

EXAMINING NEUROPSYCHOLOGICAL OUTCOMES AND NEURAL CORRELATES OF
CHILDREN DIAGNOSED WITH CONGENITAL HEART DISEASE AND CHILDREN
BORN VERY PRETERM

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Abstract

Congenital heart disease (CHD) and very preterm (VP) birth are two distinct and high-risk neonatal conditions that independently affect a significant number of newborns each year. Both conditions share common risks for altered brain development and long-term neuropsychological challenges. CHD is one of the most common congenital defects worldwide, affecting ~1 in 80-100 newborns in Canada each year, and approximately 11% of infants are born preterm. Despite medical advances that have improved survival rates in both populations, children remain vulnerable to a range of neurodevelopmental difficulties. Past research has shown that newborns with CHD and VP newborns without CHD have similar brain anomalies. To date, few studies have compared infants born with CHD to infants born VP and there is little research examining the association between neuropsychological outcomes and brain metabolites in these populations. This dissertation examined cross-sectional and long-term neurodevelopmental outcomes of infants with CHD and infants born VP, and examined associations with neurological, medical, and psychosocial characteristics. Using a large clinical sample, a series of 3 studies were conducted: 1) comparison of 18-month neurodevelopmental outcomes of children with CHD to children born VP; 2) examination of longitudinal neurodevelopmental outcome trajectories among these groups between 18-to-36 months of age; and 3) exploration of the relationship between neurometabolic concentrations of these groups and neurodevelopmental outcomes. This dissertation is one of the few to examine short and longer-term neurodevelopmental outcomes of children with CHD as compared to children born VP. Findings from the current dissertation may help inform clinical practice and direct surveillance and intervention initiatives to optimize neuropsychological outcomes.

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Conflict of Interest

The authors do not have any conflicts of interest to disclose.

Ethical Consideration and 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). Data collected as part of this research dissertation is part of two larger clinical research registries at the Hospital for Sick Children in Toronto, Ontario. These larger research registries have been approved by the Research Ethics Board at the Hospital for Sick Children with the current author, Samantha D. Roberts, listed as a doctoral student and research assistant on both projects.

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List of Abbreviations

AACN	American Academy of Clinical Neuropsychology
ACE Inhibitor	Angiotensin-converting enzyme inhibitory
ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect (AVSD)
BSID-III	Bayley Scales of Infant Development 3 rd edition
CA	Corrected Age
CBCL 1.5-5 years	Child Behavior Checklist 1.5-5 years
CHD	Congenital Heart Disease
Cho	Choline
COA	Coarctation of the Aorta
DILV	Double Inlet Left Ventricle
DORV	Double Outlet Right Ventricle
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5 th Edition
ECMO	Extracorporeal membrane oxygenation
FDR	False Discovery Rate
GA	Gestational Age
HLHS	Hypoplastic Left Heart Syndrome
IVH	Intraventricular hemorrhage
Lactate/Cho	Lactate Choline Concentration Ratio

MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-acetylaspartate
NAA/Cho	N-acetylaspartate Choline Concentration Ratio
PDA	Patent Ductus Arteriosus
RCI	Reliable Change Index
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect
VP	Very Preterm
WM	White Matter
WMI	White Matter Injury

Chapter 1: Introduction

1.1 Overview of Congenital Heart Disease

Congenital heart disease (CHD) refers to structural or functional abnormalities of the heart and great vessels that are present either in utero or at birth. CHD is one of the most common congenital defects among children with diverse conditions affecting the structural and functional integrity of the heart (Cassidy et al., 2015a; Van Der Linde et al., 2011a). In Canada, approximately 1 in 80-100 children are born with CHD each year (Canadian Congenital Heart Alliance, 2017; Gerstle et al., 2016; Van Der Linde et al., 2011). Significant improvement in surgical techniques and perioperative care has made survival the expectation for most children who are diagnosed with CHD and, because of this, CHD is now considered a chronic condition (Canadian Congenital Heart Alliance, 2017; Claessens et al., 2017; Van Der Linde et al., 2011). Forty years ago, only 20% of children born with CHD survived into adulthood. However, today 90% of children born with CHD survive (Canadian Congenital Heart Alliance, 2017; Marelli et al., 2016; Wernovsky, 2006). However, there are several adverse implications of CHD including reduction in blood oxygen being delivered to the brain, increased vulnerability to brain injury, and associated neurocognitive and motor deficits.

In a healthy developed heart, there are four main sections called chambers. These are known as the left atrium (responsible for collecting blood that returns from the lungs), left ventricle (the main pumping chamber to the body), right atrium (responsible for collecting blood returning from the body's veins), and right ventricle (pumps blood through the lungs; American Heart Association, 2022; NHS, 2021). There are also four valves that control how the blood flows through the heart and around the body. These are called the mitral valve (separates the left atrium from the left ventricle), aortic valve (separates the left ventricle from the main artery,

aorta), tricuspid valve (separates the right atrium from the right ventricle), and the pulmonary valve (separates the right ventricle from the pulmonary artery to the lungs). When working properly, the heart carries blood in a circulatory pattern where the blood is pumped through the heart to the lungs for oxygen, back to the heart and then out to the body for delivery of oxygen before returning to the heart to begin the process again (American Heart Association, 2022). A CHD is diagnosed when any of these chambers or valves do not develop properly while a baby is in utero. See Figure 1 for the anatomy of a healthy heart.

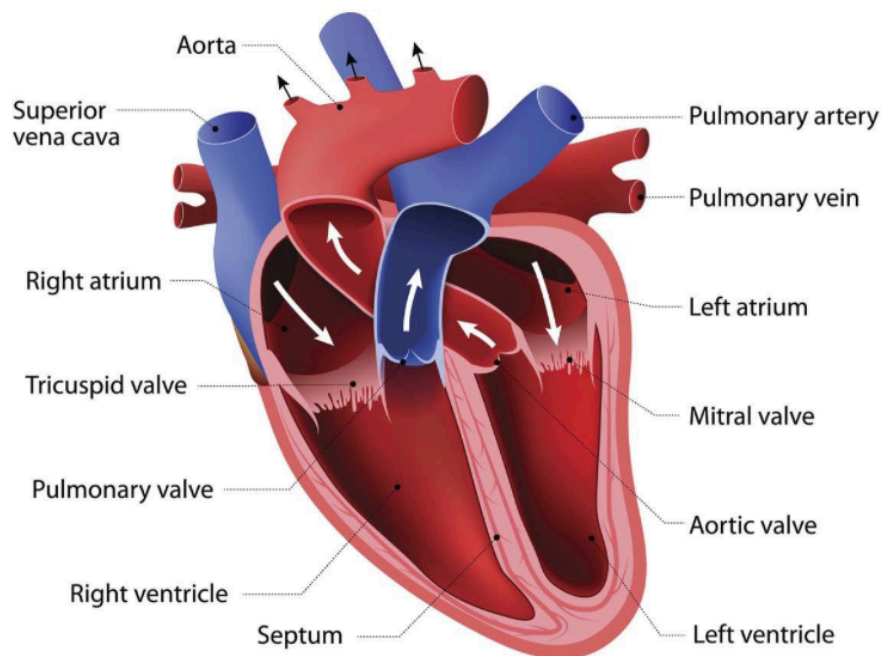


Figure 1. Anatomy of healthy heart (NHS, 2021).

Structural Subtypes and Classification of CHD. CHD encompasses a wide range of structural abnormalities, which are typically categorized based on the specific anatomical defect. CHD diagnoses are generally divided into acyanotic (i.e., normal oxygen levels) and

cyanotic (i.e., low oxygen levels) conditions (National Heart, 2022; NHS, 2021). Acyanotic heart conditions include Atrial Septal Defects (ASD), Ventricular Septal Defects (VSD), Patent Ductus Arteriosus (PDA), Coarctation of the Aorta, Aortic Stenosis, Pulmonary Stenosis, and Atrioventricular Septal Defect (AVSD). Conditions that are grouped within the cyanotic category include conotruncal defects, also referred to as outflow tract abnormalities, and obstructive lesions, in which structural anomalies block or restrict blood flow through the heart (National Heart, 2022; NHS, 2021). These include Tetralogy of Fallot, Transposition of the Great Arteries, Hypoplastic Left Heart Syndrome, Pulmonary Atresia, Total Anomalous Pulmonary Venous Return, Tricuspid Atresia, and Truncus Arteriosus. See Table 1 for an overview of different CHD conditions with descriptions of the structural or functional changes to the heart (American Heart Association, 2022; National Heart, 2022).

Table 1. Types of CHD by Oxygen Deprivation Grouping	
Acyanotic Conditions	Description
Atrial Septal Defect (ASD)	A hole in the wall between the two upper chambers in the heart
Ventricular Septal Defect (VSD)	A hole in the wall between the two lower chambers
Patent Ductus Arteriosus (PDA)	A blood vessel that normally closes after birth remains open, allowing to flow between the aorta and pulmonary artery
Coarctation of the Aorta	A narrowing of the aorta, the main artery carrying blood from the heart
Aortic Stenosis	Narrowing of the aortic valve, which controls blood flow from the left ventricle to the aorta
Pulmonary Stenosis	Narrowing of the pulmonary valve, which controls blood flow from the right ventricle to the pulmonary artery
Atrioventricular Septal Defect (AVSD)	A defect in the heart's septum, which separates the upper and lower chambers

Cyanotic Conditions	Description
Tetralogy of Fallot	A combination of four defects, including a ventricular septal defect, pulmonary stenosis, an overriding aorta, and right ventricular hypertrophy
Transposition of the Great Arteries	The aorta and pulmonary artery are switched, leading to mixing of oxygenated and deoxygenated blood
Hypoplastic Left Heart Syndrome	The left side of the heart is underdeveloped, making it difficult for the heart to pump enough blood to the body
Pulmonary Atresia	The pulmonary valve is absent or severely narrowed, preventing blood from flowing to the lungs
Total Anomalous Pulmonary Venous Return	The pulmonary veins, which normally carry oxygenated blood from the lungs to the heart, connect abnormally to the systemic circulation
Tricuspid Atresia	The tricuspid valve (separates the right atrium and ventricle) is absent or underdeveloped
Truncus Arteriosus	A single large artery arises from both ventricles instead of the two separate arteries, the aorta and pulmonary artery

CHD can be further classified based on ventricular anatomy and the presence or absence of aortic outflow obstruction, a framework that offers clinical relevance in assessing both hemodynamic severity and neurodevelopmental risk (American Heart Association, 2022; Marino et al., 2012a; Schultz et al., 2005). This classification yields four categories: single ventricle with aortic obstruction, single ventricle without aortic obstruction, double ventricle with aortic obstruction, and double ventricle without aortic obstruction.

The most severe of these is single ventricle with aortic obstruction, in which the heart functions effectively as a single pumping chamber while systemic outflow is compromised by narrowing or atresia of the aorta (i.e., obstruction of the aortic pathway). This significantly

compromises oxygen delivery to other parts of the body and typically necessitates urgent staged surgical intervention beginning in the neonatal period (Kelly et al., 2017). HLHS is an example of a condition falling within this category. In conditions classified as single ventricle without aortic obstruction, univentricular physiology is also present but without the added complication of outflow tract narrowing. Although this group of conditions is considered the second most severe, systemic perfusion (i.e., delivery of blood to the body's organs for oxygen and nutrient supply, and removal of waste products) may be more stable in the early postnatal period. Tricuspid atresia, for instance, can fall within this category when systemic outflow is unobstructed, relying instead on the existence of a patent ductus arteriosus or VSD for adequate circulation prior to surgery (Rychik et al., 2019). Double ventricle with aortic obstruction refers to conditions where anatomically there are two functioning ventricles but the blood flow through the aortic pathway is restricted, placing strain on one or both ventricles. An example of this category is a VSD in conjunction with subaortic stenosis, where the left ventricle may be structurally intact, yet systemic outflow is limited by obstructive lesions at or below the aortic valve (Marino et al., 2012). Finally, the least severe category is double ventricle without aortic obstruction, in which both ventricles are present and systemic outflow is unobstructed. Conditions such as isolated VSDs or ASDs are typically in this group. In these cases, the primary concern is intracardiac shunting rather than impaired oxygen delivery (Van Der Linde et al., 2011b).

Etiology. The etiology of CHD is multifactorial, often involving a mix of genetic and environmental factors. Chromosomal abnormalities (e.g., trisomy 21, 22q11.2 deletion, and Turner's syndrome) and single-gene mutations (e.g., NKX2-5, GATA4, NOTCH1) account for approximately 20-30% of CHD diagnoses (Shabana et al., 2020). Furthermore, maternal illness

such as diabetes or rubella infection in the first trimester, teratogens (i.e., medication or substance exposure during pregnancy), and low folic acid may all contribute to neural and heart defects (Sayasathid et al., 2012). For example, ASDs are often sporadic in origin, though some cases have been linked to familial patterns and specific genetic mutations such as NKX1-5 and GATA4 (Sayasathid et al., 2012; Shabana et al., 2020). VSDs, the most prevalent form of CHD overall (Van der Linde et al., 2011), are frequently associated with chromosomal syndromes such as trisomy 21, as well as single-gene mutations and certain maternal conditions, including poorly controlled diabetes (Blue et al., 2012; Shabana et al., 2020). TOF is strongly associated with 22q11.2 deletion syndrome, found in up to 20% of cases, and other mutations affecting cardiac development (Goldmuntz et al., 1998; McDonald-McGinn et al., 2015).

