Long-Term Neurodevelopmental Outcomes of Children with Congenital Heart Defects

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Objective To assess whether children with symptomatic congenital heart defects (CHDs) at birth (cyanosis and/or heart failure) are at greater risk of adverse neurodevelopmental outcomes at 8 years of age.

Study design From a prospective population-based cohort study of newborns with CHDs (EPICARD), we included 473 children with available neurodevelopmental assessments at 8 years of age. We grouped the CHD based on symptoms at birth and need for early neonatal intervention. Ventricular septal defects that closed spontaneously within the first year of life were considered the control group. Neurodevelopmental outcomes were assessed using the Kauffman Assessment Battery Test for Children, Second Edition, for IQ (mean 100 ± 15), and the Developmental NEuroPSYchological Assessment Battery, Second Edition, for detailed assessment of specific neurocognitive domains (mean 10 ± 3). Multivariable regression analysis was used to compare the outcomes across the CHD groups after considering potentially confounding variables.

Results Compared with the control group, children with cyanotic CHD without heart failure had lower scores for IQ, −7.2 (95% CI −13.4 to −1.2). Children with noncyanotic CHD with heart failure had lower scores in the specific domains of language −1.5 (95% CI −2.2 to −0.7), and memory and learning −1.3 (95% CI −2.4; −0.3). Those with both cyanotic CHD and heart failure had lower scores for IQ, −7.6 (95% CI −13.5 to −1.8), as well as the specific domains of language and memory and learning, −2.0 (95% CI −2.9 to −1.0) and −1.1 (95% CI −2.3 to −0.1), respectively.

Conclusions Children with symptomatic CHD at birth are at greater risk of adverse neurodevelopmental outcomes at 8 years of age, with the greatest risk for those who were born with both cyanosis and heart failure. *(J Pediatr 2021;■:1-6)*.

Progress in clinical and surgical care of newborns with congenital heart defects (CHDs) has resulted in a significant reduction in the risk of mortality for newborns with CHD.[1,2] Currently, nearly 90% of children born with CHD will reach adulthood.[1] Consequently, the long-term health and neurodevelopmental outcomes of children with CHD have become an increasingly important issue.

Several studies have investigated the neurodevelopmental outcomes of children with CHD. These studies have found that some groups of children with complex CHD have lower IQ scores than their peers. They also have lower scores in specific domains (eg, executive function, attention, language, or visual–spatial skills) that can affect academic achievement.[3-6] However, most of the existing literature includes hospital-based studies, with potentially limited power and issues of internal and external validity. The only population-based prospective cohort study of neurodevelopmental outcomes with CHD investigated outcomes for children at 3 years of age.[4] This study showed that children born small for gestational age with an operated CHD were at risk of cognitive dysfunction. However, this study could not assess specific neurocognitive domains that can only be assessed reliably in older children (eg, attention and executive functions). Moreover, developmental trajectories can and do vary in high-risk populations (eg, newborns who are preterm) and early outcomes are not always predictive of those at older ages.[3,6,7]

CHD	Congenital heart defect
CPC-CHD	Clinical and Pathophysiologic Classification of Congenital Heart Defects
KABC-II	Kauffman Assessment Battery Test for Children, Second Edition
NEPSY-II	Developmental NEuroPSYchological Assessment Battery, Second Edition
VSD	Ventricular septal defect

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The impact of CHD on cognitive outcomes is at least in part due to their effects on the developing brain as mediated by the perinatal pathophysiology and neonatal expression of the CHD.[3,8] These factors also determine symptoms of CHD at birth and the need for early surgical intervention during the neonatal period. The extent to which these factors may be associated with long-term neurodevelopmental outcomes of children with CHD is not well known.

Using data from a population-based prospective cohort study of newborns with CHD [the EPIdémiologie des CARDiopaties congénitales (EPICARD) study], our objectives were to evaluate the neurodevelopmental outcomes of children with CHD at 8 years of age using standardized instruments (Kauffman Assessment Battery Test for Children, Second Edition [KABC-II]/Developmental NEuroPSYchological Assessment Battery, Second Edition [NEPSY-II]) that allow a detailed, domain-specific assessment of neurodevelopmental outcomes, and test the hypothesis that children with symptomatic CHD at birth (cyanosis and/or heart failure) are at greater risk of adverse neurodevelopmental outcomes at 8 years old.

Methods

EPICARD is a population-based, prospective cohort study of children with CHD born in Paris and its surrounding areas.[9] All cases (live births, terminations of pregnancy for fetal anomaly, fetal deaths) diagnosed in the prenatal period, or up to 1 year of age in the birth cohorts between May 1, 2005, and April 30, 2008, were eligible for inclusion. Diagnoses of CHD and associated comorbidities (ie, genetic or extracardiac anomalies) were confirmed in specialized pediatric cardiology departments.

Follow-up of children at 8 years of age included a neurodevelopmental assessment and parental questionnaires about the child's life habits (eg, diet, sleep, family, and school arrangements), as well as the child's quality of life. All children were evaluated by a pediatrician, a pediatric cardiologist, and a pediatric neuropsychologist. Informed consent was obtained from all study participants, and the study was approved by the ethics committee of the French National Committee of Information and Liberty: CPP Ile de France III (2013-A00234-14).

The standardized neurodevelopmental assessment at 8 years included a global cognitive assessment (IQ) as measured by the KABC-II and specific neurocognitive domains assessed by the NEPSY-II. The KABC-II for children 8 years old consists of 7 subtests evaluating specific cognitive skills. A global cognitive score (mean = 100, SD = 15) is calculated based on all subtest scores. The NEPSY-II assesses the child's neuropsychological outcomes in specific functional domains, consisting of several subtests.

