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Population-based study of cognitive outcomes in congenital heart defects

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ABSTRACT

Objective To characterise and compare cognitive outcomes in children with operated (open-heart surgery) and non-operated (catheter-based interventions only or no intervention) congenital heart defects (CHD) and to determine associated risk factors.

Design This prospective population-based study reports outcomes of 3-year-old children with CHD with or without open-heart surgery.

Main outcome measures Standardised cognitive scores (mean scores and proportions below normative values) were assessed with the Kaufman Assessment Battery for Children II. We analysed demographic, perinatal and operative variables as predictors of cognitive outcomes.

Results 419 children participated (154 with open-heart surgery; 265 without surgery). Global cognitive scores did not differ between the groups. Compared with the non-operated group, children who underwent surgery obtained lower scores in expressive language (p=0.03) and logical reasoning (p=0.05). When compared with test norms, the frequency of global cognitive scores >1 SDs below the expected mean was higher in the surgical group (25% vs 16% in the general population) (p=0.03). A higher-than-expected proportion of children in the non-operated group scored >2 SDs below the expected mean (7% vs 2%) (p=0.05). Being small for gestational age (SGA) significantly increased the risk of cognitive impairment in the surgical group, after adjustments for multiple covariates including maternal education, complexity of the CHD and operative-related variables (adjusted OR=5.9; 95% CI (1.7 to 20.1)).

Conclusions Despite mean scores within the normative range, a high proportion of preschool children with CHD with or without surgery are at early cognitive risk. SGA is a strong predictor of the neurodevelopmental prognosis in CHD.

What is already known on this topic?

- Neurodevelopmental impairment is the most frequent morbidity in children with complex congenital heart defects (CHD).
- Data on the cognitive outcomes in children with CHD who do not undergo open-heart surgery are scarce.
- Limited data exist regarding the impact of patient-specific perinatal factors such as being small for gestational age (SGA) in cognitive outcomes in CHD.

What this study adds?

- Children with non-operated CHD did not differ from those who underwent open-heart surgery on most cognitive outcomes.
- The proportion of children with non-operated CHD scoring at the threshold for severe cognitive dysfunction was three times higher than expected in the general population.
- Children with CHD who were SGA and who underwent open-heart surgery had nearly a sixfold increased risk of cognitive dysfunction.

INTRODUCTION

Neurodevelopmental sequelae are frequent morbidities in the population with congenital heart defects (CHD).[1 2] Most studies reporting cognitive outcomes come from specialised centres and have primarily included cases with critical CHD after infant open-heart surgery.[3–10] CHD comprises a heterogeneous group of malformations. On the one hand, CHD requiring early cardiac surgery is associated with neurological risks that may adversely impact cognitive development.[2 11] Although risk factors such as preterm birth[12] and operative variables[11] have been identified for this subgroup, less is known regarding the role of other perinatal factors, such as being small for gestational age (SGA) on cognitive outcomes. On the other hand, CHDs that do not require open-heart surgery represent more than half of the cases.[13] Despite their high prevalence, few studies have addressed the cognitive outcomes and associated risk factors in children with CHD treated with percutaneous procedures only,[14 15] and there are no data available for those who did not undergo any cardiac intervention in the first years of life.

This is the first population-based prospective study (EPIdemiological study of long-term outcomes of children with congenital CARDiac defects, EPICARD) investigating cognitive outcomes in children with CHD. Our first aim was twofold. We sought to compare outcomes of children who underwent open-heart surgery versus those who did not, that is, CHD treated with catheter-based interventions only or without any type of cardiac intervention. We also sought to characterise outcomes in each CHD subgroup with respect to normative values in the general population. Our second

