	93.6±11.3	103.2±10.5	-9.7 (-15.1, -4.3)
≤85	10 (21)	0	
Fine motor	9.8±2.1	11.0±2.1	-1.2 (-2.3, -0.2)
Gross motor	8.1±2.2	10.0±2.1	-2.0 (-3.0, -0.9)
ABAS-3	n=45	n=25	
General adaptive composite	103.1±13.0	108.8±10.1	-5.7 (-11.5, 0.2)
≤85	6 (13)	0	

ABAS-3 indicates Adaptive Behavior Assessment System, Third Edition; Bayley-III, Bayley Scales of Infant Development, Third Edition; and CHD, congenital heart disease.

**Table 3.** Correlations Between Regional Brain Volume Residuals and Neurodevelopmental Outcomes in the CHD Group (Table view)

Brain volume	Bayley-III					ABAS-3
	Cognitive composite	Receptive communication	Expressive communication	Fine motor	Gross motor	General Adaptive Composite

Brain volume	Bayley-III					ABAS-3
	Cognitive composite	Receptive communication	Expressive communication	Fine motor	Gross motor	General Adaptive Composite
Total brain volume (per mL)*	0.40‡	0.32†	0.40‡	0.41‡	0.42‡	0.47§
Fetal cortex	0.36†	0.29†	0.23	0.43‡	0.34†	0.43‡
All white matter	0.33†	0.26	0.41‡	0.31†	0.36†	0.39‡
Proliferative compartments	0.30†	0.21	-0.02	0.44‡	0.27	0.31†
Subcortical gray matter	0.30†	0.24	0.42‡	0.13	0.30†	0.16
Diencephalon	0.11	0.17	0.33†	0.11	0.17	0.13
Brainstem	0.16	0.16	0.17	0.18	0.28	0.31†
Cerebellum	0.22	0.25	0.41‡	0.22	0.31†	0.25

ABAS-3 indicates Adaptive Behavior Assessment System, Third Edition; Bayley-III, Bayley Scales of Infant Development, Third Edition; and CHD, congenital heart disease.

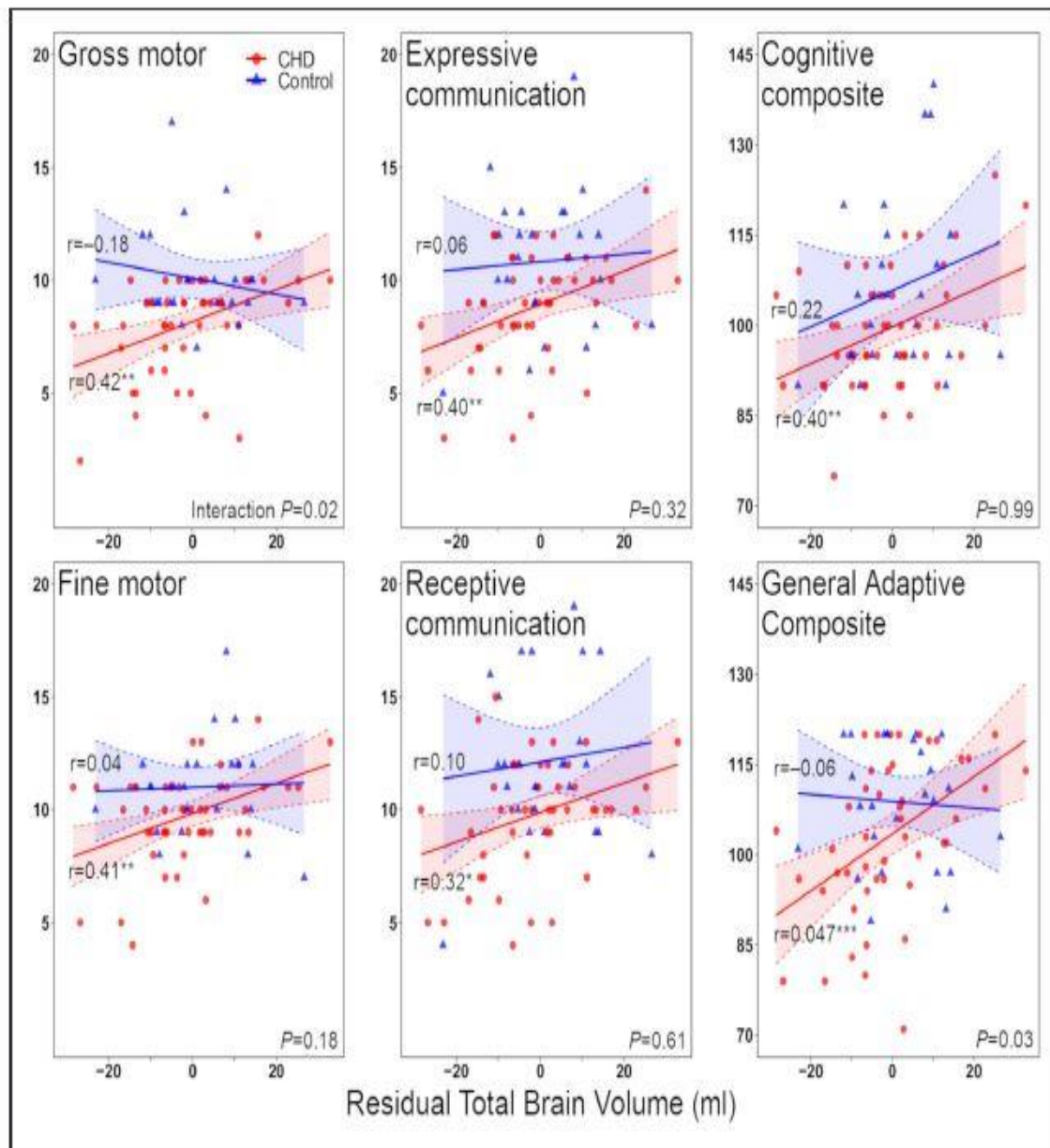
\* Total brain volume refers to residual after adjustment of fetal total brain volume for sex and gestational age (linear and quadratic terms).