Language was evaluated using the subtests *Comprehension of Instructions* and *Repetition of Non-sense Words*. The subtest *Comprehension of Instruction* assesses the ability to process and respond to verbal instructions of increasing syntactic complexity. The subtest *Repetition of Non-sense Words* assesses phonological encoding and decoding. The domain learning and memory corresponds to the ability to acquire, retain, and recall new information. In this study, the subtest selected was *List Memory*, which includes memory and word lists with immediate and delayed recalls. This subtest evaluates various aspects of verbal learning and verbal memory, including immediate and delayed recall, speed of learning, and the role of interference from previous and new learning. The Attention and Executive function domain was evaluated using the subtest *Auditory Attention and Response set* (ie, a measure of auditory attention and sustained vigilance) and the *Inhibition* subtest (ie, assessment of the ability to inhibit automatic responses, self-regulate behavior and alternate strategies as a measure of flexibility).

Finally, visual-spatial processing was evaluated with the *Geometric Puzzle* subtests measuring mental rotation, visuospatial analysis, and attention to detail. All NEPSY-II subtests domain-specific assessments have a mean of 10 (SD = 3).

The main predictor variable was type of CHD. We aimed to group CHD into a manageable number of groups based on clinical relevance, the underlying perinatal pathophysiology of the CHD, its neonatal expression, and the timing for its optimal management (urgent intervention required or not). We have termed our classification the Clinical and Pathophysiological Classification of Congenital Heart Defects (CPC-CHD). However, we do not intend this classification to serve as a precise proxy, nor do we claim it to characterize in any detail the complex and incompletely understood underlying mechanisms of CHD and their effects on long-term neurodevelopmental outcomes of newborns with CHD.

Specifically, based on clinical and pathophysiologic characteristics and the optimal timing of interventions in clinical management of the CHD, we divided them into 5 groups. These groups were chosen based on the permutations of the following characteristics: (1) cyanotic CHD, (2) CHD with heart failure, and (3) need for early surgical intervention during the neonatal period as follows: group 1: cyanotic CHD with heart failure (overt or potential), requiring early surgery (eg, hypoplastic left heart syndrome or transposition of the great arteries); group 2: noncyanotic CHD with heart failure (overt or potential), requiring early surgery (eg, coarctation of the aorta); group 3: cyanotic CHD with surgery after the neonatal period (eg, tetralogy of Fallot); group 4: noncyanotic CHD that can gradually lead to heart failure, which requires surgical intervention after the neonatal period (eg, atrioventricular septal defect or atrial septal defect); group 5: minor noncyanotic CHD without significant alteration of cardiac physiology and no need for intervention (eg, mild pulmonary valvar stenosis); and the control group: isolated ventricular septal defect (VSD) with spontaneous closure within the first year of life.

The initial assignment of the CHD into the 5 categories of CPC-CHD was done by the first author. This was then discussed and evaluated by 2 senior pediatric cardiologists,

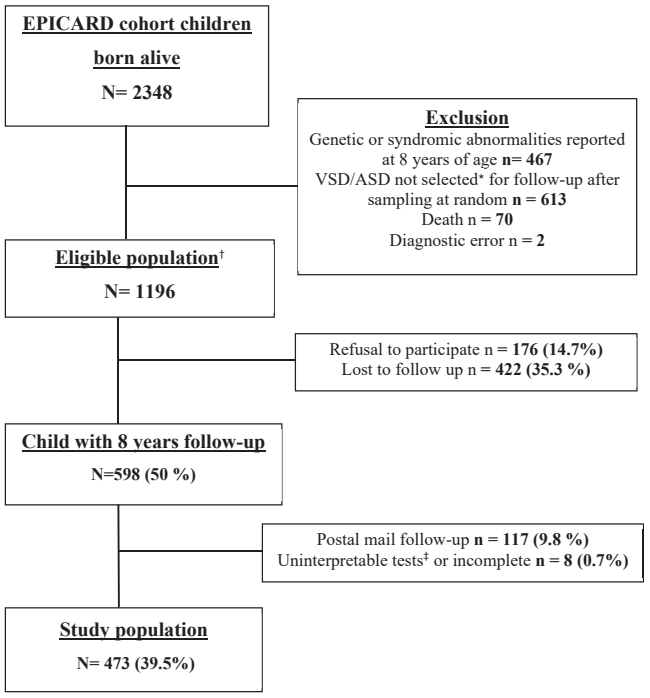

Figure. Flow chart for study population. *Children with VSD or ASD with spontaneous closure. †Reference for all percentages. ‡Severe hearing and/or visual impairment, language barrier. *ASD*, atrial septal defect.

and the final categories were assigned by consensus. Details of the CHD included in each category are provided in **Table I** (available at www.jpeds.com).

The initial cohort included 2348 newborns (**Figure**). All newborns were eligible for follow-up at 1 year of age. Thereafter, all children with a major CHD plus a 15% random sample of children with nonsurgical cases of atrial septal defects and VSDs were eligible for follow-up.

