Cardiology in the Young

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Neurodevelopmental outcomes at 18 months of children diagnosed with CHD compared to children born very preterm

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Abstract

Children with CHD or born very preterm are at risk for brain dysmaturation and poor neurodevelopmental outcomes. Yet, studies have primarily investigated neurodevelopmental outcomes of these groups separately. *Objective:* To compare neurodevelopmental outcomes and parent behaviour ratings of children born term with CHD to children born very preterm. *Methods:* A clinical research sample of 181 children (CHD [n = 81]; very preterm [≤32 weeks; n = 100]) was assessed at 18 months. *Results:* Children with CHD and born very preterm did not differ on Bayley-III cognitive, language, or motor composite scores, or on expressive or receptive language, or on fine motor scaled scores. Children with CHD had lower ross motor scaled scores compared to children born very preterm ($p = 0.047$). More children with CHD had impaired scores (<70 SS) on language composite (17%), expressive language (16%), and gross motor (14%) indices compared to children born very preterm (6%; 7%; 3%; ps < 0.05). No group differences were found on behaviours rated by parents on the Child Behaviour Checklist (1.5–5 years) or the proportion of children with scores above the clinical cutoff. English as a first language was associated with higher cognitive ($p = 0.004$) and language composite scores ($p < 0.001$). Lower median household income and English as a second language were associated with higher total behaviour problems (ps < 0.05). *Conclusions:* Children with CHD were more likely to display language and motor impairment compared to children born very preterm at 18 months. Outcomes were associated with language spoken in the home and household income.

Children diagnosed with CHD and children born very preterm are at risk for poorer neurodevelopmental outcomes including cognitive, language, motor, behaviour, social, and academic delays.[1,2] Research has highlighted similar patterns of brain dysmaturation in term neonates with CHD and very preterm neonates without CHD.[3] Despite these similarities in brain development, studies to date have primarily investigated neurodevelopmental outcomes of these children independently, leaving commonalities in neurodevelopmental profiles unclear. Having a better understanding of shared and unique neurodevelopmental outcomes among these populations will provide directions for developmental surveillance and potential transdiagnostic intervention services.

CHD is one of the most common congenital defects, encompassing diverse conditions that impact the structural and/or functional integrity of the heart.[4,5] In Canada, approximately 1 in 80–100 children are born with CHD.[5,6] Significant improvements in surgical techniques and perioperative care have made survival the expectation for the majority of children diagnosed with CHD, with 90% of children surviving to adulthood.[7] Multiple factors have been identified that contribute to the neurocognitive risk profile of children with CHD, including reduction in blood oxygen delivered to the brain, a predisposition for brain injury due to prenatal abnormal white matter maturation,[8] and perioperative and medical factors (i.e., genetics, physical and social environment, severity of cardiac lesion, and gestational age at birth).[9,10] Changes to brain volume, dysmaturation, and microstructure of the brain are directly related to poorer neuropsychological outcomes, with documented impacts on language, executive dysfunction, and motor deficits.[11–14]

Very preterm birth, defined as a gestational age of < 32 weeks,[2,15] impacts approximately 8% of children in Canada.[16] Despite steady improvements in obstetric and neonatal care that have reduced mortality,[17] there is considerable diversity in neurodevelopmental outcomes among

very preterm children. Children born very preterm are more likely to develop significant impairments such as cerebral palsy and exhibit deficits in cognition, academics, and behaviour compared to term-born children.[2,15,18,19]

The commonality in neuropsychological risk among children born very preterm and children diagnosed with CHD can be attributed to similar antenatal and postnatal neurobiological vulnerability.[20,21] Infants born full term with CHD have brain structures similar to infants born preterm and have a remarkably high rate of white matter injury.[10,22–24] Common mechanisms proposed include, among others, oxygen disruption to the brain resulting from premature birth or from structural and functional changes to the heart that alter blood flow to the brain. One of the only studies to conduct a topology and comparison analysis of infants born with CHD and infants born very preterm found similar brain anomalies with concordance of total punctate white matter injury volumes for both groups.[25]