Similarly, Truncus Arteriosus is frequently linked to the same genetic deletion, as well as abnormalities in neural crest cell migration, a key process in cardiac embryogenesis (McDonald-McGinn et al., 2015). TGA is most often sporadic but has also been associated with maternal diabetes and certain chromosomal abnormalities (Blue et al., 2012), suggesting a multifactorial etiology. Coarctation of the aorta frequently co-occurs with bicuspid aortic valve and is commonly associated with Turner syndrome (Bondy, 2008). HLHS, characterized by the severe underdevelopment of left-sided cardiac structures, is usually sporadic, though it has been linked to genetic mutations such as NOTCH1 (McBride et al., 2008). However, in many cases there is no single direct cause and rather a complex interaction of multifactorial inheritance relating to a number of factors including genetic predisposition, environmental exposures, and developmental variation during early embryogenesis (Blue et al., 2012; Sayasathid et al., 2012).

Medical treatment for CHD. The medical treatment of children with CHD is individualized and depends on the specific cardiac lesion or combination of lesions, severity of

the defect, and the child's physiological stability. Care typically involves a combination of medical support, surgical intervention, and long-term monitoring. In the neonatal period, many infants with critical CHD require medications such as prostaglandin E1 infusion, to keep a blood vessel open (i.e., the ductus arteriosus), which is essential for maintaining adequate blood flow to the body, brain, and lungs (Aykanat et al., 2016). Many children undergo surgical intervention to repair their heart, or in more complex cases, undergo a series of palliative operations to reroute blood flow (Ohye et al., 2010). Examples of these procedures include the Norwood, Glenn, and Fontan procedures used for single-ventricle conditions (Shmukler et al., 2020). In addition to surgical intervention, some children need cardiac catheterization, which in addition to being used for diagnostic clarity, can provide interventional procedures such as balloon atrial septostomy or stent placements (Shmukler et al., 2020). In some cases, mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO), is required to stabilize critically ill patients perioperatively (Perry et al., 2022).

Postoperative care involves close monitoring in pediatric cardiac intensive care units, with attention to hemodynamic management, fluid balance, and prevention of complications such as arrhythmias or low cardiac output syndrome (Wessel, 2001). As children age, additional surgical procedures may be required together with ongoing medical therapy which may include medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or anticoagulants, depending on the nature of the residual cardiac function and the presence of complications like heart failure or arrhythmia (Blue et al., 2012). Importantly, children with CHD require lifelong cardiology follow-up, with a multidisciplinary approach that integrates neurodevelopmental, nutritional, and psychosocial support to optimize both cardiac and neurodevelopmental outcomes.

Antenatal Neurophysiological Implications of Systemic Perfusion. In utero, the fetal circulatory system is designed to deliver nutrient-rich and highly oxygenated blood from the placenta to the fetus' brain (Claessens et al., 2017). Twenty-five percent of ventricular output (i.e. blood flow) from the heart flows to the fetus' brain, and 50% of all blood oxygen is consumed by the brain (Claessens et al., 2017; Ward, 2015). In typically developing fetuses there is a right-to-left shunt naturally present that secures the oxygenated and nutrient-rich blood flow from the placenta to the left ventricle and out the aortic valve to the brain and other essential organs via the internal carotid arteries and bilateral vertebral arteries prior to branching (Blumenfeld, 2018; Claessens et al., 2017). However, the anatomical changes associated with CHD causes a disturbance to this naturally occurring right-to-left shunt which results in either reduced oxygen and blood flow to the brain, or mixed blood being sent to the brain (mixed blood referring to a combination of oxygen rich and oxygen poor blood; Claessens et al., 2017; Lim et al., 2016). Specifically, research has demonstrated a 10% reduction in oxygen saturation of the blood supply to the brain in infants diagnosed with CHD, which results in a 15% reduction in oxygen delivery to the brain and a 32% reduction in oxygen consumption by the brain during critical periods of brain development (Claessens et al., 2017). This disturbance in blood flow and oxygen delivery creates suboptimal conditions for brain maturation and places the child at risk for pre-and-postnatal acquired brain injuries.

Hypoxia-ischemia is a condition in which body issues, including the brain, experience both insufficient oxygen supply (hypoxia) and reduced blood flow (ischemia). The changes to brain development caused by hypoxia-ischemia begin in the fetal stages of life, most notably in the third trimester (Licht et al., 2009; Marelli et al., 2016; Peyvandi et al., 2018; Polito et al., 2015). In typically developing fetuses, brain development involves rapid and predictable

sequences of structural alterations, cortical folding, and myelination of the cortical and subcortical structures. Cortical folding and neuronal migration are accelerated towards the end of the second trimester and peaks at the third trimester of pregnancy (Licht et al., 2009; Marelli et al., 2016). During the third trimester there is significant neuronal connectivity and activity that is fueled by adequate blood flow and oxygen consumption in the fetal brain, resulting in a dramatic increase in axon path finding, synapse formation, and refining of cortical networks (Marelli et al., 2016; Peyvandi et al., 2018). Myelination of the cerebral hemispheres can be detected in the optic radiations and posterior limbs of the internal capsule beginning at approximately 35 weeks of gestation and progressing steadily until 2 years of age (Licht et al., 2009).

A consequence of hypoxia-ischemia in neonates with CHD is the delayed or failed cortical folding and myelination seen (Birca et al., 2016; Peyvandi et al., 2018). Specifically, there is a failure of the oligodendrocyte progenitor cells (OPC) to differentiate into myelin-forming oligodendrocytes resulting in dysmaturation (Marelli et al., 2016). Oligodendrocytes are responsible for supporting axons and providing electrical insulation in the form of myelin sheath, enabling faster action potentials without increased axonal diameter (Blumenfeld, 2018). However, when there is a lack of differentiated oligodendrocytes, it results in a loss of myelination and subsequently brain volume. Additionally, neuroimaging studies have shown that neonates with CHD have less complex sulci at 30 weeks gestation than typically developing fetuses (Claessens et al., 2017). Further, neonates have an underdeveloped autoregulatory capability and less antioxidant scavenging abilities that would typically act as a protective measure against such hemodynamic and brain changes (Claessens et al., 2017). The dysmaturation of the autoregulation in addition to the suboptimal antenatal brain development places neonates with CHD at a high risk for brain injury.

Postnatal Neurophysiological and Neuroanatomical Implications of Hypoxia. Several studies have described immature brain development associated with CHD, with extensive research focused on postnatal structural and functional brain alterations. Current literature posits a reduction in total brain volume (approximately 20%), as well as reduced volume in cortical grey and white matter areas of the brain, and disruption of networks in the prefrontal cortex (Birca et al., 2016; Claessens et al., 2017; Lim et al., 2016; Sun et al., 2015; von Rhein et al., 2015). Approximately 90% of children with CHD have incomplete closure of the cerebral operculum. The cerebral operculum comprises an area that is important for sensory motor abilities, as well as receptive and expressive language. Bilateral abnormalities due to incomplete closure are associated with feeding and language delays (Licht et al., 2009). Additional volumetric reductions have been observed in the basal ganglia and thalami, particularly in children with single-ventricle physiology and TGA, compared to healthy controls both in utero and in the neonatal period (Claessens et al., 2017). These structural alterations have been associated with language and attentional deficits often observed in children with CHD (Claessens et al., 2017).

Neuroimaging studies have identified evidence of brain dysmaturation in the deep frontal and interhemispheric sulcation, as well as myelination of the posterior limb of the internal capsule beyond what is expected for a term baby (Licht et al., 2009). The germinal matrix remains present in the posterior and anterior lateral ventricles postnatally, there is bilateral underdeveloped opercular space, and evidence of bands of migrating glial cells visibly seen in term babies with CHD that would not typically be present in healthy babies (Licht et al., 2009).

Electrophysiological studies support structural findings noted above, such that young children with CHD have been found to have decreased frontal beta frequencies and abnormal

patterns on EEG studies at 18 months of age, with greater discrepancies related to increased cognitive impairment (Birca et al., 2016). Functionally, brain dysmaturation has been associated with decreased white matter connectivity between the anterior and sub-cortical regions, dorsolateral prefrontal cortex, anterior cingulate cortex, and the orbitofrontal cortex, which are all utilized in executive functioning (Bellinger & Newburger, 2010; Calderon & Bellinger, 2015; Panigrahy et al., 2015; Schaefer et al., 2013; Ward, 2015). White matter structural network topology analysis in adolescents with CHD has found that disruptions in these areas are associated with neurocognitive and executive dysfunctions (Panigrahy et al., 2015).

White matter injury (WMI) is a common consequence of these maturational delays. Bilateral WMI, including periventricular leukomalacia (PVL), has been reported in approximately 20-40% of children with CHD, particularly those undergoing surgery in the neonatal period (Birca et al., 2016; Claessens et al., 2017; Marelli et al., 2016). PVL is a brain injury to the white matter located in the vascular watershed zone adjacent to the lateral ventricles – regions particularly susceptible to hypoxic-ischemic injury due to limited perfusion from the distal branches of the cerebral arteries and is one of the most common white matter patterns of injury in premature infants and children with CHD (Licht et al., 2009).

Focal strokes are also a significant neurological morbidity among children with CHD, often occurring post-surgically or as a result of cardiac insufficiency and repeated catheterizations. These strokes are typically thromboembolic in origin and most frequently impact branches of the middle cerebral artery (MCA), which supplies blood to key brain regions including the frontal, parietal, and temporal lobes, as well as the thalamus, basal ganglia, and insular cortex (Blumenfeld, 2018; Claessens et al., 2017; Kirton & deVeber, 2007). Damage to these areas can result in a range of deficits, including motor, cognitive, and language

impairments, depending on the site and extent of the injury. In particular, strokes involving the posterior limb of the internal capsule or the cerebral peduncles may lead to spastic cerebral palsy due to disruption in communication between the cerebrum and cerebellum—structures critical for both motor coordination and cognitive functioning (Blumenfeld, 2018). Additionally, deep grey matter injuries, which are frequently observed in the context of hypoxia and delayed brain maturation, further contribute to motor dysfunction in this population (Claessens et al., 2017, 2018).

Importantly, even after surgical correction, children with CHD continue to show higher incidence of structural brain abnormalities compared to typically developing peers (Marelli et al., 2016). Overall, these children exhibit delayed patterns of brain microstructure and metabolism, with brain development often appearing approximately one month behind infants born full term without CHD (Birca et al., 2016; Kirton & deVeber, 2007; Licht et al., 2009; Marelli et al., 2016; Peyvandi et al., 2018). These alterations in brain volume, structure, and connectivity have been strongly associated with adverse neuropsychological outcomes, especially in the domains of language, executive function, and motor deficits (Panigrahy et al., 2015b; Sun et al., 2015a; von Rhein et al., 2015a). Therefore, it is important to consider and understand the brain changes related to hypoxia in children diagnosed with CHD for clinical decision making within the field of clinical neuropsychology.

Neuropsychological and Psychosocial Outcomes. Children with CHD are at heightened risk for a range of neurodevelopmental challenges that can affect cognitive, academic, motor, and behavioural functioning throughout development. These difficulties often emerge in early childhood and may persist or become more apparent as cognitive and social demands increase with age. The neuropsychological profile of children with CHD is notably heterogeneous,

influenced by factors such as the complexity of the cardiac lesion, perioperative care, and ongoing medical complications in addition to genetics with increasing attention to social determinants of health (Cassidy et al., 2024; Sood et al., 2021). Children with CHD exhibit a variety of difficulties associated with intelligence, language, executive functioning, attention, visual-spatial skills, motor development, and emotional-behavioural regulation (Bellinger et al., 2011; Cassidy et al., 2017; Shillingford et al., 2008; Wernovsky & Licht, 2016), as summarized below.

Research examining intellectual functioning in children with CHD has been equivocal. Some studies have reported no significant differences in IQ scores compared to healthy peers, while others have reported slightly lower scores, though still within the clinically Average range (i.e., standard score range of 90 – 109; Bellinger & Newburger, 2010; Brosig et al., 2007; Forbess et al., 2001; Goldberg et al., 2000; Wernovsky et al., 2000). This includes children with more complex cardiac conditions, such as single-ventricle lesions and TGA (Bellinger & Newburger, 2010). These findings suggest that although global intelligence may not be significantly impaired in CHD populations, subtle deficits may still be present. More recent meta-analyses have shown that children with severe forms of CHD, demonstrate consistent and meaningful reductions in intellectual performance, with mean scores often being reported within the low-average range (i.e., standard scores between 80-89; Feldman et al., 2021; Karsdorp et al., 2007; Siciliano et al., 2019).