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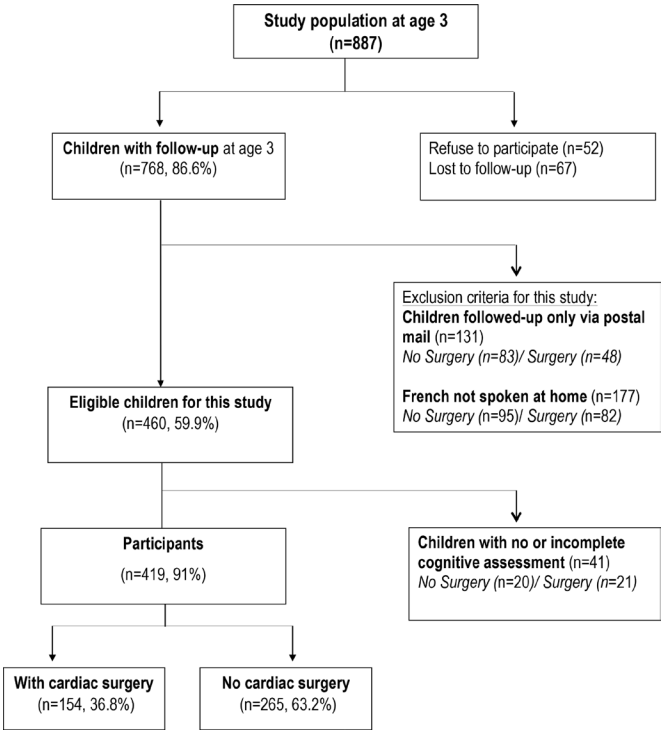

Figure 1 Flow chart of the study population of children with CHD followed up at age 3 in EPICARD. CHD, congenital heart defects; EPICARD, EPIdemiological study of long-term outcomes of children with congenital CARDiac defects.

aim was to identify patient-related risk factors associated with outcomes, including perinatal factors such being SGA, in surgical and non-surgical subgroups.

METHODS

Subjects

The EPICARD study is a population-based, prospective cohort study of children with CHD born in the Paris area. All cases (live births, terminations of pregnancy for fetal anomaly, fetal deaths) diagnosed in the prenatal period or up to 1 year of age were eligible for inclusion. Diagnoses of CHD and associated comorbidities (ie, genetic or extracardiac anomalies) were confirmed in specialised paediatric cardiology departments. Clinical and epidemiological data for this cohort are provided elsewhere.[13 16 17] The study population comprised a total of 887 live cases without known genetic or extracardiac anomalies at enrolment, that is, all complex anomalies and a random sample of newborns with small ventricular septal defects (VSD) without haemodynamic consequences. For this study, French-speaking children who completed an on-site evaluation were eligible (n=460). Informed consent was obtained and the study was approved by the hospitals' ethics committees. Results from 419 eligible children (mean age=3 years, 7 months) with completed cognitive assessment are presented (figure 1). Comparisons between participants and non-participants on demographic and medical characteristics are presented in (online supplementary appendix 2).

Demographic, medical and operative data

We recorded participants' gender and maternal level of education based on classifications from the National Institute of Statistics and Economic Studies. Medical characteristics were extracted from records by nurses or paediatricians. These include prenatal diagnosis of CHD, birth weight, proportion classified as preterm, that is, gestational age (GA) <37 weeks, proportion born SGA (10th percentile), head circumference, use of catheter-based interventions, complexity of the CHD[18] (ie, simple, moderate and CHD of great complexity), as well as age at cognitive assessment. SGA was calculated using birth weight, GA and gender reference curves from the National French Obstetric and Perinatal clinical recommendations. For children who underwent at least one open-heart procedure, we recorded the timing of first surgery, that is neonatal, ≤30 days versus postneonatal, the duration of the first cardiopulmonary bypass (CPB), the duration of the first intensive care unit (ICU) stay and the number of open-heart surgeries.