Decades of research findings pertaining to neuropsychological outcomes of these populations independently also highlight several overlapping outcomes. Specifically, children with CHD and children born very preterm exhibit deficits in attention, executive function, visual-spatial memory, motor skills, working memory, visual perception, and an increased risk of psychological disorders such as anxiety and depression.[2,26,35–37,27–34] Both populations exhibit speech and language difficulties; children with CHD exhibit problems with speech production, phonological awareness, and letter fluency,[14,38] and children born very preterm display receptive language deficits.[18,35] Furthermore, children born with CHD and children born very preterm have a higher incidence of being diagnosed with attention deficit-hyperactivity disorder compared to term-born healthy controls.[36,39]

Despite similar patterns of brain dysmaturation and overlapping neurodevelopmental concerns, research to date has primarily investigated outcomes of these populations separately leaving similarities and differences in outcomes unknown. Further, there is a dearth of research directly comparing impacts of common biopsychosocial risk factors in very preterm children and term children with CHD in relation to their neurodevelopmental profiles, leaving correlates of progress unclear. Both groups continue to represent a substantial number of children in need of neurodevelopmental follow-up care. Examining common outcomes and associated risks from medical and neuroanatomical perspectives, but importantly, considering potential common social determinants of health would direct future care with greater precision. The objectives of the current study were to compare the early neurodevelopmental and behavioural outcomes of term children diagnosed with CHD to very preterm children at 18 months of age and to examine their association with socio-demographic and white matter injury characteristics.

Methods

Patients

A clinical research sample of 181 children diagnosed with CHD (i.e., ≥ 37 weeks gestational age; n = 81) or born very preterm (i.e., ≤ 32 weeks gestational age; n = 100) was included from a larger cohort followed in the neonatal follow-up services at the Hospital for Sick Children and Mount Sinai Hospital in Toronto, Canada. Inclusion criteria were a diagnosis of CHD or very preterm birth, completion of a neurodevelopmental assessment, and a child behaviour questionnaire completed by parent/guardian at 18-month corrected age. Exclusion criteria were extensive brain injury/malformation or presence of conditions that significantly impact cognitive functioning beyond what is common among children diagnosed with CHD and those born very preterm (e.g., congenital infection, intraventricular haemorrhage level 3 or 4, periventricular leukomalacia, neonatal stroke [severe ≥ 2/3], and/or hypoxic-ischaemic encephalopathy). See Figure 1 for patient inclusion flow chart and Table 1 for groups' characteristics. As shown in Figure 1, non-participation was largely due to missing Bayley-III and Child Behaviour Checklist data given transition to virtual appointments during the COVID-19 pandemic.

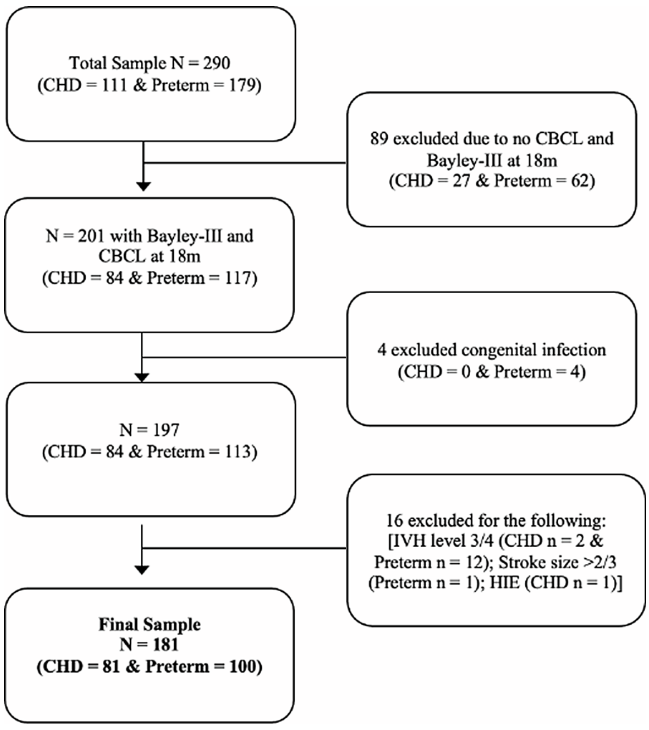

Figure 1. Patient inclusion flow chart.