In contrast, speech and language difficulties appear to be more pervasive and consistent across the literature. For example, one study found that approximately 24% of children with TGA met criteria for apraxia of speech by the age of four (Bellinger, Wypij, et al., 2003). Vulnerabilities have been noted across multiple language domains, including expressive and

receptive language, phonological awareness, letter fluency, and sentence formulation (Beck et al., 2002; Bellinger, Wypij, et al., 2003; Bellinger & Newburger, 2010). One study identified a specific weakness in single-word reading, which may contribute to broader deficits in integrating basic reading skills to meet more complex language demands (Bellinger, Wypij, et al., 2003). Additionally, children with TGA often have difficulty with the social and structural conventions of communication, such as maintaining structured conversations or telling coherent stories (Bellinger, Wypij, et al., 2003).

Executive functioning deficits are among the most well-documented cognitive impairments among individuals with CHD, observed across the lifespan. These difficulties tend to emerge more prominently at school age, coinciding with increasingly complex cognitive demands (Bellinger et al., 2011; Calderon & Bellinger, 2015; Claessens et al., 2017; Schaefer et al., 2013). Compared to normative samples, children with CHD consistently underperform on standardized measures of executive functioning (Cassidy et al., 2015; Gerstle et al., 2016). Alarming, approximately 75% of these children score at least 1.5 standard deviations below the mean on at least one executive functioning measure, and parent ratings suggest they are four times more likely to exhibit executive dysfunction (Cassidy et al., 2015; Gerstle et al., 2016). These deficits are critical, as they are strongly associated with poor academic achievement, diminished social adaptation, and a greater need for early intervention services (Calderon et al., 2013; Calderon & Bellinger, 2015; Gerstle et al., 2016).

Attention-related difficulties are also prevalent among children with CHD. Parent reports indicate that these children are three to four times more likely to exhibit symptoms of hyperactivity, with nearly 30% scoring in the high-risk range for attentional issues (Bellinger & Newburger, 2010; Shillingford et al., 2008). Children with complex CHD conditions, such as

TGA, demonstrate poorer performance on direct measures of attention and executive control including on the Continuous Performance Test (CPT) and the Attention Network Test (ANT; (Bellinger, Wypij, et al., 2003; Bellinger & Newburger, 2010; Hövels-Gürich et al., 2006).

Children with CHD often exhibit difficulties in both motor and visual-spatial domains, which can significantly impact their academic functioning. Fine and gross motor delays are consistently observed, particularly at school age, with studies reporting that approximately 25% to 50% of children experience coordination difficulties—especially in cases involving more severe cardiac defects (Bellinger, Wypij, et al., 2003; Bjarnason-Wehrens et al., 2007; Hövels-Gürich et al., 2006; Majnemer et al., 2006). In addition to motor challenges, deficits in visual-spatial processing are also common and tend to extend beyond motor coordination to include broader issues with visual perception and spatial reasoning (Bellinger, Bernstein, et al., 2003; Bellinger & Newburger, 2010; Brosig et al., 2007). These visual-spatial difficulties frequently manifest in academic settings, particularly on tasks requiring mathematical reasoning and calculation. Together, these findings underscore the need for early identification and intervention targeting both motor and visual-spatial skills in children with CHD (Bellinger & Newburger, 2010).

Behavioural outcomes in children with CHD appear to vary with age and measurement method. While some studies have found that parents of toddlers with TGA report fewer behavioural symptoms compared to normative samples (e.g., at 30 months on the CBCL) (Bellinger et al., 1997), this trend is often reversed by later childhood. By age eight, parent ratings indicate elevated total problem behaviours, with approximately 20% of children scoring in the borderline or clinical range (Bellinger et al., 2009; Bellinger & Newburger, 2010). Internalizing and externalizing symptoms appear relatively balanced across studies, with about

15–16% of parents reporting concerns related to attention, aggression, depression, withdrawal, and somatization (Bellinger & Newburger, 2010; Ellerbeck et al., 1998; Hövels-Gürich et al., 2006).

Social Determinants of Neuropsychological and Psychosocial Outcomes.

Sociodemographic factors have been found to influence neuropsychological outcomes, often interacting with medical variables to shape developmental trajectories in children with CHD. Parental education level, household income, and access to healthcare services are among the key sociodemographic variables associated with cognitive, behavioural, and emotional outcomes in this high-risk population (Cassidy et al., 2024; Sood et al., 2021). For example, studies have shown that lower maternal education and socioeconomic disadvantage are linked to poorer executive functioning, language development, and behavioural regulation even after controlling for surgical complexity and perioperative variables (Gaynor et al., 2015; Treyvaud, Inder, et al., 2012). Moreover, higher parental stress more commonly found in lower socioeconomic households, has been associated with poorer cognitive, emotional, and behavioural outcomes in children with CHD (Roberts et al., 2021; Woolf-King et al., 2017). A growing body of literature has identified elevated rates of psychiatric disorders in children and adolescents with CHD, particularly mood, anxiety, and attention deficit/hyperactivity disorder. Structured clinical interviews have shown significantly higher rates of psychopathology in adolescents with CHD compared to typically developing peers, even in cases where their IQ has been within normative ranges (Demaso et al., 2014; 2017). Similarly, increased rates of psychiatric disorders among children with single ventricle physiology has been documented emphasizing the importance of routine mental health screening (Holland et al., 2017). Furthermore, there is emerging evidence that children with CHD may be at nearly twice the risk of developing Autism Spectrum Disorder

(ASD) compared to typically developing peers (Tsao et al., 2017). These findings underscore the importance of the systematic family context and social determinants of health in both clinical care and research, as sociodemographic variables may serve as either protective or compounding influence on neurodevelopmental outcomes of children with CHD.

1.2 Overview of Very Preterm Birth

Preterm birth is described as a gestational age of <37 weeks with specific classifications as follows: birth at 34–36 weeks is designated as *late preterm*, 32–33 weeks as *moderate preterm*, <32 weeks as *very preterm*, and <28 weeks as *extremely preterm* (Anderson, 2014; Williams et al., 2019). Approximately, 11% of infants are born preterm worldwide (Blencowe et al., 2012); steady improvements in obstetric and neonatal care have resulted in increasing numbers of preterm infants surviving to childhood (Saigal & Doyle, 2008). Preterm infants are also characterized in reference to their birth weight where a weight of <2500g is considered low birth weight (LBW), <1500g as very low birth weight (VLBW), and <1000g as extremely low birth weight (ELBW; (Williams et al., 2019). From a biological perspective, preterm infants frequently present as small for gestational age due to intrauterine growth restriction, which further compounds their risk for adverse outcomes. Very preterm birth in particular is associated with a cascade of subsequent developmental challenges that persist beyond the neonatal period.

Etiology. Very preterm birth has a complex multifactorial etiology that involves an interplay of biological, maternal, fetal, and environmental factors. Etiological factors include placental insufficiencies, preeclampsia, multiple gestation, uterine anomalies, maternal infections, chronic health conditions, and lifestyle factors (Abbot et al., 2018; Monangi et al., 2015). Preterm delivery is often spontaneous but can also be medically indicated in the presence of a medical emergency, such as maternal or fetal distress. Genetic predispositions and

inflammatory pathways have also been recognized as critical contributors, underscoring the biological complexity of these early deliveries (Abbot et al., 2018; Monangi et al., 2015; Ophelders et al., 2020). In many cases, the etiology of very preterm birth is interlaced with broader socioeconomic and environmental risk factors, including limited prenatal care, low maternal education, and maternal stress or substance use (Goldenberg et al., 2008). Collectively, these factors have been implicated in disrupting fetal brain development due to preterm birth, contributing to white matter vulnerability and long-term neurologic compromise.

Medical Treatment. Standard medical care for very preterm infants in the neonatal intensive care unit (NICU) focuses on three main goals: keeping the baby’s heart and lungs stable, helping them grow and feed properly, and avoiding additional medical problems (Lee, 2024). Over the years, several advances have greatly improved survival for these infants. For example, surfactant therapy helps keep fragile lungs open and working; modern ventilator techniques provide more gentle and targeted breathing support; and neuroprotective care strategies aim to protect the brain from injury during this critical period. Neuroprotective care strategies include stabilizing oxygen and blood flow, managing temperature and glucose levels, minimizing pain and stress, using supportive positioning, and promoting parental involvement through skin-to-skin contact (Als & McAnulty, 2011; Lee, 2024; Urbina et al., 2024).

Adjustments are made to mimic the in-utero environment as much as possible to help support healthy brain development. Despite significant advances in neonatal care, many very preterm infants continue to experience neurodevelopmental challenges. Although medical interventions have greatly improved survival rates, they do not fully mitigate the risk of altered brain development or injury—particularly for infants born at the earliest gestational ages or those requiring prolonged and medically complex NICU admissions. Consequently, these children

remain at elevated risk for long-term impairments in cognitive, attentional, motor, and behavioural functioning.

Neurophysiology and Dysmaturation. In typically developing fetuses, brain development involves rapid and predictable sequences of structural alterations, cortical folding, and myelination of the cortical and subcortical structures. Cortical folding and neuronal migration accelerate significantly towards the end of the second trimester and peaks at the third trimester of pregnancy (Kostović & Judoš, 2010; Licht et al., 2009). This phase is characterized by increased axon path finding, synapse pruning, and refinement of long-range connectivity, particularly between cortical and subcortical structures, and is supported by robust cerebral blood flow and high metabolic demands (Kostović & Judoš, 2010; Stiles & Jernigan, 2010). Myelination of the cerebral hemispheres can be detected in the optic radiations and posterior limbs of the internal capsule beginning at approximately 35 weeks of gestation and progressing into childhood (Back et al., 2001; Stiles & Jernigan, 2010). These processes are essential for the organization and efficiency of neural signaling and underlie the foundation for higher-order cognitive and behavioural functions (Back & Miller, 2014). See Figure 2 for brain maturation process.

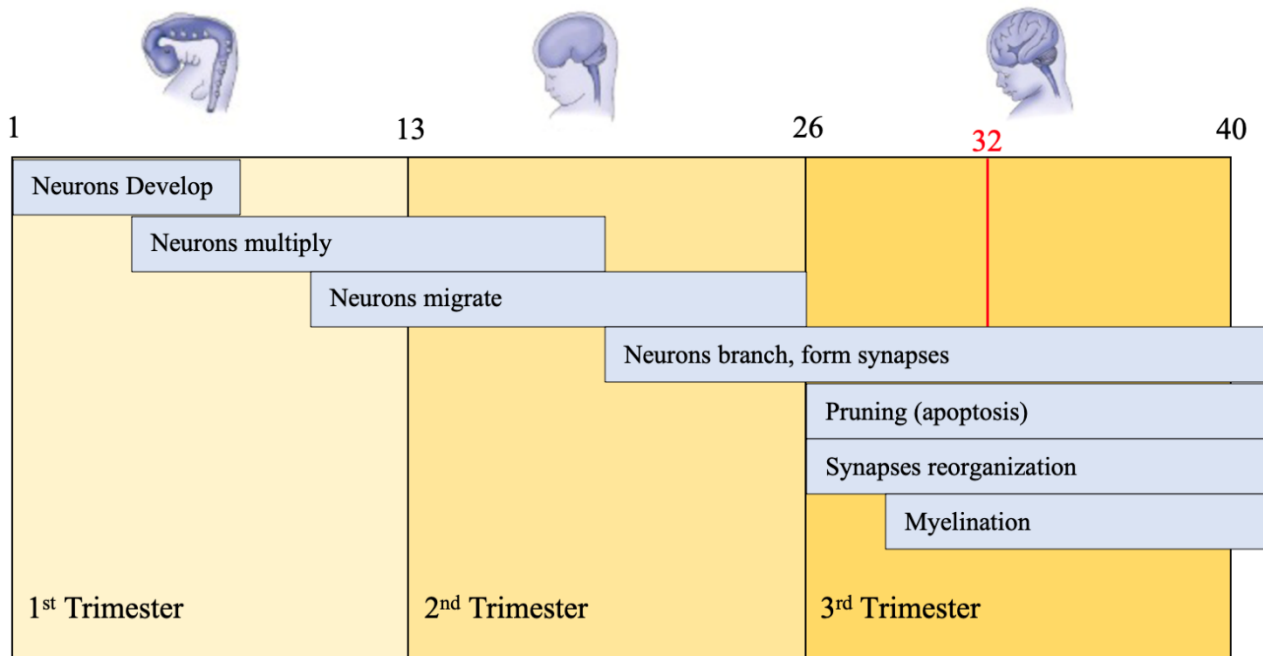


Figure 2. Brain Maturation in Utero by Trimester

When a baby is born very preterm, the neuronal development process is abruptly shifted from the controlled, intrauterine environment to the variable conditions of the NICU which can alter the normal trajectory of neural maturation. By this point, the brain has initiated early synaptogenesis, dendritic branching, and although myelination is underway, the majority of white matter development remains incomplete (Abbot et al., 2018; Stiles & Jernigan, 2010; Williams et al., 2019). The absence of the intrauterine environment during this critical period deprives the brain of essential growth-promoting stimuli and exposes it instead to fluctuating oxygen levels, nutritional variability, and medical interventions. These environmental and physiological stressors have been shown to alter normal trajectories of synaptic organization and network connectivity (Abbot et al., 2018; Stiles & Jernigan, 2010). Moreover, the very preterm

brain is more susceptible to oxidative stress (Back, 2006) and hemodynamic brain changes due to arrested maturation of the oligodendrocyte lineage at the pre-oligodendrocyte stage (Buser et al., 2012). Consequently, while the brain continues its developmental processes postnatally, the altered timing and environmental influences may predispose these infants to later neurodevelopmental delays and neuropsychological challenges (Back, 2006; Baron et al., 2012; Morton et al., 2017; Xu & Vigneron, 2010).