†  $P < 0.05$ .

‡  $P < 0.01$ .

§  $P < 0.001$ .





**Figure 3.** Associations between fetal total brain volume residuals and neurodevelopmental outcomes

Congenital heart disease (CHD) group is shown in red; control group, in blue. Total brain volume refers to residual after adjustment of fetal total brain volume for sex and gestational age (linear and quadratic terms).

Within-group correlations are shown. Interaction term significance is shown in the bottom right corner of each pane. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ .

**Table 4.** Final Hierarchical Regression Models to Predict Neurodevelopmental Outcomes in the CHD Group (Table view)

Outcome	$\beta$ coefficient (95% CI)	Partial adjusted R <sup>2</sup>	Total adjusted R <sup>2</sup>
<b>Bayley-III</b>			
<b>Cognitive composite</b>			
Total brain volume (per mL)*	0.28 (0.08, 0.48)	0.14	0.32
White race	1.85 (-5.80, 9.50)	-0.02	
Stroke or seizure	7.20 (-3.05, 17.45)	0.02	
Length of stay (per day)	-0.10 (-0.19, -0.02)	0.17	
<b>Language composite</b>			
Total brain volume (per mL)*	0.32 (0.03, 0.60)	0.08	0.22
Education, college or greater†	8.95 (1.48, 16.42)	0.09	
<b>Motor composite</b>			
Total brain volume (per mL)*	0.32 (0.09, 0.55)	0.16	0.39
Male sex	-3.79 (-9.93, 2.35)	0.01	
Cardiac class II	0.34 (-7.02, 7.69)	0.03	
Cardiac class III	-7.88 (-16.37, 0.61)	—	
Cardiac class IV	-4.45 (-13.15, 4.24)	—	
Length of stay (per day)	-0.10 (-0.19, -0.01)	0.10	
ECMO	-9.92 (-23.82, 3.98)	0.03	
<b>Receptive communication</b>			
Total brain volume (per mL)*	0.05 (-0.002, 0.11)	0.06	0.18
Education, college or greater†	1.75 (0.25, 3.25)	0.09	