The children eligible for our study were those with an isolated CHD (without any known genetic anomalies or malformations in other systems, including syndromes at 8 years of age) who were alive and could have had a neurodevelopmental evaluation at the 8-year follow-up visit (N = 1196). Among them, 176 (14.7%) refused to participate, and 422 (35.3%) were lost to follow-up. We were then able to contact 598 children (50% of the eligible population) to invite them for the follow-up visit at 8 years. Parents of 117 (9.8%) children responded only via written questionnaires sent by mail and did not attend the visit required for the detailed neurodevelopmental assessments. In addition, 8 children were unable to undergo testing due to severe hearing loss and/or visual impairments. The final study population included 473 children who had a complete neurodevelopmental assessment, ie, 39.5% of the eligible population.

We show descriptive data as proportions for categorical variables and means and SDs for continuous variables. We used multiple linear regression for comparing the neurodevelopmental scores of each of the 5 categories of CHD vs the control group of isolated VSD with spontaneous closure. In addition to the main predictor variable of type of CHD, we included the potentially confounding variables preterm birth, sex, language spoken at home, maternal geographic origin, and maternal education in the multiple regression models.

We used the Heckman selection model to account for differential loss to follow-up. By modeling the "selection process," ie, whether an eligible subject was in the study population, the Heckman model can "correct" bias in estimates due to sample selection. It is a crucial requirement of the Heckman model that relevant data for modeling the selection process be available. We had several potentially important variables for comparing the study participants vs those who could not or did not wish to participate in the study. Hence, we were able to model the selection process based on the complexity of the CHD, that was the main difference between the study participants and the on-participants. The analyses were performed with STATA, version 15 (StataCorp LLC). A value of $P < .05$ was defined as significant. We used the STROBE guideline to report on our study design and analysis.

Results

In total, 473 (39.5% of the initially eligible cohort) children completed the detailed neurodevelopmental evaluation and were included in our analyses. Study participants were more likely to have a complex CHD and a prenatal diagnosis than those who did not have a complete follow-up at 8 years of age (**Table II**; available at www.jpeds.com). The number of patients in the CPC-CHD groups varied from 33 (group 3: cyanotic CHD with delayed surgery beyond the neonatal period) to 117 (control group). The proportion of cases with prenatal diagnosis, preterm birth, and the sex ratio were significantly different across the groups. The proportion of children with a prenatal diagnosis was greater in the cyanotic CHD with heart failure, noncyanotic CHD with heart failure, and cyanotic CHD without heart failure groups (60%, 40%, and 69.7%, respectively vs 8.6% in the control group, $P < .001$). The proportion of preterm births was greater in minor CHD requiring intervention and minor CHD not requiring intervention groups (17.1% and 27.6%, respectively, vs 11.1% in the control group, $P < .01$). The proportion of male patients was greater in the cyanotic CHD with heart failure and in the noncyanotic CHD with heart failure groups (70.9% and 70.1%, respectively, vs 46.2% $P < .001$) (**Table III**; available at www.jpeds.com).

The mean global IQ score was 94.3 ± 17.0 for all CHD. The mean global IQ scores for the control group was 96.3 ± 16.8, whereas the mean score reached 99.1 ± 16.3 specifically for children from the control group who spoke French at home (**Table IV**). The adjusted score for all CHD groups was lower than the control group; however, this difference

Table IV. Mean scores for global IQ (KABC II) and certain neurocognitive specific domains (NEPSY-II)

		Learning and memory	Language	
Subtest	Global IQ scores	List memory and list Memory delayed	Comprehension of Instructions	Repetition of non-sense words
All CHD	94.3 ± 17.0	10.8 ± 2.8	10.8 ± 2.5	10.2 ± 2.2
CHD groups				
Cyanotic CHD with heart failure (n = 55)	93.6 ± 17.5	10.5 ± 2.6	10.7 ± 2.1	10.6 ± 2.2
Non-cyanotic CHD with heart failure (n = 50)	94.2 ± 17.9	10.1 ± 3.2	10.1 ± 2.9	9.5 ± 2.6
Cyanotic CHD without heart failure (n = 33)	90.6 ± 20.0	10.8 ± 2.8	11.1 ± 2.4	10.1 ± 2.1
Minor CHD requiring intervention (n = 105)	94.0 ± 16.8	10.5 ± 3.1	10.7 ± 2.7	10.1 ± 2.2
Minor CHD not requiring intervention (n = 113)	94.1 ± 16.0	11.3 ± 2.6	10.9 ± 2.4	10.2 ± 2.1
Control (n = 117)	96.3 ± 16.8	11.2 ± 2.5	11.1 ± 2.5	10.5 ± 1.9
Control bias* (n = 93)	99.1 ± 16.3	11.4 ± 2.5	11.3 ± 2.5	10.4 ± 1.9

Note: no statistically significant difference between groups.
*Excluded children who do not speak French at home.

did not reach statistical significance. In the multivariable model, the IQ score was significantly lower for the cyanotic CHD with heart failure, −7.6 (95% CI −13.5 to −1.8), and cyanotic CHD without heart failure, −7.2 (95% CI −13.4 to −1.2), compared with the control group (Table V).

The mean score for the subtest *Comprehension of Instructions* for all CHD was 10.8 ± 2.5 and 11.1 ± 2.5 for controls. The unadjusted scores were not significantly different across groups (Table IV). The adjusted scores, however, were significantly lower for cyanotic CHD with heart failure, −2.0 (95% CI − 2.9 to −1.0), and for noncyanotic CHD with heart failure, − 1.5 (95% CI − 2.2 to −0.7), than for the control group.

Regarding the subtest assessing *Repetition of Non-sense Words,* the adjusted scores were significantly lower for non-cyanotic CHD with heart failure, −1.1 (95% CI − 1.8 to −0.3), than for the control group (Table VI).