Cognitive evaluation

Cognitive assessment was conducted using the standardised French version of the Kaufman Assessment Battery for Children (K-ABC II) second edition.[19] Trained paediatric psychologists conducted all assessments. The K-ABC II for children 3–4 years old consists of seven subtests (mean=10; SD=3) evaluating specific cognitive skills: (1) triangles (visuospatial and visuoperceptive skills); (2) face recognition (visuoperceptual skills for facial stimuli); (3) conceptual thinking (general fluid intelligence, logical reasoning); (4) word order (speed of processing, overall executive functions); (5) Atlantis (associative memory); (6) riddles (everyday life knowledge and receptive language); and (7) expressive vocabulary (lexical knowledge/word access). A global cognitive score (mean=100, SD=15) is calculated based on all subtest scores. Global scores ≤85 (≥1 SD below the expected mean) are suggestive of a global cognitive impairment, and scores ≤70 (≥2 SD below the expected mean) indicate a severe intellectual impairment. Specific deficits can be detected by means of identifying subtests scores ≤7 (≥1 SD below the expected mean). Scores ≥1 SD and ≥2 SD below normative mean values are expected in 16% and 2% of the general population, respectively.

Statistical methods

Results are presented in proportions and means (SD) when appropriate. The cohort was stratified by cardiac surgical status (cardiac surgery vs no cardiac surgery) for analyses. Comparisons of demographic and clinical characteristics between CHD subgroups were conducted using X^2 or Fisher's exact test for categorical variables and t-tests for continuous measures. Comparisons of cognitive outcomes between the surgical and non-surgical group were performed with multiple linear and logistic regression models with adjustments for concurrent maternal educational level, CHD complexity (simple vs moderate or severe) and preterm birth. In order to compare children at highest risk (ie, who underwent surgery with or without catheter-based interventions in the interim) with those at lowest expected risk (ie, who did not undergo any procedure), we conducted a sensitivity analysis excluding children who had had catheter-based interventions from the non-surgical group. We also compared outcomes in each CHD group with normative values using two-sample t-tests and χ^2 as appropriate. Finally, risk factors of interest in both CHD groups included maternal level of education, the child's gender, proportion classified as SGA, proportion born preterm, CHD complexity and use of catheter-based interventions. For those who had cardiac surgery, we included timing of surgery, duration of first ICU stay, total number of cardiac surgeries and duration of the first CPB. We estimated the effects of risk factors on

Table 1 Demographic and clinical characteristics for children with CHD

	All (n=419)	No cardiac surgery (n=265)	Cardiac surgery (n=154)	p Value
	n (%) or mean±SD			
Gender, male	196 (46.8)	106 (40.0)	90 (58.4)	<0.01
Maternal level of education*				0.38
Low	64 (15.3)	37 (14.0)	27 (17.5)	
Intermediate	138 (33.0)	84 (31.8)	54 (35.1)	
High	216 (51.7)	143 (54.2)	73 (47.4)	
Prenatal diagnosis	108 (25.8)	30 (11.3)	78 (50.7)	<0.01
Birth weight (kg)	3.1±0.6	3.1±0.7	3.2±0.6	0.20
Prematurity, <37	58 (13.9)	43 (16.3)	15 (9.7)	0.06
Small for gestational age (SGA)†	51 (12.2)	29 (11.0)	22 (14.3)	0.32
Head circumference (cm)‡	34.0±2.2	34.0±2.4	34.2±1.5	0.37
Catheter-based interventions	60 (14.3)	25 (9.4)	35 (22.7)	<0.01
Neonatal surgery§	–	–	69 (44.8)	–
Duration of first CPB (min)	–	–	79.5±4.7	–
Duration of first ICU stay (days)	–	–	9.6±6.7	–
Number of surgeries				–
1	–	–	126 (81.8)	
2	–	–	20 (13.0)	
3 and more	–	–	8 (5.2)	
Complexity of CHD				<0.01
Simple	252 (60.1)	221 (83.4)	31 (20.1)	
Moderate	104 (24.8)	40 (15.1)	64 (41.6)	
Great	63 (15.1)	4 (1.5)	59 (38.3)	
Age at assessment (year±month)	3.7±0.2	3.7±0.2	3.7±0.2	0.17

p<0.05 for comparisons between the groups with and without cardiac surgery. p Values are determined by X^2 or Fisher's exact test for categorical variables, t-tests for variables with means reported.
*High: bachelor's degree and above; intermediate: high school; low: middle school or lower.
†SGA was calculated using birth weight, GA and gender reference curves from the National French Obstetric and Perinatal clinical recommendations (www.audipog.net).
‡54 missing values (19 in the group with no surgery and 35 in the group with surgery).
§Open-heart surgery (thoracotomy or sternotomy).
¶CPB, cardiopulmonary bypass with or without deep hypothermic circulatory arrest.
CHD, congenital heart defect; GA, gestational age; ICU, intensive care unit; SGA, small for gestational age.