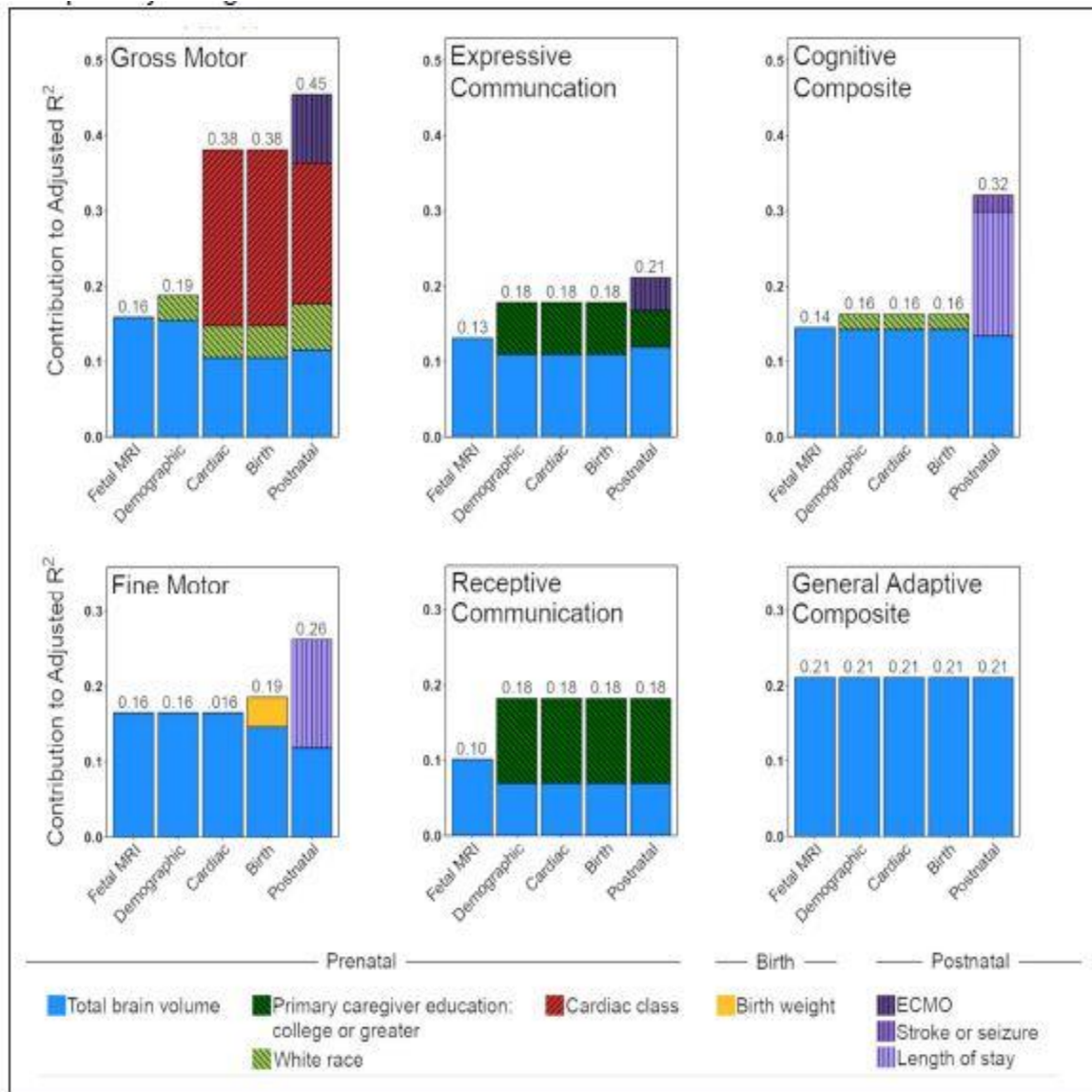
Outcome	$\beta$ coefficient (95% CI)	Partial adjusted R <sup>2</sup>	Total adjusted R <sup>2</sup>
<b>Expressive communication</b>			
Total brain volume (per mL)*	0.06 (0.014, 0.12)	0.11	0.21
Education, college or greater†	1.19 (-0.17, 2.54)	0.05	
ECMO	-2.61 (-5.71, 0.49)	0.04	
<b>Fine motor</b>			
Total brain volume (per mL)*	0.05 (0.003, 0.10)	0.08	0.26
Male sex	0.49 (-0.53, 1.51)	-0.001	
Length of stay (per day)	-0.02 (-0.04, -0.003)	0.10	
<b>Gross motor</b>			
Total brain volume (per mL)*	0.06 (0.02, 0.10)	0.15	0.45
White race	1.39 (0.09, 2.70)	0.08	
Cardiac class II	-0.44 (-1.62, 0.75)	0.25	
Cardiac class III	-2.53 (-3.99, -1.06)	—	
Cardiac class IV	-1.98 (-3.32, -0.64)	—	
ECMO	-3.12 (-5.54, -0.71)	0.12	
<b>ABAS-3 General Adaptive Composite</b>			
Total brain volume (per mL)*	0.49 (0.22, 0.76)	0.21	0.21

ABAS-3 indicates Adaptive Behavior Assessment System, Third Edition; Bayley-III, Bayley Scales of Infant Development, Third Edition; CHD, congenital heart disease; and ECMO, extracorporeal membrane oxygenation.

\* Total brain volume refers to residual after adjustment of fetal total brain volume for sex and gestational age (linear and quadratic terms).

† Education refers to primary caregiver education.





**Figure 4.** Bar plots depicting the contribution to the variance explained by each set of predictors in hierarchical regression models for each developmental domain. Stage 1 included fetal total brain volume residual; stage 2 could add demographic information (primary caregiver education, race, or fetal sex); stage 3 could add cardiac class; stage 4 could add birth weight; and stage 5 could add postnatal medical variables (eg, total support time, stroke or seizure, extracorporeal membrane oxygenation [ECMO], or length of stay). MRI indicates magnetic resonance imaging.

### Hierarchical Regression of Fetal Brain Volume and Neurodevelopment

Hierarchical regression models identified risk factors associated with lower Bayley-III and ABAS-3 scores in the CHD group. Total brain volume at the first (univariable) stage explained 10% to 21% of the variance across developmental domains, dropping slightly to 6% to 21% after including all other risk factors (Table 4 and Figure 4). Final hierarchical models including total brain volume and other significant risk factors explained 18% to 45% of the variance in neurodevelopmental scores. The highest percentage of explained variance was in the gross motor domain (45%), with total brain volume accounting for 15% of the variance.