The mean score for the *List Memory Delayed* subtest for all CHD was 10.8 ± 2.8 and 11.2 ± 2.5 for control group (Table IV). The adjusted scores were significantly lower for cyanotic CHD with heart failure, −1.1 (95% CI − 2.3 to −0.1), noncyanotic CHD with heart failure, −1.3 (95% CI −2.4 to −0.3), and minor CHD requiring intervention, −0.8 (95% CI −1.5 to −0.1), than for the control group (Table VI).

Table V. Linear regression coefficient of the global IQ (KABC-II)

	Global IQ scores	
CHD groups	Unadjusted (95%CI)	Adjusted*(95%CI)
Cyanotic CHD with heart failure	**−9.2 (−15.6 to −2.7)**	**−7.6 (−13.5 to −1.8)**
Non-cyanotic CHD with heart failure	**−5.8 (−11.7 to 0.0)**	−4.4 (−9.7 to 0.9)
Cyanotic CHD without heart failure	**−9.6 (−16.4 to −2.8)**	**−7.2 (−13.4 to −1.2)**
Minor CHD requiring intervention	−3.3 (−7.6 to 1.1)	−1.6 (−5.4 to 2.3)
Minor CHD not requiring intervention	−3.6 (−7.9 to 0.7)	−3.1 (−7.0 to 0.7)

Note: Heckman model with the covariate "complexity" in the equation of selection.
*Adjusted for sex of infant, prematurity, maternal geographic origin, maternal education, and French language only spoken at home. $P < .05$ (level of significance) are in bold.

The mean score of the *Flexibility* score for all CHD was 9.4 ± 3.1, and 9.8 ± 3.1 for the control group (Table VII; available at www.jpeds.com). The adjusted scores were significantly lower for cyanotic CHD with heart failure, −1.2 (95% CI −2.4 to 0.0), compared with the control group (Table VIII; available at www.jpeds.com). For subtests *Inhibition* and *Auditory Attention*, there were no significant difference across groups. Regarding the visuospatial domain, there was no statistically significant differences between CHD groups and controls (Table VIII).

Discussion

As compared with hospital-based studies, our study is more likely to avoid selection bias due to survival/transfer bias. Moreover, as most hospital-based studies are from referral centers, our study results are more likely to be generalizable to comparable populations, for example, high-resource countries with availability of high-quality, specialized health services.

Our results are generally consistent with the previous hospital-based studies that found that children with "complex" CHD had a significant decrease in overall IQ,[3,7,10] executive functions,[3,5,6,11] language,[3,7,10] and memory and academic learning scores.[3,12,13] As in most previous studies, the effect sizes we found had an order of magnitude of approximately 0.5 SDs in mean differences, which is meaningful at the population-level.

The CPC-CHD classification may be considered to represent 2 dimensions of the pathophysiology of CHD. One related to the "inherent" characteristics of the CHD, in particular its perinatal pathophysiology and neonatal expression, and the second, related to medical management, ie, the optimal timing for surgical intervention. The pathophysiology of neurodevelopmental outcomes of children with CHD, including possible links to effects on specific domains, is not well-understood. Nevertheless, 2 pathways may explain these effects brain immaturity and brain injury.

Table VI. Linear regression coefficient of neurocognitive specific domains (NEPSY-II)

	Language				Learning and memory	
	Comprehension of instructions		Repetition of non-sense words		List memory + delayed	
CHD groups	Unadjusted (95%CI)	Adjusted* (95%CI)	Unadjusted (95%CI)	Adjusted* (95%CI)	Unadjusted (95%CI)	Adjusted*
Cyanotic CHD with heart failure	**−2.0 (−3.0 to −1.1)**	**−2.0 (−2.9 to −1.0)**	0.2 (−1.1 to 1.4)	−0.6 (−1.4 to 0.3)	**−1.3 (−2. to −0.1)**	**−1.1 (−2.3 to −0.1)**
Non-cyanotic CHD with heart failure	**−1.7 (−2.5 to −0.8)**	**−1.5 (−2.2 to −0.7)**	−0.9 (−1.9 to 0.0)	**−1.1 (−1.8 to −0.3)**	**−1.5 (−2.5 to −0.5)**	**−1.3 (−2.4 to −0.3)**
Cyanotic CHD without heart failure	**−1.2 (−2.2 to −0.2)**	−0.7 (−1.6 to 0.3)	−0.3 (−1.4 to 0.9)	−0.7 (−1.6 to 0.2)	−0.8 (−2.1 to 0.5)	0.4 (−1.7 to 0.8)
Minor CHD requiring intervention	−0.6 (−1.2 to 0.0)	−0.4 (−0.9 to 0.2)	−0.3 (−0.9 to 0.3)	−0.3 (−0.8 to 0.2)	**−0.8 (−1.5 to − 0.1)**	**−0.8 (−1.5 to −0.1)**
Minor CHD not requiring intervention	−0.4 (−1.1 to 0.1)	−0.3 (−0.9 to 0.2)	−0.2 (−0.8 to 0.4)	−0.2 (−0.8 to 0.3)	−0.0 (−0.8 to 0.7)	−0.1 (−0.8 to 0.6)

Note 1: Heckman model with the covariate "complexity" in the equation of selection.
Note 2: Other NEPSY-II domains are presented in **Table VIII**; available at www.jpeds.com.
*Adjusted for sex of infant, prematurity, maternal geographic origin, maternal education, and French language only spoken at home. $P < .05$ (level of significance) are in bold.