One of the most prevalent forms of brain injury in very preterm infants is periventricular leukomalacia (PVL), a form of white matter damage primarily affecting the periventricular regions. PVL may be focal or diffuse and is strongly associated with cerebral palsy, cognitive impairment, and attentional difficulties (Imamura et al., 2013). While PVL was historically understood in its cystic form, advances in MRI have revealed that multifocal non-cystic WMI is now the dominant pathology, often subtler but equally impactful (Hamrick et al., 2004; Williams et al., 2019). In addition to white matter injury, there is increasing recognition of abnormalities in grey matter of the cerebral cortex, thalamus, and cerebellum, which are critical for sensorimotor integration and cognitive control (Tam, Miller, et al., 2011; Vinall et al., 2013; Volpe, 2009). Grey matter abnormalities may be less visible on conventional imaging but are equally important for cognitive and behavioural regulation (Waller et al., 2020).

Other significant injuries seen in very premature infants include intraventricular hemorrhage (IVH), particularly in the germinal matrix, a highly vascularized area susceptible to rupture under conditions of pressure fluctuation and hypoxia (Inder et al., 2003; Inder, 2006; Volpe, 2009). Severe IVH can extend into the ventricular system, leading to post-hemorrhagic hydrocephalus and secondary injury to developing white matter tracts. These hemorrhagic injuries can disrupt thalamocortical connectivity, impair synaptogenesis, and result in broader

cortical dysfunction (Dorner et al., 2018). Compounding these structural risks are systemic influences such as inflammation, infection, and mechanical ventilation, all of which increase the likelihood of diffuse white matter dysmaturation through inflammatory cascades and excitotoxic injury (Ophelders et al., 2020). These processes can arrest or alter the maturation of glial cells, compromise axonal development, and impair functional circuit integration—laying the groundwork for a wide spectrum of neuropsychological outcomes (Back & Miller, 2014; Spittle et al., 2008; Volpe, 2000).

Neuropsychological and Psychosocial Outcomes. Children born very preterm are at heightened risk for a range of neuropsychological and psychosocial challenges. These difficulties span multiple developmental domains including cognition, language, executive functioning, motor skills, and socioemotional behaviour, and may persist across the lifespan. While there is notable heterogeneity in outcomes, a consistent body of longitudinal and meta-analytic research highlights a pattern of increased vulnerability from infancy through adolescence (Anderson, 2014; Aylward, 2014; Bhutta et al., 2002; Hack et al., 2005; Kerr-Wilson et al., 2012; Saigal & Doyle, 2008).

Cognitive impairments are among the most consistently reported outcomes in children born very preterm. Mean IQ scores in this group tend to fall 0.5 to 1 standard deviation below those of healthy term-born peers, with lower gestational age and the presence of neonatal brain injury associated with greater risk for intellectual disability (Aarnoudse-Moens et al., 2009; Anderson & Doyle, 2003; Bhutta et al., 2002). While some preterm children display relatively preserved cognitive abilities, many show a global cognitive delay or selective deficits in domains such as processing speed and working memory (Anderson, 2014). These differences are apparent in infancy and tend to persist into adolescence and adulthood, with little evidence of

developmental convergence with term-born peers over time (Hack et al., 2005). Impairments in cognitive functioning among very preterm children are associated with increased risk for subsequent challenges in both academic achievement and adaptive daily functioning (Saigal & Doyle, 2008).

Language outcomes in children born very preterm are heterogeneous but often marked by delays in expressive language, with relatively better performance in receptive vocabulary (Briscoe et al., 2001; Guarini et al., 2016). While some children demonstrate adequate single-word vocabulary, more complex linguistic processes—such as verbal reasoning, narrative generation, and discourse comprehension—are often impaired by preschool and school age (Omizzolo et al., 2013). Language delays may persist into adolescence, particularly in individuals with a history of neonatal complications such as bronchopulmonary dysplasia or IVH. These impairments are thought to be linked to disrupted maturation of frontotemporal white matter tracts and altered thalamocortical connectivity (Volpe, 2009). Poor language ability in early life can contribute to reduced academic attainment and reduced social competence later in development.

Executive function and inattention represent some of the most common and persistent areas of neuropsychological concerns among very preterm children. Deficits are frequently reported in working memory, cognitive flexibility, inhibitory control, and sustained attention (Anderson, 2014; Howard et al., 2008; Pascoe et al., 2021). These deficits are evident by preschool age and often become more pronounced in the school years when academic and behavioural demands increase. Notably, children born preterm are up to three times more likely to be diagnosed with ADHD, particularly the inattentive subtype (Johnson & Marlow, 2011; Montagna et al., 2020; Treyvaud et al., 2016). Functional neuroimaging studies have

documented disruptions in fronto-striatal and fronto-parietal circuitry (imperative for attentional abilities), likely stemming from white matter injury and immature cortical development (Castellanos & Proal, 2012; Montagna et al., 2020). These executive functioning and attention difficulties have been associated with classroom learning, peer interactions, and emotional self-regulation (Howard et al., 2008; Lynn et al., 2011; Taylor & Clark, 2016). While some children benefit from structured environments and targeted interventions, many continue to experience impairments into adolescence (Saigal & Doyle, 2008).

Fine and gross motor delays are widely observed in children born very preterm, often emerging in infancy and persisting into adolescence. These impairments are typically associated with injury to white matter tracts, cerebellar underdevelopment, and delayed myelination (Spittle et al., 2008; Williams et al., 2019). Children may demonstrate delayed motor milestones, poor coordination, graphomotor difficulty, and weaknesses in balance and postural control. Visual-spatial and visual-motor integration are also affected, even in the absence of major visual or sensory impairments (Böhm et al., 2010). These deficits may manifest as difficulty with tasks requiring visual tracking, spatial reasoning, copying, or constructional ability—skills that are critical for early math learning and science education. Motor and visual-spatial weaknesses can undermine independence in daily tasks, limit participation in play, and reduce opportunities for socialization, further exacerbating psychosocial vulnerabilities.

Very preterm children often show delayed academic readiness and reduced achievement across core academic subjects of reading, mathematics, and written language (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002; Hack et al., 2005). These difficulties are strongly correlated with underlying impairments in executive functioning, language, and processing speed, and they frequently persist into adolescence. As a result, preterm children are

more likely to require special education services, academic accommodations, or individualized educational plans (IEPs). Longitudinal studies show elevated rates of grade retention, reduced high school completion, and lower likelihood of postsecondary education (Kerr-Wilson et al., 2012; Saigal & Doyle, 2008). Early intervention and academic supports can mitigate risk, but outcomes vary widely depending on the severity of neonatal brain injury, family environment, and access to educational resources.

In addition to cognitive vulnerabilities, children born very preterm are at increased risk for internalizing and externalizing behavioural problems, including anxiety, depression, aggression, and social withdrawal (Johnson & Marlow, 2011; Treyvaud, Doyle, et al., 2012; Treyvaud et al., 2016). Early difficulties with emotional regulation and peer interaction have been associated with later social immaturity and low self-esteem in adolescence (Johnson & Marlow, 2011; Luu et al., 2011; Saigal et al., 2002; Spittle et al., 2009). Preterm children also demonstrate higher rates of autism spectrum disorder (ASD) traits, though clinical differentiation can be challenging due to overlapping symptoms with intellectual and language delays (Johnson & Marlow, 2011). Rates of psychiatric diagnoses are significantly higher than in term-born peers, even after adjusting for cognitive functioning and socioeconomic status. Parental stress, maternal mental health, and early bonding experiences can all moderate socioemotional outcomes (Treyvaud, Inder, et al., 2012). Psychosocial risk may increase over time if cognitive and behavioural difficulties lead to peer rejection or academic failure.

Neuropsychological and psychosocial outcomes in children born very preterm reflect the combined effects of early brain dysmaturation, placement in the NICU, and developmental demands. Across domains—cognition, language, executive function, motor skills, academic achievement, and behaviour—these children consistently demonstrate lower performance

compared to their term-born peers. Although individual trajectories vary, many very preterm children experience persistent challenges that interfere with academic progress, social integration, and overall quality of life. Importantly, outcomes are not deterministic. Early identification, targeted interventions, enriched caregiving environments, and long-term multidisciplinary follow-up can significantly improve developmental trajectories. Given the complexity and persistence of challenges, a domain-specific understanding of neurodevelopment is essential for informing intervention strategies and educational planning for this high-risk population.

Social Determinants of Neuropsychological and Psychosocial Outcomes. Similar to children with CHD, children born very preterm are vulnerable to sociodemographic influences, which can either mitigate or exacerbate the neurodevelopmental risks associated with premature birth. Lower socioeconomic status, limited parental education, and restricted access to early intervention services have consistently been associated with poorer cognitive, language, and behavioural outcomes in this high-risk population (Benavente-Fernández et al., 2020; Johnson & Marlow, 2011; Luu et al., 2011; Treyvaud, Doyle, et al., 2012). Conversely, supportive home environments that provide emotional warmth, cognitive stimulation, and consistent caregiving, along with higher parental education levels, have been associated with more favourable neurodevelopmental trajectories and improved school readiness among very preterm children (Spittle et al., 2008, 2015). Sociodemographic variables play a key role in fostering resilience and adaptive functioning among children born very preterm. Thus, it is important to investigate the role of sociodemographic factors in neurodevelopmental outcomes in order to understand how best to promote resilience and optimize long-term outcomes among this population.

1.3 Overlap between CHD and Very Preterm Birth

Neurophysiology. Although children with CHD and those born very preterm represent distinct clinical populations, both groups are exposed to early neurologic risk factors that significantly impact brain development and long-term neuropsychological outcomes. Importantly, while the underlying etiologies differ (i.e., circulatory disruption in CHD versus early post uterine transition in prematurity), there are marked parallels in patterns of brain dysmaturation and cognitive vulnerability.

Both populations experience disruption to brain development during a critical window of rapid neuron formation, connectivity, and myelination, particularly in the late second and third trimesters (Birca et al., 2016; Buser et al., 2012; Licht et al., 2009; Marelli et al., 2016; Peyvandi et al., 2018). However, the nature of disruption to this process differs. In very preterm infants, the abrupt shift from the intrauterine to the extrauterine environment truncates typical maturation and exposes the immature brain to a high-risk neonatal intensive care environment. Fluctuations in oxygenation, inflammation, and medical stressors lead to delayed myelination and atypical synaptic connectivity, often resulting in periventricular leukomalacia (PVL) and multifocal white matter injury (Abbot et al., 2018; Back & Miller, 2014; Birca et al., 2016; Claessens et al., 2017; Kostović & Judaš, 2010; Marelli et al., 2016). In contrast, fetuses with CHD often experience compromised cerebral perfusion in utero even before birth, due to altered cardiovascular physiology. Due to malformations in cardiovascular anatomy, these fetuses experience chronic hypoxia and altered cerebral oxygen delivery in utero, impeding axonal migration and oligodendrocyte differentiation, and leading to similar patterns of white matter dysmaturation (Back et al., 2001; Licht et al., 2009; Peyvandi et al., 2018; Stiles & Jernigan, 2010).

Despite these mechanistic differences, neuroimaging studies in both populations consistently reveal reduced brain volume, impaired cortical folding, and delayed myelination, especially in periventricular and subcortical regions. Children with CHD frequently show reductions in cortical and subcortical grey matter, abnormalities in the cerebral operculum, and impaired sulcal complexity (Claessens et al., 2017; Licht et al., 2009). Likewise, very preterm children often exhibit delayed maturation of the thalamus and cerebellum, along with diffuse white matter injury and disrupted thalamocortical connectivity (Back et al., 2001; Volpe, 2021). More specifically, babies born full term with CHD have brain structures similar to those of preterm babies born at 34-36 weeks gestation (Birca et al., 2016; Claessens et al., 2017; Clouchoux et al., 2013; Desai et al., 2015; Miller et al., 2007; Peyvandi et al., 2016, 2018). Both groups exhibit similar patterns of injury and high incidence of periventricular leukomalacia (Claessens et al., 2017; T. Inder et al., 2003; Marelli et al., 2016). Research has highlighted similar brain anomalies in term neonates with CHD and preterm newborns without CHD, showing concordance of total punctate WMI volumes and lower gestational age at birth predicting increased WMI for both groups (Guo et al., 2019). These shared structural vulnerabilities help explain overlapping functional impairments, particularly in the domains of executive functioning, attention, language, and motor coordination.