cognitive outcomes using linear regression for continuous (mean total K-ABC global score), and with logistic regression for binary outcomes (K-ABC global score ≤85; ie, scores below ≤1 SD) for each group independently. The effects are reported with regression (β) coefficients and 95% CI or ORs, as appropriate. We first obtained unadjusted estimates for each factor and subsequently adjusted estimates in multiple regression models, which included all the available variables of interest (fully adjusted models). A p value of 0.05 was considered significant. Statistical analyses were performed with SAS V. 9.3 software.

RESULTS

Participants' characteristics

Four hundred and sixty children were eligible for this study; however, cognitive assessment could not be completed in 41 children. The most frequent reasons included (1) lack of child's cooperation for testing, (2) behavioural difficulties and/or (3) motor and sensory disabilities not previously identified. This study presents data from 419 eligible children with CHD who completed the cognitive evaluation. Among these, 154 had undergone cardiac surgery (open-heart surgery with or without CPB) and 265 had either undergone only closed interventions or had not undergone any cardiac procedure at the time of the evaluation. CHD types included in each group with CHD are presented in online supplementary appendix 1).

Demographic and medical characteristics are presented in table 1. Children who underwent surgery had a higher proportion of male gender, prenatally diagnosed CHD, greater CHD complexity as well as a higher use of catheter-based interventions (all p values <0.01).

Cognitive outcomes

Compared with the group without cardiac surgery and after adjustments for maternal level of education, CHD complexity and prematurity, children who underwent surgery had significantly lower scores in expressive language (p=0.03) and logical reasoning (p=0.05). No differences in mean global cognitive scores or in the frequencies of global scores ≥1 SD or ≥2 SD below the expected mean were found between the CHD subgroups (table 2). Sensitivity analysis excluding cases with a history of catheter-based intervention in the non-surgical group (n=25) did not reveal any changes in the comparisons between CHD with and without surgery.

When compared with expected population norms, the frequency of scores ≥1 SD below the expected mean was higher in the group who underwent surgery (25% vs 16%) (p=0.03) but not in the group without surgery (19% vs 16%) (p>0.05). Children who underwent cardiac surgery also scored lower than expected at subtests assessing associative memory, logical reasoning and executive functions (all p<0.05). Conversely,

Table 2 Cognitive outcomes of children with CHD by surgical status

	All (n=419)	No cardiac surgery (n=265)	Cardiac surgery (n=154)	
	Mean±SD	Mean±SD	Mean±SD	p Value*
Global K-ABC score	100.0±18.2	101.3±18.3	97.6±17.9	0.08
≤1 SD, n (%)	89 (21)	50 (19)	39 (25)	0.17
≤2 SD, n (%)	27 (6)	18 (7)	9 (6)	0.26
Specific subtests				
Associative memory				
Atlantis	9.5±3.4	9.6±3.4	9.2±3.4	0.44
Logical reasoning				
Conceptual thinking	9.6±3.2	9.9±3.4	9.3±2.9	0.05
Visual-perceptual skills				
Face recognition	10.3±3.2	10.5±3.2	9.9±3.2	0.10
Expressive language				
Expressive vocabulary	10.5±3.5	10.8±3.5	9.9±3.4	0.03
Visual-spatial skills				
Triangles	10.7±3.6	10.9±3.7	10.4±3.5	0.33
Executive functions				
Word order	9.3±3.5	9.5±3.5	9.1±3.5	0.70
Everyday life knowledge				
Riddles	9.6±3.5	9.7±3.5	9.5±3.4	0.93

*p<0.05 for comparisons between cardiac surgery and no cardiac surgery CHD subgroups adjusting for maternal level of education, complexity of the CHD (simple vs moderate or great) and prematurity (birth <37 weeks of gestation). p Values are determined by linear regression models for numerical variables and logistic regression models for categorical variables.
CHD, congenital heart defect; K-ABC, Kaufman Assessment Battery for Children.

mean scores at expressive language and visual-spatial skills were higher than expected for children in the non-surgical group (p<0.05). Finally, the proportion of children with scores ≥2 SD below the expected population mean was significantly higher in the group without cardiac surgery only (7% vs 2%) (p=0.02).