Brain immaturity results from developmental lesions due to the lack of maturation of 1 or more of the following processes: myelination, cortical folding, glial cell migration, and germinal matrix distribution.[14,15] Certain CHD can result in impaired blood flow to the brain during the antenatal and postnatal periods,[16-18] exposing the fetal and neonatal brain to hypoxia. These are in turn associated with cellular alterations, particularly in the frontal cortex areas corresponding to language, executive function, memory, and attention.[3] These pathophysiologic alterations can lead to a reduction in brain and cortical volume,[19-21] a decrease in gyrification,[21,22] and an alteration in brain connections resulting in brain immaturity[8,17,23,24] before any interventions are possible.

Brain injury is defined as acquired lesions mostly represented by hypoxic ischemic lesions and intracranial hemorrhage.[25,26] Brain injury was initially thought to be related to surgery (cardiopulmonary bypass time, aortic crossclamping time, etc) and the postoperative management of the infants with CHD. However, lesions suggestive of brain injury in the fetus were found on magnetic resonance imaging examinations before surgery.[27] Hence, lesions suggestive of brain injury are probably not entirely a consequence of the surgery and the postoperative factors.[27]

Brain immaturity and brain injury may be related and may act in tandem. Brain immaturity may make the newborn brain more vulnerable to subsequent brain injury. Hence, both brain immaturity and brain injury could potentially result in adverse neurodevelopmental outcomes.

Children with cyanotic CHD without heart failure are exposed to moderate but prolonged hypoxia until the time of surgery. Those with noncyanotic CHD with heart failure are exposed to cerebral hypoperfusion until the time of surgery correction. Children with cyanotic CHD and heart failure are exposed to both severe antenatal/postnatal hypoxia and cerebral hypoperfusion. Cyanotic CHD is associated with overall perfusion disorders, whereas noncyanotic CHD with left outflow obstruction has more localized perfusion disorders, despite the autoregulatory mechanism of cerebral vasodilation called "brain sparring."[28,29] This autoregulation is presumably not sufficient to compensate for hypoxia or hypoperfusion of the brain.

Neurodevelopmental outcomes may be related to the degree and duration of hypoxia and hypoperfusion. This is consistent with our results that both cyanosis and heart failure were associated with the risk for adverse neurodevelopmental outcomes. Brain sparing is affected by factors related to clinical management (eg, ventilation parameters). Therefore, despite the results of the studies that show the limited role of co-factors related to management,[8,30] an adverse effect of management-related co-factors on long-term neurodevelopment outcomes cannot be excluded.

Our study has certain limitations and caveats. As in many prospective population-based cohort studies with a long period of follow-up, data on the outcomes were not available for a considerable proportion of the eligible study population. We used the Heckman method to "correct" our estimates for differential loss to follow-up across different groups of CHD. However, our estimates may have residual bias due to differential loss to follow-up for different groups of CHD.

In addition, given the timing of our recruitment and the required period of follow-up for the cohort, we did not have access to detailed genetic information that would be available for a current cohort of newborns with CHD in a high-resource setting. Therefore, we could not analyze the specific effects that may be related to genetic factors vs those related to the pathophysiology of the CHD per se.

We did not have a control group of children without CHD. However, our control group included children with isolated minor VSD with spontaneous closure within the first year of life who had outcomes comparable with those observed for the general population. Given that our population base comprised newborns in Paris and its surrounding suburbs, our results may not be generalizable, to other, particularly low-resource settings. France has specific perinatal policies and practices, including decisions regarding terminations of pregnancy for fetal anomaly that can potentially affect the outcomes of newborns with CHD. In addition, our population has access to high-quality, reimbursed access to specialized services,[14] which may not always be the case in other countries.

Children with symptomatic CHD (cyanosis and heart failure) at birth had lower neurodevelopmental scores at 8 years of age and may be at greater risk of longer-term adverse