For adaptive functioning, total brain volume was the only significant predictor, accounting for 21% of the variance. Different clinical factors contributed to the models for each developmental domain. For example, primary caregiver education accounted for 5% and 9% of the variance in expressive and receptive language scores, respectively, and cardiac class accounted for 25% of the variance in gross motor scores. The percent variance contributed by the fetal brain did not appreciably change with either the clinically based alternative hierarchical regression approach or the stepwise forward selection approach on the basis of the Akaike information criterion. Total brain volume predicted 6% to 21% of the variance in neurodevelopmental scores for both of these final models (Tables S2 and S3).

## Discussion

Recent reports have shown brain dysmaturity in fetuses with CHD, yet the extent to which fetal brain development impacts later neurodevelopment has not been studied. This hypothesis generating study sought to evaluate whether fetal brain volume predicts 2-year neurodevelopment using a cohort of fetuses with isolated CHD and a sociodemographically comparable control group. Fetal total brain volume correlated with scores in all neurodevelopmental domains assessed in the CHD group, but not the control group. A predictive model including total brain volume along with sociodemographic and medical data accounted for up to 45% of the variance in neurodevelopmental outcome within the CHD group. These findings suggest that small fetal brain volume in CHD may be an important imaging biomarker of future neurodevelopmental risk. The findings highlight the need for studies to assess the role of fetal brain volume as an imaging biomarker, its mechanisms, and its validity as an outcome marker for fetal neuroprotective intervention trials.

This study is the first to show a direct relationship between fetal brain MRI measures and neurodevelopmental outcome in CHD. Fetal brain volume alone predicted 10% to 21% of the variance in neurodevelopment scores in the hierarchical regression models and remained a significant predictor in all domains after accounting for other known prenatal and postnatal risk factors. Although these associations were observed across all domains of development, age 2 years is early in the developmental trajectory; thus, definitive conclusions cannot be made about associations between fetal brain volume and long-term functioning. Further study of this cohort is underway to determine whether these associations persist at school age. Fetal brain volume was the only variable that predicted adaptive functioning, for which it explained 21% of the variance. This finding is of particular interest given that deficits in functional outcomes (eg, self care, communication, and social skills) often persist throughout life.<sup>27</sup>

Our results build on existing literature suggesting a relationship between fetal brain health and subsequent outcomes. Williams and colleagues<sup>28,29</sup> found that in utero cerebrovascular resistance was associated with Bayley-III neurodevelopment scores in CHD, although the relationship varied depending on cardiac class. An exploratory study of at-risk fetuses, including 12 with CHD, found an association between ultrasound-based fetal brain measures and questionnaire-based neurodevelopment.<sup>30</sup> In other populations, such as preterm populations and older children with CHD, brain MRI measures have been associated with long-term brain structure and neurodevelopment.<sup>18,31–34</sup>

We used a hierarchical regression approach for primary analysis in this study, first assessing the predictive value of fetal brain volume (the variable of interest) and then sequentially adding other prenatal, birth, and postnatal data. We adopted this approach because we sought to identify biomarkers of neurodevelopmental risk that could be deployed for prenatal counseling or antenatal medical care, when birth and postnatal medical data would not be available. The results appear robust to analysis approach; 2 alternative approaches, a clinically based alternative hierarchical regression model and a stepwise forward selection model, yielded similar results.

This study was not designed to determine the underlying mechanisms contributing to impaired fetal brain growth and neurodevelopmental impairment, but existing literature suggests several possibilities. The developing fetal brain is highly dependent on cerebral oxygen/nutrient delivery and may be particularly vulnerable to physiologic disturbances.<sup>35,36</sup> Abnormal cardiac anatomy can directly reduce oxygen/nutrient delivery to fetal brain; lower oxygen consumption has been associated with smaller brain size in CHD.<sup>16</sup> The importance of fetal cerebral hemodynamics is supported by variation in fetal brain growth among congenital heart lesions with differing physiologies. A previous analysis of the current cohort found that fetuses with hypoplastic left heart syndrome and transposition of the great arteries, diagnoses with the greatest disruption in prenatal brain oxygen/nutrient delivery, displayed the most significant reductions in regional brain volumes.<sup>15</sup> Single ventricle status was also associated with smaller total brain volume. Although the current study was not powered to investigate differences by diagnosis, those within class III and IV (single ventricle anatomy) had the lowest gross motor scores. In the current study, fetal brain volume accounted for a greater percentage of variance in neurodevelopmental outcome than cardiac class.

Placental abnormalities may also affect the developing brain,<sup>37</sup> with maternal factors that are more common in CHD pregnancies (eg, preeclampsia, diabetes) influencing placental development and function that may enhance physiologic disturbances.<sup>38–40</sup> Socioeconomic factors may contribute to an adverse maternal–fetal environment through maternal comorbidities such as smoking or diabetes that alter placental physiology or social determinants of health (eg, access to care, home environment).<sup>41–43</sup> Regardless of mechanism, our data suggest that fetal brain volume may be a useful biomarker for future fetal neuroprotection trials addressing these different physiologic pathways.