Measures

Demographic information

Parents completed study questionnaires that included demographic information. Maternal age at birth and primary language spoken in the home were collected for the purpose of this study. Of note, a medical interpreter was utilised for families completing the study measures (i.e., Bayley-III and Child Behaviour Checklist 1.5–5) when English was not their primary language. To determine neighbourhood median income level, the first three digits of the patient"s postal code were collected. Median income data were extracted from the most recent Statistics Canada Census (2016) through the Computing in the Humanities and Social Sciences data centre at the University of Toronto. Using Statistics Canada postal code conversion file, the patient postal code data were linked to the appropriate census dissemination area and aggregated median neighbourhood household income (i.e., the amount that divides the income distribution of that group into two halves).

Medical information

Child birth history (i.e., gestational age, biological sex, and birth weight) was collected from medical charts.

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Table 1. Patient medical characteristics and demographic information (N = 181)

	Term CHD (n = 81)	Very preterm (n = 100)	p *(d or V)*
Gestational age at birth *(weeks) M(SD)*	39.04 (1.07)	27.42 (2.34)	< 0.001 (5.961)
range	37.14–41.57	22.71–31.57	
Sex assigned at birth *(males)*	55 (68%)	55 (55%)	0.09 (.131)
Birth weight (g) *M(SD)*	3355.85 (430.23)	1014.69 (359.58)	< 0.001 (6.178)
Current seizures	3 (4%)	1 (1%)	0.18 (.119)
White matter injury volume	42.35 mm^3 (98.74 mm^3)	28.26 mm^3 (154.96 mm^3)	0.48 (.107)
Maternal age at birth* *(years)*	32y 5 m (5y 6m)	33y 0 m (4y 7m)	0.45 (.128)
range	18–43	21–41	
English primary language	64 (79%)	85 (85%)	0.23 (.103)
Estimated median income level			1.00 (.006)
Lower income level (<$41, 873)	58 (73%)	77 (78%)	
Higher income level (≥ $41,873)	14 (18%)	18 (18%)	
CHD diagnostic categories			
Two ventricles with no arch obstruction	45 (56%)		
Two ventricles with arch obstruction	3 (4%)		
Single ventricle with no arch obstruction	28 (35%)		
Single ventricle with arch obstruction	5 (6%)		

*There were 25 patients in the CHD group and 1 patient in the preterm group missing maternal age at birth. There are 9 patients from the VP group missing data for white matter injury volume. There are 9 missing median income in the CHD group and 5 in the VP group. There are 2 patients missing English language in the VP group.
**CHD diagnoses included a variety of conditions such as transposition of great arteries (TGA), hypoplastic left heart syndrome (HLHS), ventricular septal defect (VSD), coarctation of the aorta (COA), double outlet right ventricle (DORV), and double inlet left ventricle.

White matter injury

Imaging for the CHD group was completed pre- and post-surgery and at term equivalent for the very preterm group. White matter injury was characterised as areas of T1 hyperintensity using 3D T1-weighted image and white matter injury volume was calculated based on the manual segmentation of all white matter injury lesions on the brain images. A study team member and study physician manually delineated scans using *Display* software (http://www.bic.mni.mcgill.ca/ServicesSoftwareVisualization) with high inter-rater reliability. Detailed methods have been previously described by Guo et al.[3,40]

Bayley scales of infant and toddler development Third Ed. (Bayley-III)

Neurodevelopment was assessed using the Bayley-III at 18 months[41,42] administered in English. This measure assesses neurodevelopmental functioning between 1 and 42 months of age across five neurodevelopmental domains: cognition, receptive and expressive language, fine and gross motor functioning. The Bayley-III is a gold-standard measure of infant and child development displaying strong validity and reliability (ranging from 0.90–.97).[41] The Bayley-III yields standard scores with a mean of 100 and standard deviation of 15 for cognitive, language, and motor composite scores, and subscale scores for receptive and expressive language and fine and gross motor ability (mean 10, standard deviation). Mild impairment was defined as a standard score of < 85 (i.e., 1 standard deviation below the mean), and moderate/severe impairment was defined as a standard score < 70 (i.e., 2 standard deviations below the mean). Ages for the very preterm patients were corrected for prematurity when scoring the Bayley-III.