developmental outcomes. Those who have cyanotic CHD with heart failure that requires early surgical intervention during the neonatal period may be at the greatest risk of adverse outcomes. Targeted screening of these children at an early age may improve their outcomes and quality of life. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Raissadati A, Nieminen H, Jokinen E, Sairanen H. Progress in late results among pediatric cardiac surgery patients: a population-based 6-decade study with 98% follow-up. Circulation 2015;131:347-53. discussion 353.
2. Mandalenakis Z, Rosengren A, Skoglund K, Lappas G, Eriksson P, Dellborg M. Survivorship in children and young adults with congenital heart disease in Sweden. JAMA Intern Med 2017;177:224-30.
3. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation 2012;126:1143-72.
4. Calderon J, Willaime M, Lelong N, Bonnet D, Houyel L, Ballon M, et al. Population-based study of cognitive outcomes in congenital heart defects. Arch Dis Child 2018;103:49-56.
5. Calderon J, Jambaqué I, Bonnet D, Angeard N. Executive functions development in 5- to 7-year-old children with transposition of the great arteries: a longitudinal study. Dev Neuropsychol 2014;39:365-84.
6. Calderon J, Bonnet D, Courtin C, Concordet S, Plumet M-H, Angeard N. Executive function and theory of mind in school-aged children after neonatal corrective cardiac surgery for transposition of the great arteries. Dev Med Child Neurol 2010;52:1139-44.
7. Bellinger DC, Wypij D, duPlessis AJ, Rappaport LA, Jonas RA, Wernovsky G, et al. Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg 2003;126:1385-96.
8. International Cardiac Collaborative on Neurodevelopment (ICCON) Investigators. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. Ann Thorac Surg 2016;102:843-9.
9. Khoshnood B, Lelong N, Houyel L, Thieulin A-C, Jouannic J-M, Magnier S, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. Heart 2012;98:1667-73.
10. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobes DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. Pediatrics 2000;105:1082-9.
11. Sanz JH, Berl MM, Armour AC, Wang J, Cheng YI, Donofrio MT. Prevalence and pattern of executive dysfunction in school age children with congenital heart disease. Congenit Heart Dis 2017;12:202-9.
12. Bellinger DC, Wypij D, Kuban KC, Rappaport LA, Hickey PR, Wernovsky G, et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. Circulation 1999;100:526-32.
13. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neuropsychological performance in school-aged children with surgically corrected congenital heart disease. J Pediatr 2007;151:73-8. 78.e1.
14. Leonetti C, Back SA, Gallo V, Ishibashi N. Cortical dysmaturation in congenital heart disease. Trends Neurosci 2019;42:192-204.
15. Childs AM, Ramenghi LA, Cornette L, Tanner SF, Arthur RJ, Martinez D, et al. Cerebral maturation in premature infants: quantitative assessment using MR imaging. AJNR Am J Neuroradiol 2001;22:1577-82.
16. Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. Ultrasound Obstet Gynecol 2005;25:32-6.
17. Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, et al. Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy. Circulation 2009;119:709-16.
18. Nagaraj UD, Evangelou IE, Donofrio MT, Vezina LG, McCarter R, du Plessis AJ, et al. Impaired global and regional cerebral perfusion in newborns with complex congenital heart disease. J Pediatr 2015;167:1018-24.
19. Rudolph AM. Impaired cerebral development in fetuses with congenital cardiovascular malformations: is it the result of inadequate glucose supply? Pediatr Res 2016;80:172-7.
20. Zeng S, Zhou QC, Zhou JW, Li M, Long C, Peng QH. Volume of intracranial structures on three-dimensional ultrasound in fetuses with congenital heart disease. Ultrasound Obstet Gynecol 2015;46:174-81.
21. Kelly CJ, Makropoulos A, Cordero-Grande L, Hutter J, Price A, Hughes E, et al. Impaired development of the cerebral cortex in infants with congenital heart disease is correlated to reduced cerebral oxygen delivery. Sci Rep 2017;7:15088.
22. Ortinau C, Beca J, Lambeth J, Ferdman B, Alexopoulos D, Shimony JS, et al. Regional alterations in cerebral growth exist preoperatively in infants with congenital heart disease. J Thorac Cardiovasc Surg 2012;143:1264-70.
23. Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, 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.
24. Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, et al. Brain maturation is delayed in infants with complex congenital heart defects. J Thorac Cardiovasc Surg 2009;137:529-36; discussion 536-7.
25. Glauser TA, Rorke LB, Weinberg PM, Clancy RR. Acquired neuropathologic lesions associated with the hypoplastic left heart syndrome. Pediatrics 1990;85:991-1000.
26. McQuillen PS, Barkovich AJ, Hamrick SEG, Perez M, Ward P, Glidden DV, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke 2007;38:736-41.
27. Mebius MJ, Kooi EMW, Bilardo CM, Bos AF. Brain injury and neurodevelopmental outcome in congenital heart disease: a systematic review. Pediatrics 2017;140:e20164055.
28. Donofrio MT, Bremer YA, Schieken RM, Gennings C, Morton LD, Eidem BW, et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. Pediatr Cardiol 2003;24:436-43.
29. Giussani DA. The fetal brain sparing response to hypoxia: physiological mechanisms. J Physiol (Lond) 2016;594:1215-30.
30. Hövels-Gürich HH. Factors influencing neurodevelopment after cardiac surgery during infancy. Front Pediatr 2016;4:137.

Table I. Distribution of CHD by CPC-CHD classification

Congenital heart defects	Number of children
Cyanotic CHD with heart failure (overt or potential), requiring early surgery (N = 55)	
TAPVR	6
Common arterial trunk	1
TGA	38
Isolated TGA	27
TGA, with VSD	4
TGV with VSD and CoA	6
TGA with VSD and hypoplasia of aortic arch	1
Functional univentricular heart	9
Hypoplastic left heart syndrome	1
Noncyanotic CHD with heart failure (overt or potential), requiring early surgery (N = 50)	
CoA	39
Isolated CoA	25
CoA with VSD	11
CoA with Ebstein malformation	1
Shone syndrome	2
Interruption of the aortic arch	1
Valvar aortic stenosis	3
Cor triatriatum	2
ALCAPA	5
Cyanotic CHD with surgery after the neonatal period (N = 33)	
Tetralogy of Fallot	28
Tetralogy of Fallot with pulmonary atresia	1
Double-outlet right ventricle	4
Noncyanotic CHD that can gradually lead to heart failure, which requires surgical intervention after the neonatal period (N = 105)	
VSD with mal-tolerated increase pulmonary blood flow	47
Isolated VSD	25
VSD and ASD	15
VSD, and PDA	1
VSD, ASD, PDA	1
VSD and PVS	2
VSD and partial APVR	1
Multiple VSD and PDA	1
VSD associated with aortic insufficiency	1
PDA	1
AVSD	11
Pulmonary valvar stenosis	25
Coronary artery fistula	1
Bicuspid aortic valve	3
Double aortic arch	1
ASD	15
Ostium secundum type	7
Sinus venosus type	1
ASD and PVS	6
Single atrium and mitral regurgitation	1
Congenitally corrected TGA, VSD and PVS	1
Minor noncyanotic CHD without significant alteration of cardiac physiology and no need for intervention (N = 113)	
ASD	28
Isolated ASD	21
ASD and PDA	2
Partial APVR, VSD	1
Dysplastic mitral valve	1
Dysplastic mitral valve and VSD	1
Dysplastic tricuspid valve	1
Ebstein malformation	5
Pulmonary valvar stenosis	65
Isolated PVS	50
PVS and PDA	1
PVS and ASD	8
PVS and VSD	4
PVS, VSD, ASD	1
PVS, partial ARVP and ASD	1
Pulmonary arterial stenosis	2
Bicuspid aortic valve	9
Control: Isolated VSD with spontaneous closure within the first year of life (N = 117)	