Neuropsychological and Psychosocial Outcomes. Children born very preterm and those with CHD both face elevated risks for neuropsychological and psychosocial difficulties that may persist across development. While there is significant variability within each group, research consistently identifies an increased prevalence of cognitive, emotional, and behavioural concerns relative to their healthy, term-born, typically developing peers (Anderson, 2014; Baron et al., 2012; Bellinger & Newburger, 2010; Ehrler et al., 2023; Williams et al., 2019). Despite these

shared vulnerabilities, the nature and trajectory of difficulties in each population may differ in meaningful ways, particularly in how challenges present over time and the degree to which they impact daily functioning.

Cognitive functioning presents as a relative area of weakness in both groups but with notable differences in severity and presentation. Children born very preterm often demonstrate a more generalized reduction in intellectual functioning, with average IQ scores falling 0.5 to 1 standard deviation below term-born peers (Aarnoudse-Moens et al., 2009; Anderson & Doyle, 2003; Bhutta et al., 2002). This group is also more likely to present with global cognitive delays, particularly in those with lower gestational age or neonatal complications. In contrast, in the absence of a genetic condition, children with CHD typically score within the average range on standardized cognitive assessments, though subtle deficits are often observed—especially in children with complex lesions or perioperative complications (Bellinger & Newburger, 2010; Brosig et al., 2007; Forbess et al., 2001; Goldberg et al., 2000; Wernovsky et al., 2000). These deficits may go unnoticed without comprehensive evaluation but can nonetheless impact academic functioning.

Both groups frequently experience difficulties with working memory, cognitive flexibility, and inhibitory control, contributing to high rates of executive dysfunction and attention-related concerns, including ADHD (Anderson et al., 2017; Bellinger & Newburger, 2010; Johnson & Marlow, 2011; Licht et al., 2009; Shillingford et al., 2008). Language impairments are also common, though they may present differently. Very preterm children often struggle with expressive language and complex verbal tasks, while children with CHD may exhibit broader deficits, including challenges with understanding language, speech production, and phonological processing (Beck et al., 2002; Bellinger, Wypij, et al., 2003; Bellinger &

Newburger, 2010; Briscoe et al., 2001; Guarini et al., 2016; Omizzolo et al., 2013). Social communication issues, particularly among children with early brain injury or surgical complications, are more frequently reported in the CHD population. Motor and visual-spatial weaknesses are another shared area of concern. Children in both groups can experience fine and gross motor delays that interfere with daily functioning and academic skills (Bjarnason-Wehrens et al., 2007; Böhm et al., 2010; Bolduc et al., 2020; Cameron et al., 2021; de Kieviet et al., 2009; Snookes et al., 2010).

Psychosocial outcomes are another domain of shared concern. Both groups are at elevated risk for emotional-behavioural difficulties, including anxiety, depression, and social withdrawal (Bellinger & Newburger, 2010; Ellerbeck et al., 1998; Hövels-Gürich et al., 2006; Johnson & Marlow, 2011; Treyvaud, Doyle, et al., 2012; Treyvaud et al., 2016). Children born very preterm show higher rates of internalizing problems and social immaturity, often related to early difficulties with self-regulation and peer relationships (Luu et al., 2011; Lynn et al., 2011; Saigal et al., 2002; Spittle et al., 2009). In children with CHD, behavioural outcomes appear to vary more with age. Early childhood may be marked by relatively few concerns, but by school age, rates of emotional and behavioural problems often rise, particularly in those with more complex cardiac histories (Bellinger & Newburger, 2010; Hövels-Gürich et al., 2006).

Taken together, the parallels in neurodevelopmental vulnerabilities between children born very preterm and those with CHD, despite differing underlying medical etiologies, underscore the need for research that directly compares these populations. Comparative studies are essential to disentangle shared versus condition-specific risk factors, clarify neurodevelopmental trajectories, and guide more tailored, condition-informed clinical care. By directly examining both the commonalities and distinctions between these high-risk groups, we can better

understand how early neurologic insults translate into long-term outcomes and ultimately improve the precision and effectiveness of support provided across childhood and adolescence.

1.4 Identified Gaps in the Literature

Despite increasing recognition of the neurodevelopmental vulnerabilities in both children born very preterm and those with CHD, research to date has largely investigated these populations in isolation. As a result, the extent to which their neuropsychological profiles converge or diverge remains poorly understood. While both groups exhibit similar patterns of brain dysmaturation and face overlapping challenges in cognitive, motor, and psychosocial domains, direct comparisons are rare. This limits our ability to identify condition-specific risk factors and trajectories, and hinders efforts to develop targeted, population-specific interventions.

Recent studies have begun to explore these overlaps. For example, neuroimaging comparisons have revealed concordant patterns of punctate white matter injury in both very preterm and CHD infants (Guo et al., 2019). However, no studies to date have systematically examined how shared and unique biopsychosocial risk factors contribute to long-term neurodevelopmental outcomes across both of these high-risk infant populations. Additionally, while magnetic resonance spectroscopy (MRS) has identified early alterations in brain metabolite profiles in each population, there is a lack of research linking these neurochemical markers to later cognitive and behavioural functioning. Together, these gaps highlight the value of comparative, longitudinal studies that examine predictors of neurodevelopmental trajectories in both very preterm and CHD populations. This dissertation addresses these gaps by directly comparing these high-risk infant populations across two critical early developmental periods (18 and 36 months), with a focus on identifying early medical, psychosocial, and neurometabolic predictors of long-term outcomes.

Chapter 2: Aims and Hypothesis

The current dissertation has three research aims divided into individual studies. These studies are iterative in nature, with results of each step informing the direction of the subsequent study.

Our first research aim (study 1) was to compare the early neurodevelopmental and behavioural outcomes of term children diagnosed with CHD to very preterm (VP) children at 18 months of age, and to examine associated sociodemographic and white matter injury characteristics. It was hypothesized that both CHD and VP groups would demonstrate delays in neurodevelopmental and behavioural outcomes relative to normative peers, with no anticipated differences between the two clinical groups in overall functioning. This is based on prior research indicating that both CHD and VP infants experience early brain injury and disruption to brain maturation, resulting in overlapping neurodevelopmental vulnerabilities. Furthermore, it was expected that lower socioeconomic status and greater white matter injury would be associated with poorer outcomes across both groups, reflecting well-established links between these factors and early child development.

Our second research aim (study 2) was to examine trajectories and clinical change in neurodevelopmental and behavioural outcomes from 18 to 36 months of age among CHD and VP children and compare neurodevelopmental outcomes at 36 months. Additionally, we examined their associations with sociodemographic and white matter injury characteristics. It was hypothesized that both groups would show persistent neurodevelopmental vulnerabilities over time, with domain-specific differences emerging by 36 months. Specifically, children born VP were expected to demonstrate greater deficits in motor development, whereas children with CHD were expected to show more deficits in language and behavioural regulation. These

hypotheses were based on previous research showing emerging neurodevelopmental profiles in each group, potentially linked to different etiologies of early brain disruption. White matter injury and sociodemographic disadvantage were again hypothesized to be associated with less favorable developmental outcomes and trajectories.

Our third research aim (study 3) was to describe brain metabolite composition in the groups (i.e., term CHD and very preterm) using magnetic resonance spectroscopy (MRS) and to explore correlations between MRS and neurodevelopmental outcomes at 36 months within each group. We also examined whether associated metabolite ratios accounted for unique variability in models predicting 36-month neurodevelopmental outcomes, after accounting for condition specific variables. It was hypothesized that both groups would show altered brain metabolite profiles, particularly in N-acetylaspartate (NAA), choline (Cho), and creatine (Cr) ratios reflecting impaired neuronal integrity and altered brain maturation. It was further expected that metabolite ratios would be significantly correlated with neurodevelopmental outcomes and would account for unique variability in 36-month outcomes beyond traditional clinical and sociodemographic predictors. These hypotheses were informed by growing evidence linking neurometabolic alterations in early life to later cognitive and motor functioning, particularly in high-risk infant populations.

Chapter 3: Neurodevelopmental Outcomes at 18 months of Children Diagnosed with Congenital Heart Disease Compared to Children Born Very Preterm

3.1 Publication status and author contributions

The following chapter is based on the manuscript: Roberts, S.D., Sananes, R., Wojtowicz, M., Seed, M., Miller, S.P., Chau, V., Au-Young, S.H., Guo, T., Ly, L., Kazazian, V., Grunau, R.E., & Williams, T.S. (2024). Neurodevelopmental Outcomes at 18 months of Children diagnosed with CHD Compared to Children Born Very Preterm. born Preterm to Children Diagnosed with Congenital Heart Disease. *Cardiology in the Young*, 34: 1247 – 1253.

This manuscript does not exactly replicate the final version published in *Cardiology in the Young (CITY)*. It is not a copy of the original published article, and it is not suitable for citation. Samantha D. Roberts, the first author, developed the conceptual rationale for the study, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

3.2 Abstract

Objective. Children with congenital heart disease (CHD) or born very preterm (VP) are at risk for brain dysmaturation and poor neurodevelopmental outcomes. Yet, studies have primarily investigated neurodevelopmental outcomes of these groups separately. The purpose of this study was to compare neurodevelopmental outcomes and parent behaviour ratings of children born term with CHD to children born VP.

Methods: A clinical research sample of 181 children (CHD [n=81]; VP [$\leq$ 32 weeks; n=100]) were assessed at 18-months.

Results: Children with CHD and born VP did not differ on Bayley-III Cognitive, Language or Motor Composite scores, or on Expressive or Receptive Language, or Fine Motor scaled scores. Children with CHD had lower Gross Motor scaled scores compared to children born VP ($p=.047$). 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 VP (6%; 7%; 3%; $ps<.05$). No group differences were found on behaviours rated by parents on the Child Behavior Checklist (1.5-5 years) or the proportion of children with scores above the clinical cutoff. English as first language was associated with higher Cognitive ($p=.004$) and Language Composite scores ($p<.001$). Lower median household income and English as a second language were associated with higher total behaviour problems ($ps<.05$).

Conclusions: Children with CHD were more likely to display language and motor impairment compared to children born VP at 18-months. Outcomes were associated with language spoken in the home and household income.

3.3 Introduction

Children diagnosed with congenital heart disease (CHD) and children born very preterm (VP) are at risk for poorer neurodevelopmental outcomes including cognitive, language, motor, behaviour, social and academic delays (Anderson, 2014; Brosig et al., 2018). Research has highlighted similar patterns of brain dysmaturation in term neonates with CHD and VP neonates without CHD (Guo et al., 2020). 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 (Cassidy et al., 2015; Van Der Linde et al., 2011). In Canada, approximately 1 in 80-100 children each year are born with CHD (Canadian Congenital Heart Alliance, 2017; Van Der Linde et al., 2011). 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 (Marelli et al., 2016). 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 (Miller et al., 2007), and perioperative and medical factors (i.e., genetics, physical and social environment, severity of cardiac lesion, and gestational age [GA] at birth; Claessens et al., 2017, 2018). 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 (Bellinger & Newburger, 2010; Panigrahy et al., 2015; Sun et al., 2015; von Rhein et al., 2015).

VP birth, defined as a GA of <32 weeks (Anderson, 2014; Williams et al., 2019b), impacts approximately 8% of children in Canada (Shah et al., 2018). Despite steady improvements in obstetric and neonatal care that have reduced mortality (Saigal & Doyle, 2008), there is considerable diversity in neurodevelopmental outcomes among VP children. Children born VP are more likely to develop significant impairments such as cerebral palsy, and exhibit deficits in cognition, academics and behaviour compared to term-born children (Anderson, 2014; Aylward, 2014; Hack et al., 2005; Williams et al., 2019).

The commonality in neuropsychological risk among children born VP and children diagnosed with CHD can be attributed to similar antenatal and postnatal neurobiological vulnerability (Anderson et al., 2017; Donofrio & Massaro, 2010). Infants born full term with CHD have brain structures similar to infants born preterm and have a remarkably high rate of white matter injury (WMI; Anderson et al., 2017; Donofrio & Massaro, 2010). 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 VP found similar brain anomalies with concordance of total punctate WMI volumes predicting increased WMI for both groups (Birca et al., 2016; Claessens et al., 2017; Miller et al., 2007; Peyvandi et al., 2018).

Decades of research findings pertaining to neuropsychological outcomes of these populations independently also highlight several overlapping outcomes. Specifically, children with CHD and children born VP 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 (Anderson, 2014; Bellinger et al., 2011; Böhm et al., 2010; Briscoe et al., 2001; Cassidy et al., 2017; Grunau et al., 2009; Heineman et al., 2010; Howard et al., 2008; Omizzolo et al., 2013; Shillingford et al., 2008; Treyvaud et al., 2016; Wernovsky & Licht, 2016; Williams et al., 2019). Both populations exhibit speech and language difficulties; children with CHD exhibit problems with speech production, phonological awareness, and letter fluency (Bellinger & Newburger, 2010; Mussatto et al., 2014), and children born VP display receptive language deficits (Aylward, 2014; Briscoe et al., 2001). Furthermore, children born with CHD and children born VP have a higher incidence of being diagnosed with Attention Deficit-Hyperactivity Disorder (ADHD) compared to term-born healthy controls (Hansen et al., 2012; Treyvaud et al., 2016).

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 VP 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 early neurodevelopmental and behavioural outcomes at 18 months of age among term children diagnosed with CHD to VP children, and to examine their association with sociodemographic and white matter injury characteristics.