Behavioural outcomes

Parent ratings of child behaviours were examined using the Child Behaviour Checklist for Ages 1.5–5. The Child Behaviour Checklist is completed by parents/caregivers to assess specific concerns related to child behaviour problems and has adequate psychometric properties.[43] Six syndrome scales contribute to broad internalising and externalising domain scores, as well as *sleep problems*, *total problems*, and DSM-5-related domain scores. The Child Behaviour Checklist yields T-scores with a mean of 50 and standard deviation of 10. Clinically elevated scores were defined as a *T*-score of > 70; borderline elevations were defined as a *T*-score of > 60.

Statistical analysis

Inferential statistics were used to compare mean differences between groups on the Bayley-III and behavioural outcomes from the Child Behaviour Checklist. Chi-squared analyses were used to compare the proportion of children in each group that demonstrated moderate/severe impaired neurodevelopmental scores and borderline to clinically elevated behavioural scores. Correlations were conducted to explore associations between sociodemographic variables, white matter injury volume, and outcomes. Four linear regression models were used to examine associations between outcomes (i.e., cognition, language, motor, and Child Behaviour Checklist total problem scores) and independent variables (i.e., white matter injury volume, maternal age at birth, English as a first language, estimated median income,

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Table 2. Cognitive and behavioural outcomes at 18 months CCA (N = 181)

	CHD (n = 81)	Very preterm (n = 100)	p (d)
Bayley-III outcomes			
Cognitive *M(SD)*	95.99 (13.91)	97.12 (13.98)	0.588 (0.081)
Language *M(SD)*	88.46 (17.45)	92.93 (17.11)	0.097 (0.259)
Receptive language M(SD)	8.57 (3.25)	9.04 (3.28)	0.354 (0.144)
Expressive language M(SD)	7.68 (2.95)	8.48 (3.18)	0.096 (0.261)
Motor score *M(SD)*	93.66 (15.29)	95.84 (11.50)	0.291 (0.164)
Fine motor M(SD)	10.12 (2.60)	10.15 (2.46)	0.932 (0.013)
Gross motor M(SD)	7.66 (2.94)	8.60 (2.63)	**0.030 (0.338)**
CBCL 1.5-5 outcomes			
Emotional reactivity	52.40 (4.32)	52.09 (4.31)	0.637 (0.071)
Anxious/depressed	51.44 (3.03)	52.13 (4.88)	0.271 (0.165)
Somatic complaints	52.53 (5.09)	53.44 (6.20)	0.357 (0.138)
Withdrawn	52.96 (5.36)	53.41 (6.31)	0.613 (0.076)
Sleep problems	54.31 (7.17)	53.50 (5.34)	0.386 (0.130)
Attention problems	54.30 (6.18)	54.04 (5.79)	0.774 (0.043)
Aggressive behaviours	51.95 (4.36)	52.11 (4.65)	0.814 (0.035)
Internalising behaviours	43.75 (10.61)	45.32 (10.12)	0.312 (0.152)
Externalising behaviours	46.36 (8.91)	46.48 (9.52)	0.930 (0.013)
Total problems	46.32 (9.86)	46.76 (10.19)	0.770 (0.044)

*Higher scores on the Bayley-III indicate better performance. Higher scores on the CBCL indicate poorer performance. Bolded outcomes indicate significant differences.

biological sex, and group). A priori power analysis revealed that the current sample size was sufficient to conduct four regression models with six predictors based on a power of at least 80%, medium effect size, and an adjusted alpha value of 0.0125 (conservatively adjusted to account for four regression models). All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM corp. Released, 2021).