(*continued*)

Table I. Continued

ALCAPA, anomalous connection of left coronary artery to pulmonary artery; *APVR*, anomalous pulmonary venous return; *ASD*, atrial septal defect; *AVSD*, atrioventricular septal defect; *CoA*, coarctation of aorta; *PDA*, patent ductus arteriosus; *PVS*, pulmonary valvar stenosis; *TAPVR*, total anomalous pulmonary venous return; *TGA*, transposition of great arteries.

Table II. Characteristics of participants and nonparticipants

Characteristics	Participants N = 473	Nonparticipants N = 723	Refusal to participate N = 176	Lost to follow-up N = 422	Followed by mail N = 117	*P* value*
CHD complexity, %						**<.01**
Simple	57.6	73.0	68.1	78.9	59.8	
Moderate	27.1	18.6	22.7	15.1	24.7	
Complex	15.1	8.30	9.0	5.9	15.3	
Prenatal diagnosis, %	26.1	15.7	16.4	12.0	26.5	**<.01**
Mean term of birth,† mean ± SD	38.2 ±2.7	38.4 ± 2.5	38.41 ± 2.7	38.4 ± 2.6	38.2 ± 2.7	.32
Prematurity, %	16.1	13.6	15.4	12.2	14.5	.24
Weight at birth, kg, mean ± SD	3.0 ± 0.7	3.1 ± 0.6	3.0 ± 0.6	3.1 ± 0.6	3.0 ± 0.6	.52
Small for gestational age %	12.1	10.7	12.5	9.1	14.6	.58
Maternal age, y, %						.096
≤29	35.1	40.4	44.5	40.5	32.4	
30-34	37.6	36.9	30.8	38.3	42.7	
35-39	19.7	17.9	18.2	16.9	20.5	
≥40	7.3	4.6	6.2	4.1	4.2	
Maternal geographic origin, %						.252
France	51.9	50.1	49.7	45.6	67.5	
North Africa	19.8	17.1	18.8	18.4	11.1	
Sub-Saharan Africa	11.8	11.9	11.4	15.0	1.7	
Others	16.4	20.7	20	20.8	19.6	
Level of maternal education,‡ %						.789
None	4.4	5.3	7.7	7.6	0.8	
Elementary/junior high	19.9	17.5	26.9	7.6	18.8	
High school	12.2	13.5	18.1	16.6	9.4	
University education (up to bachelor's degree)	41.1	38.9	32.4	33.3	47	
University studies (master's or doctoral studies)	22.2	24.6	20.7	15.3	35	
Level of paternal education,‡ %						.1
None	3.7	5.4	6.7	9.2	0	
Elementary/junior high	23.3	26.6	33.7	31.5	18.1	
High school	12.2	14.6	10.8	15.7	16.3	
University education (up to bachelor's degree)	33.8	24.4	21.6	23.6	27.5	
University studies (master's or doctoral studies)	26.7	28.8	27	19.7	37.9	
Place of residence at the birth of the child, %						.806
Paris	32	34.7	30.6	33.4	33.5	
Hauts-de-Seine	27.1	26	30.1	25.1	24.7	
Seine-Saint-Denis	22.5	21.9	21.5	24.8	11.1	
Val-de-Marne	18.3	17.2	17.6	16.5	19.6	

**P* value comparing participating and nonparticipating groups. *P* value in bold correspond to statistically significant.
†Weeks of gestation.
‡Data collected at 3 years old.