3.4 Methods

Participants. A clinical research sample of 181 children diagnosed with CHD (i.e., ≥ 37 weeks GA; $n=81$) or born VP (i.e., ≤ 32 weeks GA; $n=100$) were 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 VP birth, completion of a neurodevelopmental assessment and a child behaviour questionnaire completed by parent/guardian at 18-months corrected age (CA). 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 VP (e.g., congenital infection, intraventricular hemorrhage level 3 or 4, periventricular leukomalacia, neonatal stroke [severe $\geq 2/3$], and/or hypoxic-ischemic encephalopathy). See Figure 3 for participant inclusion flowchart and Table 2 for groups' characteristics. As shown in Figure 3, non-participation was largely due to missing Bayley-III and CBCL data given transition to virtual appointments during the COVID-19 pandemic.

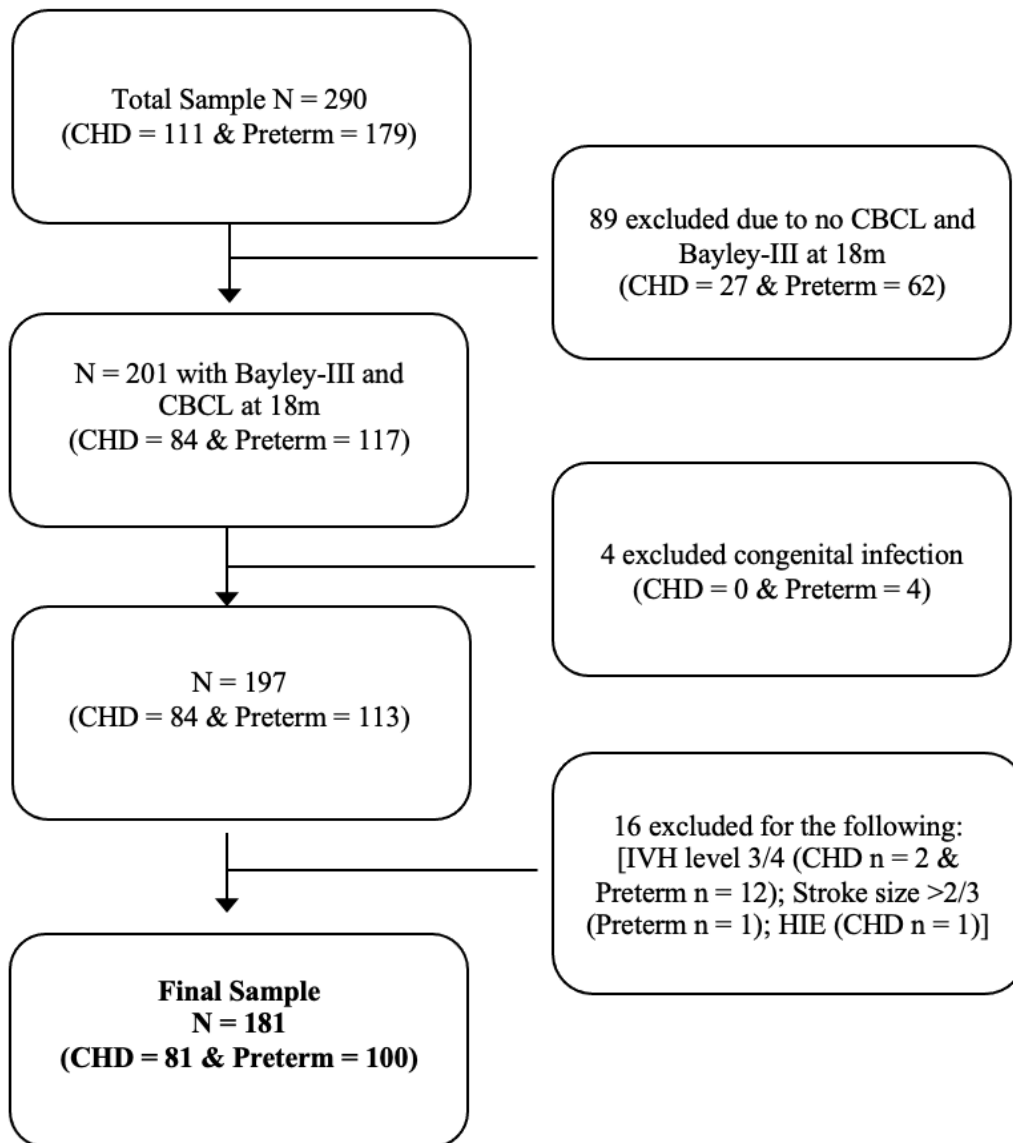


Figure 3. Participant Inclusion Flow Chart for Study 1.

Table 2. Participant Medical Characteristics and Demographic information (N =181) in Study 1			
	Term CHD (n=81)	Very Preterm (n=100)	<i>p (d or V)</i>
Gestational Age at Birth (<i>weeks</i>) <i>M(SD)</i>	39.04 (1.07)	27.42 (2.34)	<.001 (5.961)
<i>range</i>	37.14 – 41.57	22.71 – 31.57	
Sex assigned at birth (<i>males</i>)	55 (68%)	55 (55%)	.09 (.131)
Birth Weight (g) <i>M(SD)</i>	3355.85 (430.23)	1014.69 (359.58)	<.001 (6.178)
Current Seizures	3 (4%)	1 (1%)	.18 (.119)
White Matter Injury Volume	42.35mm ³ (98.74mm ³)	28.26mm ³ (154.96mm ³)	.48 (.107)
Maternal Age at Birth* (<i>years</i>)	32y 5m (5y 6m)	33y 0m (4y 7m)	.45 (.128)
<i>range</i>	18 – 43	21 – 41	
English Primary Language	64 (79%)	85 (87%)	.23 (.103)
Estimated Median Income Level			1.00 (.006)
<i>Lower income level (<\$41, 873)</i>	58 (81%)	77 (81%)	
<i>Higher income level (≥ \$41,873)</i>	14 (19%)	18 (19%)	
Age at MRI	42w 17d (2w 29d)	41w 12d (3w 9d)	.02 (.371)
CHD Diagnostic Categories			
<i>Two Ventricles with no arch obstruction</i>	45 (56%)	--	
<i>Two Ventricles with arch obstruction</i>	3 (4%)	--	
<i>Single Ventricle with no arch obstruction</i>	28 (35%)	--	
<i>Single Ventricle with arch obstruction</i>	5 (6%)	--	

Note. *There were 25 participants in the CHD group and 1 participant in the preterm group missing maternal age at birth. There are 9 participants 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 participants missing English language in the VP group.

**CHD diagnoses included a variety of conditions requiring surgery within the first few weeks of life 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), double inlet left ventricle.

3.5 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 utilized for families completing the study measures (i.e., Bayley-III and CBCL 1.5-5) when English was not their primary language. To determine neighbourhood median income level, the first three digits of the participant's postal code were collected. Median income data was 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 participant postal code data was 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., GA, biological sex, and birth weight) was collected from medical charts.

White Matter Injury. Imaging for the CHD group was completed post-surgery and at term equivalent for the VP group as part of routine clinical care collected as part of the larger study. WMI was characterized as areas of T1 hyperintensity using 3D T1-weighted image and WMI volume was calculated based on the manual segmentation of all WMI 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 previously described by Guo et al., (Guo et al., 2017, 2020).

Bayley Scales of Infant and Toddler Development - Third Ed. (Bayley-III). Neurodevelopment was assessed using the Bayley-III at 18 months (corrected age for the VP

group; Albers & Grieve, 2007; Bayley, 2006) 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 .90 – .97; Albers & Grieve, 2007). 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 VP participants were corrected for prematurity when scoring the Bayley-III.

Behavioural Outcomes. Parent ratings of child behaviours were examined using the Child Behavior Checklist for Ages 1.5-5 (CBCL; Achenbach, 1991). The CBCL is completed by parents/ caregivers to assess specific concerns related to child behaviour problems and has adequate psychometric properties (Achenbach & Rescorla, 2001). Six syndrome scales contribute to broad Internalizing and Externalizing domain scores, as well as *Sleep Problems*, *Total Problems*, and DSM-5 related domain scores. The CBCL 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.

3.6 Statistical Analysis.

Inferential statistics were used to compare mean differences between groups on the Bayley-III, and behavioural outcomes from the CBCL. Chi-squares 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, WMI volume, and outcomes. Four linear regression models were used to examine associations between outcomes (i.e., Cognition, Language, Motor, and CBCL total problem scores), and independent variables (i.e., WMI volume, maternal age at birth, English as first language, estimated median income, 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).

3.7 Results

Early neurodevelopmental and behavioural outcomes of term children diagnosed with CHD to VP children at 18 months of age (Objective 1).

See Table 3 for group means on neurodevelopmental and behavioural outcomes.

Neurodevelopmental Outcomes. The CHD and VP 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 VP group ($t(169) = -2.19, p = .047, d = .338$). 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 VP group (6%; $\chi^2(1) = 7.10, p = .014, V = .204$). There were no differences in the proportion of children with low scores (< 2 SD 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 VP group (7% and 3%, respectively; $\chi^2(1)=4.92, p=.032, V=.171$ and $\chi^2(1)=7.74, p=.009, V=.213$, respectively).

Behavioural Outcomes. Children in the CHD and VP groups did not differ in parent ratings of their behaviour on CBCL scores (i.e., mean scores or proportion of clinically elevated). Among composite scores, Internalizing problems had the highest proportion of elevated scores. Among subscales, Attention, Sleep, Withdrawal, Depression, and Somatic Complaints had the highest proportion of elevated scores.

Table 3. Cognitive and Behavioural Outcomes at 18 months CCA (N = 181) for Study 1			
	CHD (n = 81)	Very Preterm (n = 100)	p (d)
Bayley-III Outcomes			
Cognitive <i>M(SD)</i>	95.99 (13.91)	97.12 (13.98)	.588 (.081)
Language <i>M(SD)</i>	88.46 (17.45)	92.93 (17.11)	.097 (.259)
Receptive Language <i>M(SD)</i>	8.57 (3.25)	9.04 (3.28)	.354 (.144)
Expressive Language <i>M(SD)</i>	7.68 (2.95)	8.48 (3.18)	.096 (.261)
Motor Score <i>M(SD)</i>	93.66 (15.29)	95.84 (11.50)	.291 (.164)
Fine Motor <i>M(SD)</i>	10.12 (2.60)	10.15 (2.46)	.932 (.013)
Gross Motor <i>M(SD)</i>	7.66 (2.94)	8.60 (2.63)	.030 (.338)
CBCL 1.5-5 Outcomes			
Emotional Reactivity	52.40 (4.32)	52.09 (4.31)	.637 (.071)
Anxious/Depressed	51.44 (3.03)	52.13 (4.88)	.271 (.165)
Somatic Complaints	52.53 (5.09)	53.44 (6.20)	.357 (.138)
Withdrawn	52.96 (5.36)	53.41 (6.31)	.613 (.076)
Sleep Problems	54.31 (7.17)	53.50 (5.34)	.386 (.130)
Attention Problems	54.30 (6.18)	54.04 (5.79)	.774 (.043)
Aggressive Behaviours	51.95 (4.36)	52.11 (4.65)	.814 (.035)
Internalizing Behaviours	43.75 (10.61)	45.32 (10.12)	.312 (.152)
Externalizing Behaviours	46.36 (8.91)	46.48 (9.52)	.930 (.013)
Total Problems	46.32 (9.86)	46.76 (10.19)	.770 (.044)

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

Outcome Associations with Sociodemographic and White Matter Injury Characteristics (Objective 2).

The Bayley-III Cognitive Composite was positively associated with English as 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 CBCL composite score was associated with median income.