Predictors of cognitive outcomes

In the non-surgical CHD group, lower maternal level of education was associated with lower global cognitive scores. In the surgical group, SGA and lower maternal level of education were associated with lower cognitive scores (table 3). Global cognitive impairment (scores ≥1 SD below normative values) was significantly associated with lower maternal education in both CHD groups (table 4). Finally, children in the surgical group who were born SGA had a significantly higher risk of cognitive dysfunction as expressed by global scores at least 1 SD below normative values (β and CI values in tables 3-4).

DISCUSSION

Our results showed that global cognitive abilities were not significantly different between the CHD groups (surgical and non-surgical). Compared with the non-operated subgroup, children who underwent surgery obtained lower scores in expressive language (9.9 vs 10.8) and logical reasoning (9.3 vs 9.9). When compared with population norms, the frequency of global scores >1 SDs below the expected mean was higher in the surgical group (25% vs 16%). Children who underwent surgery also scored lower than expected in subtests of associative memory, logical reasoning and executive function. Our findings for the surgical CHD group confirmed, at a population-based level, the high neurodevelopmental risk in these children from an early age.[2 7 20–23]

To our knowledge, this study provides the first investigation of cognitive outcomes in children with forms of CHD who did not require infant cardiac surgery. These defects represent nearly 50% of live births with CHD (eg, small VSD, atrial septal defects)[13] and constitute an overlooked population with respect to outcomes. Children with minor CHD have a low incidence of haemodynamic complications; thus, neurodevelopment is generally expected to be normal. However, very few data have been reported to support this assumption. Our findings showed that, as a group, they obtained scores within the normal range. Nevertheless, an elevated proportion (7% vs 2% in the general population) presented with intellectual dysfunction (ie, global scores >2 SD below the mean), not previously associated with known chromosomal abnormalities and/or other diagnosed neurodevelopmental disorders at the time of evaluation. Because we did not perform DNA analyses, it cannot be excluded that undetected genetic abnormalities might have been present in cases with compromised outcomes. Of note, an important number of these children also had behavioural problems (attention, hyperactivity, oppositional behaviour), which may have interfered with the ability to capture their cognitive performance. Caution in the interpretation of this finding is warranted and longitudinal confirmation at school age is ongoing.

There is an emergent recognition of a common cognitive phenotype associated with complex CHD characterised by deficits in executive functions and visuospatial skills.[4–6 9 24] Our population-based data are consistent with this phenotype by showing that weaknesses in these areas might be identified early in the preschool years. Importantly, our findings should be interpreted within a public health perspective. Indeed, even though the differences in scores in our cohort (ie, between 0.6-point and 1-point decrement in subtest scores) may not be clinically significant for an individual child, they might be meaningful when investigating the impact of CHD at a population level. Indeed, in some populations exposed to other neurological risks, a modest shift in the mean IQ score is accompanied by a substantial increase in the proportion of cases with scores >1 or 2 SD below the mean.[25] In our study, the frequency of scores >1 or >2 SD below the mean were two to three times higher than expected, which warrants special attention. Because developmental gaps may worsen with age,[5 6] the detection of vulnerable areas in early childhood is key to adequately target interventions. Clinical professionals may consider a more in-depth preschool neuropsychological assessment, as general developmental scores may not allow to appreciate a child's emerging struggle with specific abilities (ie, executive functioning).