Results

Objective 1: compare early neurodevelopmental and behavioural outcomes of term children diagnosed with CHD to very preterm children at 18 months of age

See Table 2 for group means on neurodevelopmental and behavioural outcomes.

Neurodevelopmental outcomes

The CHD and very preterm groups did not differ on cognitive, language, and motor composite scores, subscales of expressive and receptive language, or fine motor skills. There was a significant difference on the gross motor standard score, with the CHD group having lower scores compared to the very preterm group ($t(169) = -2.19$, $p = 0.047$, $d = 0.338$). There were no differences in the proportion of children with scores in the moderate/severe impaired range on cognitive or motor performance. However, significantly more children in the CHD group (17%) had a score ≤ 70 on the language composite compared to children in the very preterm group (6%; $\chi^2(1) = 7.10$, $p = 0.014$, $V = .204$). There were no differences in the proportion of children with low scores (<2SD below the mean) on receptive language and fine motor subtest scores. Significantly, more children in the CHD group had expressive language (16%) and gross motor (14%) subtest scores at least 2 SD below the mean compared to children in the very preterm group (7 and 3%, respectively; $\chi^2(1) = 4.92$, $p = 0.032$, $V = 0.171$ and $\chi^2(1) = 7.74$, $p = 0.009$, $V = 0.213$, respectively).

Behavioural outcomes

Children in the CHD and very preterm groups did not differ in parent ratings of their behaviour on Child Behaviour Checklist scores (i.e., mean scores or proportion of clinically elevated). Among composite scores, internalising problems had the highest proportion of elevated scores. Among subscales, attention, sleep, withdrawal, depression, and somatic complaints had the highest proportion of elevated scores.

Objective 2: examine associations with sociodemographic and white matter injury characteristics

The Bayley-III cognitive composite was positively associated with English as a primary language and household median income, and the language composite score on the Bayley-III was positively associated with English as a primary language. The total problem Child Behaviour Checklist composite score was associated with median income.

The regression model examining cognitive composite scores was significant ($F(6,136) = 3.30$, $p = 0.005$, $R = 0.364$) explaining 13.2% of the variance. English as the child's primary language ($\beta = 0.253$, $p = 0.004$) was associated with higher cognitive composite scores. Higher median income approached significance

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in the model (β =0.171, p = 0.055) as a predictor of higher cognitive composite scores.

The model examining language composite scores was significant ($F(6,129) = 4.82$, $p < 0.001$, $R = 0.436$), explaining 19% of the variance. English as a primary language (β =0.389, $p < 0.001$) was associated with higher language composite scores. Biological sex approached significance in the model (β =0.149, p = 0.079), with female sex associated with higher language composite scores.

The model examining motor composite scores was not significant ($F(6,130) = 0.79$, $p = 0.58$, $R = 0.192$), explaining 3.7% of the variance. White matter injury volume approached significance in the model (β = −0.160, p = 0.085).

The model examining the Child Behaviour Checklist total problem score was significant ($F(6,137) = 3.27$, $p = 0.005$, $R = 0.361$), explaining 13% of the variance. Median income (β= −0.195, p = 0.029) and English as a primary language (β = −0.198, p = 0.024) were negatively associated with total problems. Specifically, lower median income and English as a second language were associated with higher total problem scores. Maternal age at birth approached significance (β = −0.165, p = 0.056), with lower maternal age at birth associated with higher total problems.

Discussion

The current study is one of few investigations comparing neurodevelopmental and behavioural outcomes in children with CHD and children born very preterm. Overall, this study documented many common early cognitive and behavioural outcomes among the two groups of children at 18 months of age. Two unique outcomes also emerged, with children in the CHD group having lower motor and expressive language scores and a greater proportion of children with impaired scores compared to very preterm children. While it is important not to minimise neurodevelopmental risk among these populations exemplified by the proportion of children with impaired scores, it is also important to acknowledge that group mean scores were broadly average (low average to average) for both groups at 18 months. This reflects the combined advancements in acute medical treatments and follow-up early intervention services and their associated positive impact on neurocognitive outcomes.[2,44]

Among all children, median household income was associated with scores achieved on tests of cognition, language, and reported behavioural outcomes. Not surprisingly, children with English as a primary language (very preterm > CHD) were more likely to do better on English-based assessments; this highlights the significant limitations in monolingual assessment of core developmental outcomes.[45–47] White matter injury volume approached significance as the only associated variable for motor scores, suggesting some influence of condition severity on physical outcomes. Additional research is needed to understand the interplay between brain dysmaturation and social determinants in relation to specific domains of outcome.