Beyond the physiologic environment, genetic factors are a potential contributor to fetal brain dysmaturity in CHD. Shared genetic pathways may alter both heart and brain development; for example, through single gene disorders (eg, CHARGE syndrome [coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities]), copy number variants (eg, DiGeorge syndrome), or gene variants with milder phenotypes.<sup>44</sup> The current study excluded children with known extracardiac or genetic abnormalities, lowering the likelihood that major genetic abnormalities would account for the associations in our data. Total brain volumes in fetuses with and without CHD were similar. However, universal genetic testing was not a part of this study. Damaging de novo or rare variants affecting heart and brain development may be present in our cohort and contribute to associations between brain volume and neurodevelopment.

The control group provides additional insight into the association between fetal brain volume and neurodevelopment. This group comprised healthy fetuses with a family history of CHD (usually a father or sibling<sup>15</sup>) who shared similar sociodemographic characteristics to the CHD group and had similar brain volumes. Within the control group, brain volume did not

correlate with neurodevelopment; in the CHD group, it did. Because sociodemographic variables were comparable, and a family history of CHD may provide some overlap in genetic background and in utero/maternal factors between the groups, our findings are consistent with the hypothesis that fetal circulatory derangements directly or indirectly account for the association between fetal brain volume and neurodevelopmental outcome. This hypothesis is supported by our previous findings that fetuses expected to have the lowest fetal cerebral oxygen/nutrient delivery have the most marked disturbances in fetal brain growth, particularly in regions known to be sensitive to hypoxia.<sup>15</sup>

The current study underscores the well-known multifactorial etiology of neurodevelopmental impairment in CHD. Multivariable models explained up to 45% of the variance in neurodevelopmental outcomes, a substantial advance beyond postnatal studies, which explained 30% of the variance at most.<sup>1,2</sup> In accordance with existing literature, cardiac anatomy, maternal education, and length of stay all contributed to models predicting neurodevelopmental outcomes. As expected, cardiac anatomy was associated with worse motor outcomes and lower maternal education was associated with poorer language skills.<sup>45,46</sup> In this series, overt brain injury, such as seizure or stroke, was not associated with substantial worsening in neurodevelopmental outcome; however, patients did not undergo routine postoperative electroencephalography or neuroimaging in the absence of clinical concern. Given the high rate of occult brain injury in the CHD population,<sup>6</sup> our observed rates likely represent a lower bound, and improved detection might have yielded greater predictive value. Nonetheless, across all domains in this study, fetal brain volume was the most consistent predictor of neurodevelopmental outcome.

## **Limitations**

Our study has limitations. The moderately sized sample for this study was from a single center and was not racially or ethnically diverse. This did not allow for a subgroup analysis of different CHD diagnoses to establish whether the strength of the association between fetal brain volume and neurodevelopment differs between cardiac subtypes. Future multisite studies with a larger, more diverse sample may shed light on this question. We also did not conduct whole exome or whole genome sequencing on these patients and cannot exclude an underlying genetic disorder that is not clinically apparent. Although our study was not designed to determine mechanisms, the lack of correlation between fetal brain volume and neurodevelopment in the control group of a similar sociodemographic distribution would be consistent with a cardiac physiologic mechanism. It is possible that another factor, such as genetics or the maternal environment, may account for this association. Future studies should integrate fetal brain MRI, sociodemographic measures, cardiac physiologic measures, and placental functioning with next-generation sequencing of all fetuses. The sample was evaluated at 2 years of age, but for many children with CHD, higher-order deficits in executive functioning, attention, and social cognition do not become apparent until school age. Long-term follow-up is needed to determine the persistence of associations found in the current cohort.

## **Conclusions**

We present the first data showing an association between fetal brain development and neurodevelopmental outcome in CHD. Smaller fetal brain volume correlated with worse outcome at age 2 years across all domains of development and adaptive functioning in the CHD group. Fetal brain volume was the most consistent predictor of neurodevelopment compared with other prenatal and postnatal variables examined. In an era where most children with CHD are diagnosed prenatally in economically developed countries, small fetal brain volume may be an important biomarker of future neurodevelopmental risk. Trials are underway examining whether pharmacologic approaches (eg, progesterone, allopurinol) or behavioral interventions (eg, maternal stress reduction) could improve fetal brain development in CHD. Although future studies are needed to confirm the validity of fetal brain volume as a predictor of neurodevelopment in children with CHD, our findings suggest that this imaging biomarker may inform risk stratification and be used as an outcome in trials of fetal neuroprotective interventions.

## **Acknowledgments**

The authors acknowledge contributions from Judy Estroff, Ed Yang, Reem Chamseddine, Sarah Perelman, and Jeanette Beaute.