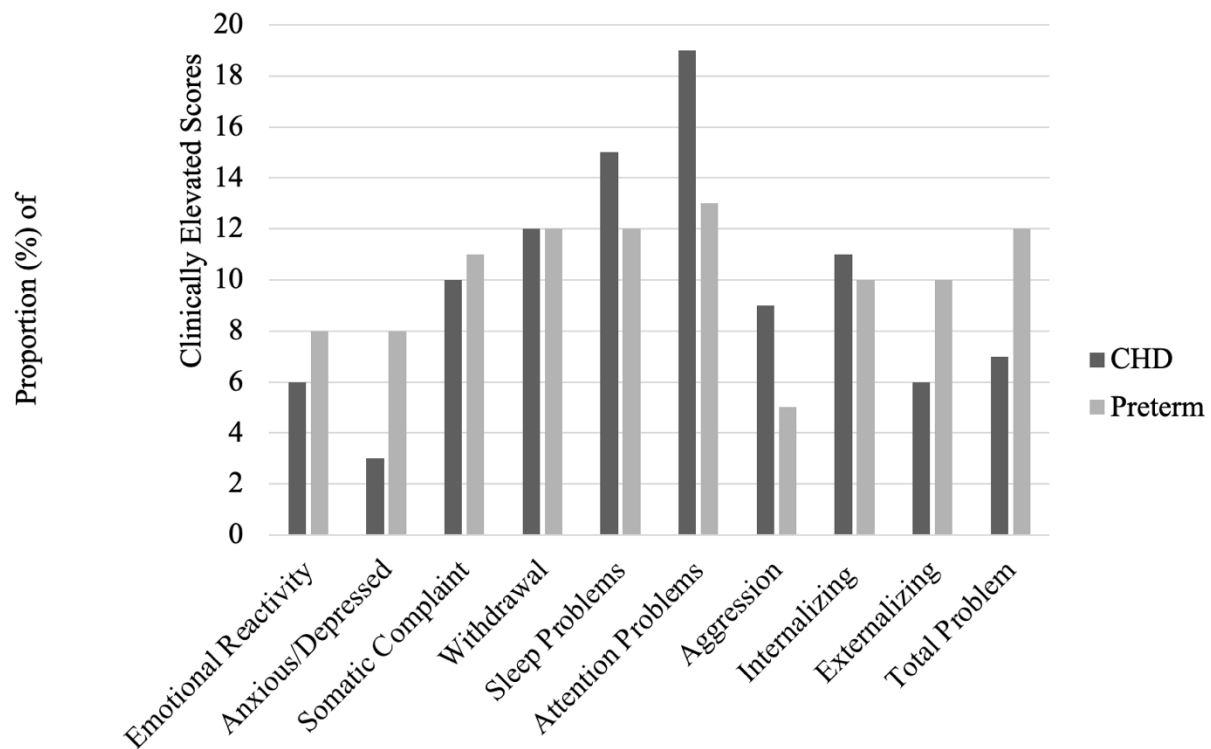
The regression model examining Cognitive Composite scores was significant ($F(6,136) = 3.30, p = .005, R = .364$) explaining 13.2% of the variance. English as the child's primary language ($\beta = .253, p = .004$) was associated with higher Cognitive Composite scores. Higher median income approached significance in the model ($\beta = .171, p = .055$) as a predictor of higher Cognitive Composite scores.

The model examining Language Composite scores was significant ($F(6,129) = 4.82, p < .001, R = .436$), explaining 19% of the variance. English as a primary language ($\beta = .389, p < .001$) was associated with higher Language Composite scores. Biological sex approached significance in the model ($\beta = .149, p = .079$), with female sex associated with higher Language Composite scores.

The model examining Motor Composite scores was not significant ($F(6,130) = 0.79, p = .58, R = .192$), explaining 3.7% of the variance. WMI volume approached significance in the model ($\beta = -.160, p = .085$).

The model examining the CBCL Total Problem score was significant ($F(6,137) = 3.27, p = .005, R = .361$), explaining 13% of the variance. Median income ($\beta = -.195, p = .029$) and English as primary language ($\beta = -.198, p = .024$) 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 ($\beta = -.165$, $p = .056$), with lower maternal age at birth associated with higher Total Problems.



Supplemental Figure 1. Proportion of Clinically Elevated Scores (≥ 60 on the CBCL 1.5-5 for CHD and VP Groups at 18m for Study 1

3.6 Discussion

The current study is one of few investigations comparing neurodevelopmental and behavioural outcomes in children with CHD and children born VP. 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 VP children. While it is important not to minimize 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 (Anderson, 2014; Geva & Genesee, 2017).

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 (VP>CHD) were more likely to do better on English based assessments and highlights significant limitations in monolingual assessment of core developmental outcomes (Geva & Genesee, 2017; Rivera Mindt et al., 2009, 2010). WMI 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 (Benavente-Fernández et al., 2020; Goldsworthy et al., 2016; Roberts et al., 2021). 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 VP and in children with CHD (Anderson, 2014; Claessens et al., 2018). However, our findings highlighted that children with CHD have greater impairment compared to those who are born VP 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., (Guo et al., 2017) in the current study total WMI volume was not significantly associated with neurodevelopmental outcomes at 18 months. However, total WMI 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 (Claessens et al., 2017; Mebius et al., 2017). 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 (Benavente-Fernández et al., 2020). 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 employ monolingual English based assessment tools (Geva

& Genesee, 2017; Rivera Mindt et al., 2009, 2010). 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 (DA et al., 2006). Data on race and ethnicity was 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 programs are well established as part of the standard of care for children with CHD or born VP, with increasingly innovative models considering ways to monitor and promote both mental health and long-term neurodevelopmental outcomes in these populations (Roberts et al., 2021; Wolfe et al., 2023). The current findings suggest that both groups are at 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 programs increase parent competence and improve behaviour in children with neurological conditions broadly (Burek et al., 2021; Williams et al., 2022). Given that both groups had similar cognitive and behavioural outcomes, a similar transdiagnostic approach to care may be warranted to help reduce waitlists and maximize access to patient care.

Overall, in our samples, common sociodemographic risk and testing factors were most influential in understanding early outcomes across CHD and VP populations and extended beyond the medical/neurobiological impacts measured in this 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 not only will promote more equitable service delivery, but also an improved scientific knowledge base regarding outcomes and needed interventions among these at-risk children and their families.

Chapter 4: Longitudinal Comparison of Neurodevelopmental Outcomes from 18m to 36m of Children born Very Preterm and Children Diagnosed with Congenital Heart Disease

4.1 Publication status and author contributions

The following chapter has been drafted as a manuscript. The contents have been reviewed by the following authors: Roberts, S.D., Sananes, R., Wojtowicz, M., & Williams, T.S., who also contributed to this work through the development of project ideas, data collection and management, psychometric expertise, and methodological discussions.

Samantha D. Roberts, the first author, developed the conceptual rationale for the study, organized, cleaned, analyzed and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions. Although in preparation, this manuscript has not yet been submitted to a journal for peer review.

4.2 Abstract

Background/Aim: Children born very preterm (VP) or diagnosed with congenital heart disease (CHD) have similar patterns of brain injury and dysmaturation and are at risk for poorer neurodevelopment. Limited research has compared neurodevelopment of these groups longitudinally to consider shared and unique developmental trajectories across the high-risk neonatal group. This longitudinal study compared cognitive, language, motor, and behaviour ratings of VP children to children with CHD at 18m and 36m of age.

Methods: 116 children born VP (≤ 32 weeks; $n=72$) or with CHD ($n=44$) were assessed at 18m and 36m of age. Development was assessed using the Bayley Scales of Infant and Toddler Development-3rd Edition (Bayley-III). Parents rated child behaviour using the Child Behaviour Checklist (CBCL; 1.5-5 years) at each age. Repeated measures ANOVA with post-hoc tests compared group differences in Bayley-III scores and CBCL ratings over time. Inferential statistics were used to compare group differences at 36m, and four separate hierarchical linear models were used to determine potential predictors (i.e., group membership, WMI, primary language spoken in the home, and median household income) of outcomes. Reliable change index (RCI) scores were calculated to identify statistically meaningful change in individual scores.

Results: In both CHD and VP children, Bayley Cognitive scores declined from 18-36 month follow up. There was a group by time interaction for Language and Motor scores. Language scores in the VP group remained stable but significantly increased from 18m to 36m in the CHD group. Motor scores in the VP group significantly declined over time but were stable in the CHD group. Fine Motor scores decreased over time in both groups, and Expressive Language scores

increased over time for both groups. Receptive Language and Gross Motor scores remained stable in the VP group but significantly improved in the CHD group. Behaviourally, there were more internalizing concerns reported at 36m than 18m for both groups, and more concerns identified in the VP group at 36m. There were no differences in reliable change scores across groups for Cognitive and Motor scores or CBCL ratings. More VP children had significant declines in Language scores (8.3%) compared to the CHD children (0%). More CHD children had significant improvement in Language scores (22.7%) compared to the VP group (11.1%). English as a primary language was a significant predictor of 36 month Cognitive and Language composite scores for both groups, and WMI volume and VP group membership were predictors of 36-month Motor composite scores.

Conclusions: Findings highlight the unique and shared cognitive and psychosocial developmental trajectories among children born preterm or with CHD in early development.

Key words: neurodevelopmental outcomes, behaviour, cardiology, preterm birth

4.3 Introduction

Infancy is a critical period for neurodevelopment that can be impacted by various medical conditions. Though their experiences and outcomes reflect distinct underlying conditions, children with congenital heart disease (CHD) and children born very preterm (VP) both exhibit notable neurodevelopmental vulnerabilities. Despite differences in etiology, these groups experience similar disruption in brain development and maturation in early critical periods that can impact the delicate developmental trajectory of cognition, language, motor, behaviour, academic, and social functioning.

Decades of research findings pertaining to the neuropsychological outcomes of children born with CHD and children born VP independently highlight several overlapping outcomes. To summarize, studies conducted with either children born VP or children born with CHD have documented impairments in motor, language, executive functioning, as well as behaviour (Anderson, 2014; Baron et al., 2012; Bellinger & Newburger, 2010; Brosig et al., 2018; Jobson, 2021). Disruption in cortical development and/or associated early brain injuries (e.g., white matter injury, hemorrhage) can hinder the development of motor pathways and coordination, thus leading to changes in muscle tone (i.e., hypertonia, hypotonia), as well as delays in gross and fine motor milestones such as sitting, crawling, walking, and grasping (Bolduc et al., 2020; Cameron et al., 2021; de Kieviet et al., 2009; Spittle et al., 2021). Children born VP may also exhibit difficulties in expressive and receptive language which can impact literacy skills including vocabulary acquisition, sentence structure, and grammar at early school age (Anderson, 2014; Barre et al., 2011; Guarini et al., 2016). Literature examining language development in children with CHD have also found impairments in early expressive and receptive language (Fourdain et al., 2019; Turner et al., 2022). Additionally, research has found

that many children in both these groups have elevated ratings on measures of anxiety, social withdrawal, and attention attributable to the combination of neurological vulnerability associated with prematurity or CHD, as well as environmental factors such as parental stress and prolonged hospitalization (Johnson & Marlow, 2011; Marino et al., 2012; Treyvaud et al., 2012, 2016; Wernovsky & Licht, 2016).

Findings in the literature across both high-risk infant populations emphasize an increased risk of experiencing challenges across multiple neurodevelopmental domains. They also emphasize the need for early and ongoing surveillance and intervention to improve long-term neurodevelopmental outcomes among these populations for them to reach their full potential and improve their quality of life (Marino et al., 2012; Spittle et al., 2015). Given the overlapping outcomes and similar emphasis on treatment, a longitudinal approach to examining similarities and differences between these populations is beneficial as it informs transdiagnostic approaches within neurodevelopmental follow-up programs. This will ultimately enhance collaboration across disciplines, improving communication among specialists, and ensuring that the expertise of diverse team members is fully leveraged to provide comprehensive, integrated care.

There is little literature that directly compares the outcomes of children born with CHD and children born VP. One study conducted a topology and comparison analysis of physiological changes within the brains of these groups of children. Specifically, the researchers found that infants born with CHD and infants born VP had similar brain anomalies with concordance of total punctate white matter injury volumes for both groups (Guo et al., 2019a). Our group was one of the first to directly compare neurodevelopmental outcomes among these groups, finding that children with CHD were more likely to display language and motor impairment compared to children born VP at 18 months of age (Roberts et al., 2024). In this study, children with CHD

had lower gross motor scores compared to children in the VP group. The CHD group also had a larger proportion of children with impaired scores in expressive language (Roberts et al., 2024). These studies offered an initial first step in understanding the overlapping and unique early outcomes among these populations. Further research is now needed to elucidate the long-term trajectories of neurodevelopment in these vulnerable populations, particularly as demands increase with age.

The objectives of the current longitudinal study were to 1) to examine trajectories in neurodevelopmental and behavioural outcomes from 18 to 36 months of age, 2) compare developmental outcomes of these children at 36 months and look at clinical change over time, and 3) to consider associations with sociodemographic and white matter injury characteristics.

4.4 Methods

Participants. A clinical research sample of 116 children diagnosed with CHD (i.e., ≥ 37 weeks gestational age; $n=44$) or born VP (i.e., ≤ 32 weeks gestational age; $n=72$) were included from a larger cohort followed in the Neonatal Follow-up Program at the Hospital for Sick Children and Mount Sinai Hospital in Toronto, Canada. Inclusion criteria were a diagnosis of CHD or VP birth, completion of a neurodevelopmental assessment at both 18 months and 36 months of age, and a child behaviour questionnaire completed by a parent/guardian at 18 months and 36 months of 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 or those born VP (e.g., congenital infection, intraventricular hemorrhage level 3 or 4, periventricular leukomalacia, neonatal stroke [severe $\geq 2/3$], and/or hypoxic-ischemic encephalopathy). See Table 4 for group characteristics.