Table III. Patient characteristics

Groups	CCHD with cardiac insufficiency N = 55 %	Non-CCHD with heart failure N = 50 %	CCHD without cardiac insufficiency N = 33 %	Minor CHD requiring intervention N = 105 %	Minor CHD not requiring intervention N = 113 %	Controls N = 117 %	*P* value
Prenatal diagnosis	60	40	69.7	23.8	9.7	8.6	<.001
Prematurity*	5.4	12	15.1	17.1	27.6	11.1	.002
Small for gestational age	5.4	16	15.1	17.1	10.7	9.4	.23
Sex of the baby (male)	70.9	70	51.5	49.6	40.7	46.2	.001
Maternal age, y							.15
≤29	40	44	36.3	31.4	34.5	32.4	
30-34	29.1	36	33.3	40.9	35.4	43.6	
35-39	29.1	10	12.1	21.9	22.1	17.9	
≥40	1.8	10	18.2	5.8	7.9	5.9	
Mother's origin							.10
France	52.7	56	33.3	42.8	56.2	58.1	
North Africa	21.8	22	24.2	21.9	17.9	17.1	
Sub-Saharan Africa	3.6	10	27.2	12.4	10.7	12.8	
Others	21.8	12	15.1	22.9	15.2	11.9	
Delivery							.38
Vaginal delivery	78.2	65.3	72.7	67.3	66.6	72.7	
Scheduled cesarean	14.6	20.4	9.1	11.5	10.8	11.9	
Emergency cesarean	7.2	14.3	18.2	21.2	22.5	15.4	
Maternal education level							.23
None	1.8	0	6.1	3.9	4.4	7.7	
Elementary/junior high	20	18.2	24.2	22.3	21.2	16.2	
High school	18.2	18.2	3	13.6	9.7	11.1	
University education (up to bachelor's degree)	45.4	52.3	39.4	37.8	44.3	35.9	
University studies (master's or doctoral studies)	14.6	11.4	27.3	22.4	20.4	29.1	
Father's education level							.42
None	1.9	2.3	0	3.9	3.8	6.3	
Elementary/junior high	24.5	20.4	21.9	26.4	27.6	17.1	
High school	18.9	15.9	21.9	6.9	11.4	10.8	
University education (up to bachelor's degree)	35.9	43.2	34.4	31.4	30.5	35.1	
University studies (master's or doctoral studies)	18.9	18.2	21.9	31.4	26.7	30.6	
Mother's place of residence							.1
Paris	20	24.4	24.2	34.3	38.9	34.2	
Hauts-de-Seine	20	24.4	30.3	32.4	23	29.9	
Seine-Saint-Denis	38.2	22.2	24.2	20.9	18.6	19.7	
Val-de-Marne	21.8	28.9	21.2	12.4	19.5	16.2	
French language only spoken at home	62.2	76	72.7	71.7	80.5	79.5	.4

CCHD, cyanotic congenital heart defect.
*Less than 37 weeks of gestation.

Table VII. Mean scores for neurocognitive specific domains (NEPSY-II)

	Attention and executive functions			Visuospatial
Subtests	**Auditory attention**	**Inhibition**	**Flexibility**	**Geometric puzzles**
All CHD	9.5 ± 3.6	9.3 ± 3.3	9.4 ± 3.1	11.0 ± 2.1
CHD groups				
Cyanotic CHD with heart failure (n = 55)	9.1 ± 3.6	9.3 ± 2.7	9.5 ± 3.3	11.1 ± 1.9
Non-cyanotic CHD with heart failure (n = 50)	9.1 ± 3.9	9.1 ± 3.8	9.3 ± 3.1	10.8 ± 2.7
Cyanotic CHD without heart failure (n = 33)	9.5 ± 3.2	9.3 ± 3.6	9.1 ± 3.4	10.9 ± 2.5
Minor CHD requiring intervention (n = 105)	9.2 ± 3.5	8.9 ± 3.6	9.4 ± 3.3	11.3 ± 2.2
Minor CHD not requiring intervention (n = 113)	9.8 ± 3.6	9.3 ± 3.1	9.4 ± 2.8	10.9 ± 2.0
Control (n = 117)	9.6 ± 3.9	9.6 ± 3.1	9.6 ± 3.1	11.0 ± 1.8
Control bias* (n = 93)	9.9 ± 3.7	9.8 ± 3.2	9.8 ± 3.1	11.5 ± 2.4

*Excluded children who do not speak French at home.

Table VIII. Linear regression coefficient of neurocognitive specific domains (NEPSY-II)

	Executive function and inhibition						Visuospatial	
	Auditory attention		Inhibition		Flexibility		Geometric puzzles	
CHD groups	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Cyanotic CHD with heart failure	0.3 (−1.5 to 2.1)	0.3 (−1.4 to 2.2)	−0.6 (−1.9 to 0.7)	−0.5 (−1.8 to 0.8)	−1.1 (−2.3 to 0.2)	**−1.2 (−2.4 to 0.0)**	−0.3 (−1.3 to 0.7)	−0.4 (−1.3 to 0.5)
Non-cyanotic CHD with heart failure	−0.1 (−1.5 to 1.3)	−0.1 (−1.5 to 1.3)	−0.6 (−1.8 to - 0.6)	−0.4 (−1.6 to - 0.7)	−0.7 (−1.9 to 0.5)	−0.7 (−1.9 to 0.5)	−0.4 (−1.2 to 0.4)	−0.4 (−1.2 to 0.4)
Cyanotic CHD without heart failure	0.5 (−1.3 to 2.3)	0.6 (−1.1 to 2.5)	−0.5 (−2.0 to 0.9)	−0.4 (−1.8 to 1.1)	−1.0 (−2.5 to 1.2)	−1.0 (−2.5 to 0.4)	−0.4 (−1.4 to 0.7)	−0.3 (−1.2 to 0.8)
Minor CHD requiring intervention	−0.2 (−1.5 to 1.0)	−0.1 (−1.4 to 1.1)	**−1.2 (-2.4 to - 0.1)**	−1.1 (−2.2 to 0.1)	−−0.2 (−1.4 to 1.1)	−0.1 (−1.2 to 1.1)	0.2 (−0.4 to 1.1)	0.3 (−0.5 to 1.1)
Minor CHD not requiring intervention	0.3 (−0.7 to 1.3)	0.2 (−0.8 to 1.2)	−0.4 (−1.2 to 0.5)	−0.3 (−1.2 to 0.5)	− 0.3 (−1.1 to 0.5)	−0.2 (−1.1 to 0.6)	−0.2 (−0.8 to 0.3)	−0.1 (−0.6 to 0.5)

*Adjusted for sex of infant, prematurity, maternal geographic origin, maternal education, and French language only spoken at home. $P < .05$ (level of significance).