It has been well documented in the literature, examining these populations independently, that factors such as maternal education, parent coping and stress, and household income are associated with neurodevelopmental and social–emotional behavioural outcomes.[48–50] Complementary to these findings, our study identified that median household income was associated with neurodevelopment in both groups. In future research, it will be important to promote recruitment methods that reduce barriers to accessing services to capture more families of diverse socioeconomic backgrounds.

Language and motor deficits are well documented in both children born very preterm and in children with CHD.[2,9] However, our findings highlighted that children with CHD have greater impairment compared to those who are born very preterm for expressive language and gross motor function at 18 months of age. This may be attributed to the multiple medical procedures and surgeries beyond the neonatal period, which can limit infant's physical activity and social engagement, possibly contributing to lags in motor and language development. At 18 months, children with CHD had scores in the low average range, which may place them at risk for falling further behind same aged peers over time depending on access and response to intervention.

Consistent with research conducted by Guo et al.,[40] in the current study total white matter injury volume was not significantly associated with neurodevelopmental outcomes at 18 months. However, total white matter injury volume approached significance in relation to motor outcome in our samples. This result is consistent with other studies examining these populations independently, reporting an association between early brain injury and motor development in early childhood.[10,51] There may also be a potential interaction with brain injury, socioeconomic status, and developmental outcomes given that previous literature has found higher socioeconomic status as a protective factor for early brain injury[52]. It is imperative to further explore the relationship between biochemical brain changes and neurological injury in order to fully understand how these characteristics contribute to the neurodevelopmental outcomes, and how they serve as potential predictive factors for need and response to early intervention.

Our study highlights an important limitation in common developmental follow-up clinical and research surveillance that largely employs monolingual English-based assessment tools.[45–47] There were additional variables that could not be addressed by the current study due to practical and other limitations. Income data reflected only neighbourhood average, as informed by census survey, which historically is only moderately correlated with self-reported income.[53] Data on race and ethnicity were not consistently available; thus, the representativeness of our sample is unknown. Outcomes were assessed at 18 months and neurodevelopmental profiles may change as the children continue to develop. Additionally, the heterogeneity of medical severity within these populations will also be associated with differential developmental trajectories of these children. Future research is warranted to examine outcomes at early school age.

Neurodevelopmental follow-up programmes are well established as part of the standard of care for children with CHD or born very preterm, with increasingly innovative models considering ways to monitor and promote both mental health and long-term neurodevelopmental outcomes in these populations.[50,54] The current findings suggest that both groups are at a similar risk of developing cognitive and behavioural problems. This study identified common parent concerns regarding child attention, sleep, social development, and health. Promising research has found that transdiagnostic telehealth intervention programmes increase parent competence and improve behaviour in children with neurological conditions broadly[55,56]. Given that both groups had similar cognitive and behavioural outcomes, a similar transdiagnostic approach to care may be warranted to help reduce waitlists and maximise access to patient care.

Overall, in our samples, common sociodemographic risk and testing factors were most influential in understanding early outcomes across CHD and very preterm populations and extended beyond the medical/neurobiological impacts measured in this

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study. This is an essential reminder to consider social determinants of health and the limits of traditional measures of neurocognitive and behavioural outcomes via English-based assessments. It is also important to consider how neurodevelopmental follow-up assessment and intervention can promote more sensitive monitoring and scaffolding in early development among such high-risk medical populations. This will promote not only more equitable service delivery but also an improved scientific knowledge base regarding outcomes and needed interventions among these at-risk children and their families.

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Competing interests. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation Research Ethics Board at the Hospital for Sick Children (REB#1000047854 and REB#1000051521) and York University (STU2022038).

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