Noteworthy, our study identified being born SGA as one of the main risk factors for impaired outcomes in the group with open-heart surgery. To date, the few studies investigating the effects of SGA on outcomes in CHD have solely focused on medical outcomes.[26 27] Our findings showed that being SGA in the context of complex CHD increases the risk of cognitive impairment, although this was not found in the non-surgical group. Some interpretations could be suggested. First, fetuses with complex CHD have also in utero abnormal circulatory brain perfusion.[28–33] They also have a higher risk of intrauterine growth restriction (IUGR) and are twice as likely to be born SGA compared with non-cardiac newborns or to newborns with mild CHD.[33 34] Thus, being born SGA in the context of complex CHD might induce an exponential risk for fetal and neonatal brain immaturity, which in turn may derail the later neurological and developmental trajectory. Second, the underlying maternal and/or fetal aetiologies of SGA may be different in complex and mild CHD and may interact differently with respect to

Table 3 Risk factors associated with cognitive outcomes (K-ABC mean global score) in children with CHD

		No cardiac surgery				Cardiac surgery			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		*	95% CI	*	95% CI	*	95% CI	*	95% CI
Gender	Female	Ref	–	Ref	–	Ref	–	Ref	–
	Male	−2.5	(−7.0 to 2.1)	−2.4	(−6.6 to 1.8)	2.5	(−3.3 to 8.3)	1.8	(−3.8 to 7.5)
Maternal education	Low	−19.8	(−26.0 to −13.7)	−19.4	(−25.7 to −13.0)	−12.9	(−20.6 to −5.20)	−14.3	(−22.1 to −6.4)
	Intermediate	−9.1	(−13.7 to −4.5)	−9.2	(−13.9 to −4.6)	−5.9	(−12.0 to 0.2)	−6.6	(−12.7 to −0.5)
	High	Ref	–	Ref	–	Ref	–	Ref	–
SGA	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	−7.7	(−14.8 to −0.7)	−5.4	(−12.1 to 1.4)	−10.4	(−18.4 to −2.5)	−14.2	(−22.3 to −6.2)
Prematurity	<37	−2.1	(−8.1 to 4.0)	−1.0	(−6.7 to 4.6)	−11.3	(−20.7 to −1.8)	−4.3	(−14.0 to 5.5)
	≥37	Ref	–	Ref	–	Ref	–	Ref	–
Complexity of the CHD	Simple	Ref	–	Ref	–	Ref	–	Ref	–
	Moderate/Great	2.0	(−4.0 to 8.0)	2.7	(−2.9 to 8.4)	−0.5	(−7.6 to 6.6)	0.3	(−6.9 to 7.4)
Catheter-based interventions	No	Ref	–	Ref	–	Ref	–	Ref	–
	Yes	2.1	(−5.5 to 9.7)	2.6	(−4.5 to 9.7)	−0.9	(−7.7 to 5.9)	3.1	(−4.2 to 10.4)
Timing of first surgery	Neonatal		–		–	−2.3	(−8.1 to 3.4)	−4.6	(−10.8 to 1.6)
	Postneonatal		–		–	Ref	–	Ref	–
Duration of first ICU stay (day)			–		–	−0.1	(−0.5 to 0.3)	0.0	(−0.5 to 0.4)
Number of surgeries	1		–		–	Ref	–	Ref	–
	≥2		–		–	−7.6	(−14.9 to −0.3)	−6.4	(−13.7 to 0.9)
Duration of first CPB (30 min)			–		–	0.0	(−1.7 to 1.7)	0.0	(−1.7 to 1.7)

*Coefficients and 95% CIs are determined by linear regression models (unadjusted and fully adjusted).
CHD, congenital heart defect; CPB, cardiopulmonary bypass; ICU, intensive care unit; K-ABC, Kaufman Assessment Battery for Children; SGA, small for gestational age.