## **Sources of Funding**

Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke (grant K23NS101120 to Dr Rollins); the National Heart, Lung, and Blood Institute (grant K23HL141602 to Dr Ortinau); the National Institute of Biomedical Imaging and Bioengineering (grant R01EB013248 to Dr Warfield and grants R01EB018988, R01NS106030, and R01EB031849 to Dr Gholipour); a National Heart, Lung, and Blood Institute Pediatric Heart Network Scholar Award (Dr Rollins); the American Academy of Neurology Clinical Research Training Fellowship (Dr Rollins); the Brain and Behavior Research Foundation NARSAD (National Alliance for Research in Schizophrenia and Depression) Young Investigator (Dr Rollins) and Distinguished Investigator (Dr Warfield) Awards; the McKnight Foundation Technological Innovations in Neuroscience Award (Dr Gholipour); the Office of Faculty Development at Boston Children's Hospital Career Development Awards (Drs Gholipour and Rollins); the Mend A Heart Foundation (Dr Ortinau); and the Farb Family Fund (Dr Newburger). The content does not necessarily represent the official views of the National Institutes of Health or other funding agencies.

## **Disclosures**

None.

## References

1. The International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. *Ann Thorac Surg*. 2016;102:843–849. doi: 10.1016/j.athoracsur.2016.05.081 [Crossref](#). [PubMed](#).
2. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, et al; International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics*. 2015;135:816–825. doi: 10.1542/peds.2014-3825 [Crossref](#). [PubMed](#).
3. Schaefer C, von Rhein M, Knirsch W, Huber R, Natalucci G, Caflisch J, Landolt MA, Latal B. Neurodevelopmental outcome, psychological adjustment, and quality of life in adolescents with congenital heart disease. *Dev Med Child Neurol*. 2013;55:1143–1149. doi: 10.1111/dmcn.12242 [Crossref](#). [PubMed](#).
4. Newburger JW, Sleeper LA, Bellinger DC, Goldberg CS, Tabbutt S, Lu M, Mussatto KA, Williams IA, Gustafson KE, Mital S, et al; Pediatric Heart Network Investigators. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the Single Ventricle Reconstruction trial. *Circulation*. 2012;125:2081–2091. doi: 10.1161/CIRCULATIONAHA.111.064113 [Crossref](#). [PubMed](#).
5. Mussatto KA, Hoffmann RG, Hoffman GM, Tweddell JS, Bear L, Cao Y, Brosig C. Risk and prevalence of developmental delay in young children with congenital heart disease. *Pediatrics*. 2014;133:e570–e577. doi: 10.1542/peds.2013-2309 [Crossref](#). [PubMed](#).
6. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH, et al; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126:1143–1172. doi:10.1161/CIR.0b013e318265ee8a [Crossref](#). [PubMed](#).
7. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A, Varley J. Randomized, controlled trial of an intervention for toddlers with autism: the Early Start Denver Model. *Pediatrics*. 2010;125:e17–e23. doi: 10.1542/peds.2009-0958 [Crossref](#). [PubMed](#).
8. Lipkin PH, Macias MM; Council on Children With Disabilities, Section on Developmental and Behavioral Pediatrics. Promoting optimal development: identifying infants and young children with developmental disorders through developmental surveillance and screening. *Pediatrics*. 2020;145:e20193449. doi:10.1542/peds.2019-3449 [Crossref](#). [PubMed](#).



9. Council on Children With Disabilities, Section on Developmental Behavioral Pediatrics, Bright Futures Steering Committee, Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics*. 2006;118:405–420. doi:10.1542/peds.2006-1231 [Crossref](#). [PubMed](#).
10. Bellinger DC, Wypij D, duPlessis AJ, Rappaport LA, Jonas RA, Wernovsky G, Newburger JW. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. *J Thorac Cardiovasc Surg*. 2003;126:1385–1396. doi:10.1016/s0022-5223(03)00711-6 [Crossref](#). [PubMed](#).
11. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, Zimmerman RA, Spray TL, Gaynor JW, Vossough A. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg*. 2009;137:529–536; discussion 536. doi: 10.1016/j.jtcvs.2008.10.025 [Crossref](#). [PubMed](#).
12. Miller SP, McQuillen PS, Hamrick S, Xu D, Glidden DV, Charlton N, Karl T, Azakie A, Ferriero DM, Barkovich AJ, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med*. 2007;357:1928–1938. doi: 10.1056/NEJMoa067393 [Crossref](#). [PubMed](#).
13. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, et al. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex*. 2013;23:2932–2943. doi: 10.1093/cercor/bhs281 [Crossref](#). [PubMed](#).
14. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, Guizard N, McGrath E, Geva J, Annese D, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121:26–33. doi: 10.1161/CIRCULATIONAHA.109.865568 [Crossref](#). [PubMed](#).
15. Rollins CK, Ortinau CM, Stopp C, Friedman KG, Tworetzky W, Gagoski B, Velasco-Annis C, Afacan O, Vasung L, Beaute JJ, et al. Regional brain growth trajectories in fetuses with congenital heart disease. *Ann Neurol*. 2021;89:143–157. doi: 10.1002/ana.25940 [Crossref](#). [PubMed](#).
16. Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, Grosse-Wortmann L, Jaeggi E, McCrindle BW, Kingdom J, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015;131:1313–1323. doi:10.1161/CIRCULATIONAHA.114.013051 [Crossref](#). [PubMed](#).
17. Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, Finucane K, Brizard C, Dance B, Shekerdemian LS. New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest. *Circulation*. 2013;127:971–979. doi: 10.1161/CIRCULATIONAHA.112.001089 [Crossref](#). [PubMed](#).