Table 4 Risk factors associated with cognitive impairment (K-ABC global score ≥1 SD below normative values) in children with CHD

		No cardiac surgery				Cardiac surgery			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender	Female	1.0	–	1.0	–	1.0	–	1.0	–
	Male	1.5	(0.8 to 2.8)	1.5	(0.8 to 2.9)	0.7	(0.3 to 1.4)	0.7	(0.3 to 1.6)
Maternal level of education	Low	7.3	(3.1 to 16.8)	7.7	(3.3 to 18.1)	7.7	(2.7 to 21.4)	11.5	(3.5 to 38.1)
	Intermediate	2.3	(1.1 to 4.9)	2.3	(1.1 to 4.8)	3.0	(1.2 to 7.4)	3.6	(1.3 to 10.2)
	High	1.0	–	1.0	–	1.0	–	1.0	–
SGA	No	1.0	–	1.0	–	1.0	–	1.0	–
	Yes	1.4	(0.6 to 3.5)	1.3	(0.5 to 3.6)	2.4	(0.9 to 6.0)	5.9	(1.7 to 20.1)
Prematurity	<37	0.7	(0.3 to 1.6)	0.6	(0.2 to 1.5)	2.1	(0.7 to 6.5)	0.7	(0.2 to 3.0)
	≥37	1.0	–	1.0	–	1.0	–	1.0	–
Complexity of the CHD	Simple	Ref	–	Ref	–	Ref	–	Ref	–
	Moderate/Great	1.1	(0.5 to 2.5)	1.3	(0.5 to 3.6)	0.5	(0.2 to 1.3)	0.4	(0.1 to 1.1)
Catheter-based interventions	No	1.0	–	1.0	–	1.0	–	1.0	–
	Yes	1.1	(0.4 to 3.0)	1.1	(0.4 to 3.2)	1.5	(0.7 to 3.4)	1.0	(0.3 to 3.0)
Timing of first surgery	Neonatal		–		–	1.1	(0.5 to 2.2)	1.7	(0.6 to 4.7)
	Postneonatal		–		–	1.0	–	1.0	–
Duration of ICU stay (day)			–		–	1.0	(0.9 to 1.1)	1.0	(0.9 to 1.1)
Number of surgeries	1		–		–	1.0	–	1.0	–
	≥2		–		–	1.9	(0.8 to 4.5)	2.4	(0.8 to 7.2)
Duration of CPB (30 min)			–		–	0.9	(0.8 to 1.2)	0.9	(0.7 to 1.2)

OR coefficients and 95% CIs are determined by logistic regression models (unadjusted and fully adjusted).
CHD, congenital heart defect; CPB, cardiopulmonary bypass; ICU, intensive care unit; K-ABC, Kaufman Assessment Battery for Children; SGA, small for gestational age.

outcomes. Finally, because SGA remains a known risk factor for lower long-term neurodevelopmental scores,[35–37] neurodevelopmental surveillance for all children with CHD born SGA is recommended.

Our study should be interpreted in light of several limitations. Our findings may underestimate the adverse impact of CHD on cognitive outcomes as there were few cases of the most severe forms of CHD including univentricular hearts. Indeed, the high rates of prenatal screening and detection of CHD and the uncertainties in prognosis lead to a significant number of terminations of pregnancies in many European countries, which limits our capacity to include these children in studies.[13] We could not explore IUGR because we did not have access to complete prenatal ultrasound information and thus could not distinguish IUGR from SGA. Finally, our findings reported at age three may not reflect long-term outcomes. Longitudinal follow-up of our cohort is currently being conducted and will assess the implications of our findings at school age.

In summary, some children with CHD who did not require surgery may be at increased risk of cognitive dysfunction. Being born SGA may be an important predictor of outcomes in CHD requiring surgery, suggesting that perinatal patient-specific factors play a critical role on neurodevelopmental prognosis. Finally, the field of cardiac neurodevelopment is rapidly moving towards the development of intervention strategies to improve outcomes.[38] Our findings support the implementation of targeted interventions for neurodevelopmental areas at higher risk in the population with CHD (ie, executive function deficits) by showing that (1) specific cognitive vulnerabilities can be detected as early as 3 years old, and (2) all children with CHD may benefit from these efforts, including children with milder forms who may be particularly underserved in terms of developmental care.

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