18. Rollins CK, Asaro LA, Akhondi-Asl A, Kussman BD, Rivkin MJ, Bellinger DC, Warfield SK, Wypij D, Newburger JW, Soul JS. White matter volume predicts language development in congenital heart disease. *J Pediatr*. 2017;181:42–48. doi: 10.1016/j.jpeds.2016.09.070 [Crossref](#). [PubMed](#).
19. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39:1890–1900. doi: 10.1016/s0735-1097(02)01886-7 [Crossref](#). [PubMed](#).
20. Kainz B, Steinberger M, Wein W, Kuklisova-Murgasova M, Malamateniou C, Keraudren K, Torsney-Weir T, Rutherford M, Aljabar P, Hajnal JV, et al. Fast volume reconstruction from motion corrupted stacks of 2D slices. *IEEE Trans Med Imaging*. 2015;34:1901–1913. doi: 10.1109/TMI.2015.2415453 [Crossref](#). [PubMed](#).
21. Gholipour A, Rollins CK, Velasco-Annis C, Ouaalam A, Akhondi-Asl A, Afacan O, Ortinau CM, Clancy S, Limperopoulos C, Yang E, et al. A normative spatiotemporal MRI atlas of the fetal brain for automatic segmentation and analysis of early brain growth. *Sci Rep*. 2017;7:476. doi: 10.1038/s41598-017-00525-w [Crossref](#). [PubMed](#).
22. Bayley, N. *Bayley Scales of Infant and Toddler Development, Third Edition*. Pearson Education: 2006.
23. Harrison, PL, Oakland, T. *ABAS-3: Adaptive Behavior Assessment System, Third Edition*. Pearson Education: 2015.
24. Studholme C, Kroenke CD, Dighe M. Motion corrected MRI differentiates male and female human brain growth trajectories from mid-gestation. *Nat Commun*. 2020;11:3038. doi: 10.1038/s41467-020-16763-y [Crossref](#). [PubMed](#).
25. Clancy RR, McGaurn SA, Wernovsky G, Spray TL, Norwood WI, Jacobs ML, Murphy JD, Gaynor JW, Goin JE. Preoperative risk-of-death prediction model in heart surgery with deep hypothermic circulatory arrest in the neonate. *J Thorac Cardiovasc Surg*. 2000;119:347–357. doi:10.1016/S0022-5223(00)70191-7 [Crossref](#). [PubMed](#).
26. Miller TA, Ghanayem NS, Newburger JW, McCrindle BW, Hu C, DeWitt AG, Cnota JF, Tractenberg FL, Pemberton VL, Wolf MJ, et al; Pediatric Heart Network Investigators. Gestational age, birth weight, and outcomes six years after the Norwood procedure. *Pediatrics*. 2019;143:e20182577. doi:10.1542/peds.2018-2577 [Crossref](#). [PubMed](#).
27. Nattel SN, Adrianzen L, Kessler EC, Andelfinger G, Dehaes M, Côté-Corriveau G, Trelles MP. Congenital heart disease and neurodevelopment: clinical manifestations, genetics, mechanisms, and implications. *Can J Cardiol*. 2017;33:1543–1555. doi: 10.1016/j.cjca.2017.09.020 [Crossref](#). [PubMed](#).
28. Williams IA, Fifer C, Jaeggi E, Levine JC, Michelfelder EC, Szwast AL. The association of fetal cerebrovascular resistance with early neurodevelopment in single ventricle congenital heart disease. *Am Heart J*. 2013;165:544–550.e1. doi: 10.1016/j.ahj.2012.11.013 [Crossref](#). [PubMed](#).

29. Williams IA, Tarullo AR, Grieve PG, Wilpers A, Vignola EF, Myers MM, Fifer WP. Fetal cerebrovascular resistance and neonatal EEG predict 18-month neurodevelopmental outcome in infants with congenital heart disease. *Ultrasound Obstet Gynecol.* 2012;40:304–309. doi: 10.1002/uog.11144 [Crossref](#). [PubMed](#).
30. Welling MS, Husen SC, Go ATJI, Groenenberg IAL, Willemsen SP, Bijma HH, Steegers-Theunissen RPM. Growth trajectories of the human fetal brain in healthy and complicated pregnancies and associations with neurodevelopmental outcome in the early life course. *Early Hum Dev.* 2020;151:105224. doi: 10.1016/j.earlhumdev.2020.105224 [Crossref](#). [PubMed](#).
31. Thompson DK, Matthews LG, Alexander B, Lee KJ, Kelly CE, Adamson CL, Hunt RW, Cheong JLY, Spencer-Smith M, Neil JJ, et al. Tracking regional brain growth up to age 13 in children born term and very preterm. *Nat Commun.* 2020;11:696. doi: 10.1038/s41467-020-14334-9 [Crossref](#). [PubMed](#).
32. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med.* 2006;355:685–694. doi:10.1056/NEJMoa053792 [Crossref](#). [PubMed](#).
33. Rollins CK, Watson CG, Asaro LA, Wypij D, Vajapeyam S, Bellinger DC, DeMaso DR, Robertson RL, Newburger JW, Rivkin MJ. White matter microstructure and cognition in adolescents with congenital heart disease. *J Pediatr.* 2014;165:936–44.e1. doi: 10.1016/j.jpeds.2014.07.028 [Crossref](#). [PubMed](#).
34. von Rhein M, Buchmann A, Hagmann C, Huber R, Klaver P, Knirsch W, Latal B. Brain volumes predict neurodevelopment in adolescents after surgery for congenital heart disease. *Brain.* 2014;137(Pt 1):268–276. doi: 10.1093/brain/awt322 [Crossref](#). [PubMed](#).
35. Morton PD, Korotcova L, Lewis BK, Bhuvanendran S, Ramachandra SD, Zurakowski D, Zhang J, Mori S, Frank JA, Jonas RA, et al. Abnormal neurogenesis and cortical growth in congenital heart disease. *Sci Transl Med.* 2017;9:eaah7029. doi:10.1126/scitranslmed.aah7029 [Crossref](#). [PubMed](#).
36. Lawrence KM, McGovern PE, Mejaddam A, Rossidis AC, Baumgarten H, Kim A, Grinspan JB, Licht DJ, Didier RA, Vossough A, et al. Chronic intrauterine hypoxia alters neurodevelopment in fetal sheep. *J Thorac Cardiovasc Surg.* 2019;157:1982–1991. doi:10.1016/j.jtcvs.2018.12.093 [Crossref](#). [PubMed](#).
37. Schlatterer SD, Murnick J, Jacobs M, White L, Donofrio MT, Limperopoulos C. Placental pathology and neuroimaging correlates in neonates with congenital heart disease. *Sci Rep.* 2019;9:4137. doi:10.1038/s41598-019-40894-y [Crossref](#). [PubMed](#).
38. Ernst LM. Maternal vascular malperfusion of the placental bed. *APMIS.* 2018;126:551–560. doi:10.1111/apm.12833 [Crossref](#). [PubMed](#).
39. Auger N, Fraser WD, Healy-Profítós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA.* 2015;314:1588–1598. doi: 10.1001/jama.2015.12505 [Crossref](#). [PubMed](#).

40. Øyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, Quertermous T, Wohlfahrt J, Melbye M. Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. *Circulation*. 2016;133:2243–2253. doi:10.1161/CIRCULATIONAHA.115.017465 [Crossref](#). [PubMed](#).
41. Bonthrone AF, Chew A, Kelly CJ, Almedom L, Simpson J, Victor S, Edwards AD, Rutherford MA, Nosarti C, Counsell SJ. Cognitive function in toddlers with congenital heart disease: The impact of a stimulating home environment. *Infancy*. 2021;26:184–199. doi:10.1111/infa.12376 [Crossref](#). [PubMed](#).
42. Wu Y, Kapse K, Jacobs M, Niforatos-Andescavage N, Donofrio MT, Krishnan A, Vezina G, Wessel D, du Plessis A, Limperopoulos C. Association of maternal psychological distress with in utero brain development in fetuses with congenital heart disease. *JAMA Pediatr*. 2020;174:e195316. doi:10.1001/jamapediatrics.2019.5316 [Crossref](#). [PubMed](#).
43. Lu YC, Kapse K, Andersen N, Quistorff J, Lopez C, Fry A, Cheng J, Andescavage N, Wu Y, Espinosa K, et al. Association between socioeconomic status and in utero fetal brain development. *JAMA Netw Open*. 2021;4:e213526. doi: 10.1001/jamanetworkopen.2021.3526 [Crossref](#). [PubMed](#).
44. Homsy J, Zaidi S, Shen Y, Ware JS, Samocha KE, Karczewski KJ, DePalma SR, McKean D, Wakimoto H, Gorham J, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science*. 2015;350:1262–1266. doi:10.1126/science.aac9396 [Crossref](#). [PubMed](#).
45. Snookes SH, Gunn JK, Eldridge BJ, Donath SM, Hunt RW, Galea MP, Shekerdeman L. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. *Pediatrics*. 2010;125:e818–e827. doi: 10.1542/peds.2009-1959 [Crossref](#). [PubMed](#).
46. Dollaghan CA, Campbell TF, Paradise JL, Feldman HM, Janosky JE, Pitcairn DN, Kurs-Lasky M. Maternal education and measures of early speech and language. *J Speech Lang Hear Res*. 1999;42:1432–1443. doi: 10.1044/jslhr.4206.1432 [Crossref](#). [PubMed](#).