Table 4. Participant Medical Characteristics and Demographic information (N =116) for Study 2

	Term CHD (n=44)	Very Preterm (n=72)	<i>p (d or V)</i>
Gestational Age at Birth - <i>weeks</i> <i>M(SD)</i>	38.98w (1.20)	27.17w (2.19)	<.001 (6.28)
<i>range</i>	37.29w – 41.57w	23.29 – 31.57w	
Sex assigned at birth - <i>males</i>	33 (75%)	38 (52.8%)	.019 (.221)
Birth Weight (g) <i>M(SD)</i>	3310.65g (357.71g)	973.89g (321.43g)	<.001 (6.96)
Seizures	1 (2.3%)	--	--
White Matter Injury Volume	45.77mm ³ (102.76mm ³)	37.81mm ³ (180.15mm ³)	.79 (.052)
Maternal Age at Birth* - <i>years</i> <i>range</i>	33y 1m (5y 6m)	32y 8m (5y 5m)	.77 (.062)
English Primary Language - <i>yes</i>	34 (77.3%)	58 (85.3%)	.202 (.102)
Estimated Median Income Level			.797 (.050)
<i>Lower income level (<\$41, 873)</i>	34 (79%)	49 (83%)	
<i>Higher income level (≥ \$41,873)</i>	9 (21%)	10 (17%)	
Age at MRI <i>M(SD)</i>	42w 7d (2w 7d)	41w 16d (3w 7d)	0.23 (.252)
CHD Diagnostic Categories			
<i>Two Ventricles with no arch obstruction</i>	28 (63.5%)	--	--
<i>Two Ventricles with arch obstruction</i>	2 (4.5%)	--	--
<i>Single Ventricle with no arch obstruction</i>	12 (27.3%)	--	--
<i>Single Ventricle with arch obstruction</i>	2 (4.5%)	--	--

Note. *There were 11 participants in the CHD group missing maternal age at birth. There are 5 participants from the VP group missing data for white matter injury volume. There is 1 missing median income in the CHD group and 13 in the VP group. There are 4 participants 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), double inlet left ventricle.

Participant Demographic and Medical Information. Participant demographic information was collected, including birth history from the child’s medical chart (i.e., gestational age, biological sex, and birth weight), and sociodemographic factors from study questionnaires (i.e., primary language spoken in the home and maternal age at birth). Of note, a medical

interpreter was provided for families completing the study measures when English was not their primary language. To determine neighbourhood median household income level, the first three digits of the participant's postal code were collected. Median household income data was 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 participant postal code data was linked to the appropriate census dissemination area and aggregated neighbourhood median household income (i.e., the amount that divides the income distribution of that group into two halves).

White Matter Injury. Magnetic resonance imaging (MRI) was completed for both groups. Imaging for the CHD group was completed pre-and-post surgery, and at birth and term equivalent for the VP group but for the purposes of this study, post-surgery and term equivalent scans were used. These scans were part of routine clinical care collected as part of the larger clinical research study. WMI was characterized as areas of T1 hyperintensity using 3D T1-weighted image and WMI volume was calculated based on the manual segmentation of all WMI 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., (Guo et al., 2017, 2020).

4.5 Measures

Bayley Scales of Infant and Toddler Development. Neurodevelopment was assessed using the Bayley Scales of Infant and Toddler Development, *Third Edition* (BSID-III; Albers & Grieve, 2007; Bayley, 2006). 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 BSID-III is a gold-standard measure of infant and child development displaying strong to excellent validity, and test-retest and inter-rater reliability (ranging from .90 – .97; Albers & Grieve, 2007; Hua et al., 2019). The BSID-III uses standard scores with a mean of 100 and standard deviation of 15 for Cognitive, Language, and Motor composite scores. 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). Expressive and Receptive Language, and Fine and Gross Motor subtests use scaled scores with a mean of 10 and standard deviation of 3. The measure was administered at 18 months of age and again at 36 months of age. Of note, the VP group was corrected for age at the 18-month assessment only, with chronological age used at the 36-month assessment, as per standard correcting guidelines.

Behavioural Outcomes. Parent ratings of child behaviour concerns were examined at 18 and 36 months using the Child Behavior Checklist for Ages 1.5-5 (CBCL). The CBCL is completed by parents/ caregivers to assess specific concerns related to child behaviour and has adequate psychometric properties (Achenbach & Rescorla, 2000). The CBCL has six syndrome scales that contribute to broad internalizing and externalizing domain scores, as well as Sleep Problems, Total Problems, and DSM-5 related domain scores. For the purposes of this paper, Total Problems, Internalizing, and Externalizing domain scores were explored, these were chosen based on findings in previous literature (Roberts et al., 2024) and by taking a theoretical framework. The CBCL 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.

Reliable Change Index Scores. Individual patterns of performance were examined by calculating reliable change index (RCI) scores for each participant's neurodevelopmental and behavioural outcomes over time (Duff, 2012). This calculation uses test-specific published norms and reliability values to calculate pre-to-post score differences for each outcome variable divided by the standard error of measurement to assesses whether the change in each participant's individual score was statistically significant over time. The purpose of using RCI scores is to determine whether the change in an individual's test scores over time is statistically significant and not due to measurement error or natural variability. Based on RCI results, participants were also categorized based on clinically meaningful change using the standard deviation index method as significantly declining or increasing over time (scores of least one standard deviations below the mean), no change (less than one standard deviation of change), or significantly increasing over time (scores of at least one standard deviation above the mean; Duff, 2012). Furthermore, for Bayley-III outcomes each individual's standard score was examined to see if it changed clinical categories (e.g., such as from Average to Below Average). Clinical categories were based on the American Academy of Clinical Neuropsychology (AACN) consensus statement for uniform labeling of performance test scores (Guilmette et al., 2020), see Table 5 below.

Table 5. Clinical Categories based on AACN consensus statement for Study 2		
Standard Score	Percentile	Score Label
≥ 130	≥ 98	Exceptionally high score
120 – 129	91 – 97	Above average score
110 – 119	75 – 90	High average score
90 – 109	25 – 74	Average score
80 – 89	9 – 24	Low average score
70 – 79	2 – 8	Below average score
≤ 70	<2	Exceptionally low score

4.6 Statistical Analysis

Objective 1: To examine neurodevelopmental outcomes over time, three repeated measures analyses of variance (ANOVA) were used to test differences in Bayley-III outcomes over time (i.e., Cognition, Language, and Motor composite scores) with time as the *within-subjects* factor (18-month and 36-month) and group as the *between-subjects* factor (CHD and VP). Significant interactions with time and group were followed up with post hoc analyses. To understand clinical neurodevelopmental trajectories, inferential statistics were used to compare mean differences between groups on the Bayley-III for 36-month data and individual patterns of performance were examined by calculating reliable change index (RCI) scores for each participant's neurodevelopmental outcomes over time (Jacobson & Truax, 1991). Chi-square analyses were used to compare the proportions of children in each group that demonstrated a change (decline or increase) of at least one standard deviation over time. Further follow-up analyses were conducted to examine whether groups changed clinical categories based on the AACN categories described above. Chi-square analyses were used to compare the proportion of those that changed clinically meaningful categories.

Objective 2. To examine behavioural outcomes over time, three repeated measures analyses of variance (ANOVA) were used to test differences in CBCL outcomes (i.e., Total Problems, Internalizing and Externalizing domain scores) with time as the *within-subjects* factor (18-month and 36-month) and group as the *between-subjects* factor (CHD and VP). Significant interactions with time and group were followed up with post hoc analyses. To examine behavioural trajectories, inferential statistics were used to compare mean differences between groups on the CBCL for 36-month data and individual patterns of performance were examined by calculating RCI scores for behaviour outcome ratings over time. Chi-square analyses were

used to compare the proportions of parents in each group that demonstrated a change (decline or increase) of at least one standard deviation over time in RCI scores.

Objective 3. Four separate linear models were used to assess predictors of Cognition, Language, and Motor outcome scores from the Bayley-III and Total Problems composite score from the CBCL over time. Independent variables entered were dummy-coded group membership (CHD versus all else), white matter injury volume (WMI), primary language spoken in the home, and median household income.

All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 29 (IBM corp. Released, 2023). A priori power analysis revealed that the current sample size was sufficient to conduct the proposed ANOVA models and the hierarchical linear regression models with 6 predictors based on a power of at least 80%, medium effect size, and an alpha value of .05 (Soper, 2024a). For all analyses, two-tailed alpha values of less than .05 were considered statistically significant. To account for multiple comparisons, p values were adjusted using the false discovery rate (FDR) criteria (Benjamini & Hochberg, 1995).

4.7 Results

Neurodevelopmental Outcomes Over Time (Objective 1).

There was a main effect of time for Bayley Cognitive composite scores ($F(1,109) = 6.30$, $p = .014$, $\eta^2 = .055$), with lower scores at 36 months than 18 months for both groups. There was no time by group interaction or group difference at 36 months for the Cognitive composite.

There was a time by group interaction for Language ($F(1,92) = 9.11$, $p = .003$, $\eta^2 = .090$) and Motor composite scores ($F(1,94) = 6.89$, $p = .010$, $\eta^2 = .068$). Language composite scores in the VP group were relatively stable but significantly increased from 18 months to 36 months in the CHD group. Follow-up post hoc analyses demonstrated that there was a significant difference in

mean scores on Language composite at 36 months ($t(1,97) = 2.37, p = .02$), with the CHD group having a higher mean score compared to the VP group. Motor composite scores in the VP group significantly decreased over time but remained stable in the CHD group. Follow-up post hoc analyses demonstrated a significant difference at 36 months for the Motor Composite ($t(1,102) = 2.14, p = .003$) with children in the CHD group having higher scores (performing better) than children in the VP group. See Figure 4 demonstrating the time by group interactions. Of note, only significant interactions are denoted in the figure.

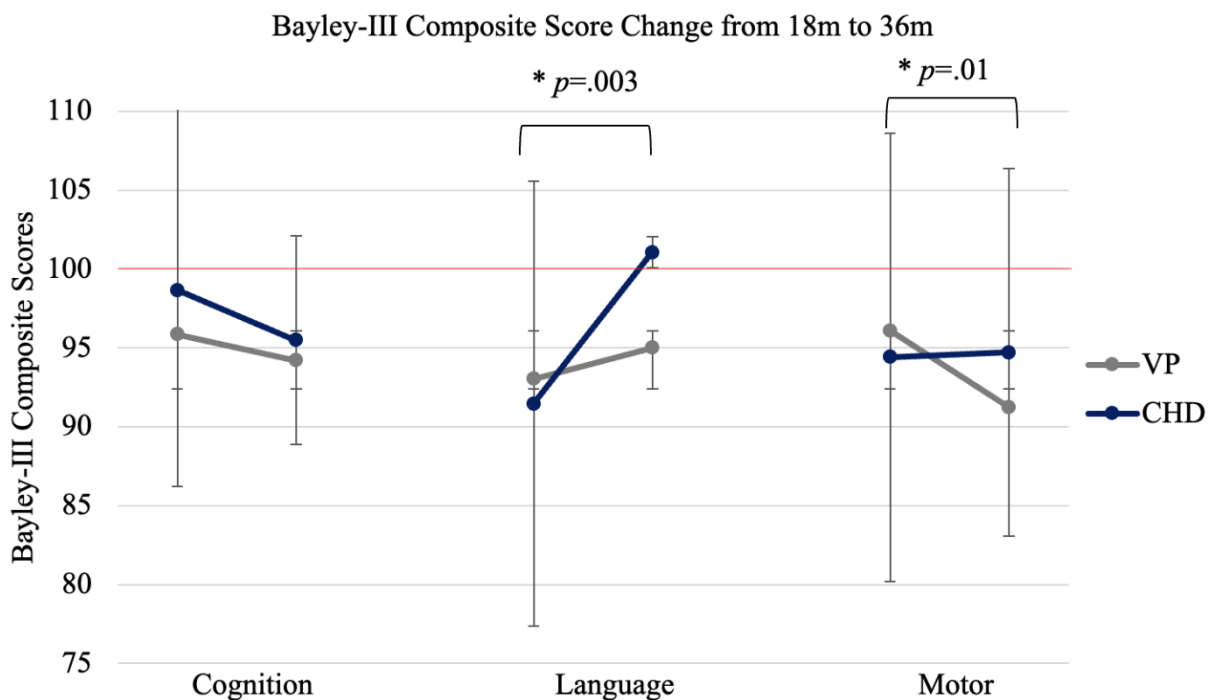


Figure 4. Group comparison of Bayley-III composite scores over time for Study 2.

To better understand changes in Language and Motor composite scores described above, further exploration was conducted using subscales of Expressive and Receptive Language, and Fine and Gross Motor. Specifically, there was a time by group interaction for the Receptive

Language subscale score ($F(1,99) = 8.36, p = .005, \eta^2 = .078$). The VP group remained stable over time while the CHD group significantly improved from 18 months to 36 months. Post hoc analyses demonstrated a significant difference at 36 months for the Receptive Language subscale ($t(1,104) = 3.11, p = .002$), with the CHD group having a higher mean score than the VP group. For the Expressive Language subscale, there was a main effect of time ($F(1,94) = 13.61, p < .001, \eta^2 = .126$) with both groups improving over time. For the Fine Motor subscale, there was a main effect of time ($F(1,103) = 20.24, p < .001, \eta^2 = .164$), with scores decreasing over time for both groups. There was a time by group interaction for the Gross Motor subscale ($F(1,98) = 5.57, p = .020, \eta^2 = .054$) with children in the CHD group improving from 18 months to 36 months while the VP group scores remained stable. See Table 6 for Bayley scores at 18 months and 36 months for both groups, as well as Figure 5 for subscale time by group interactions.

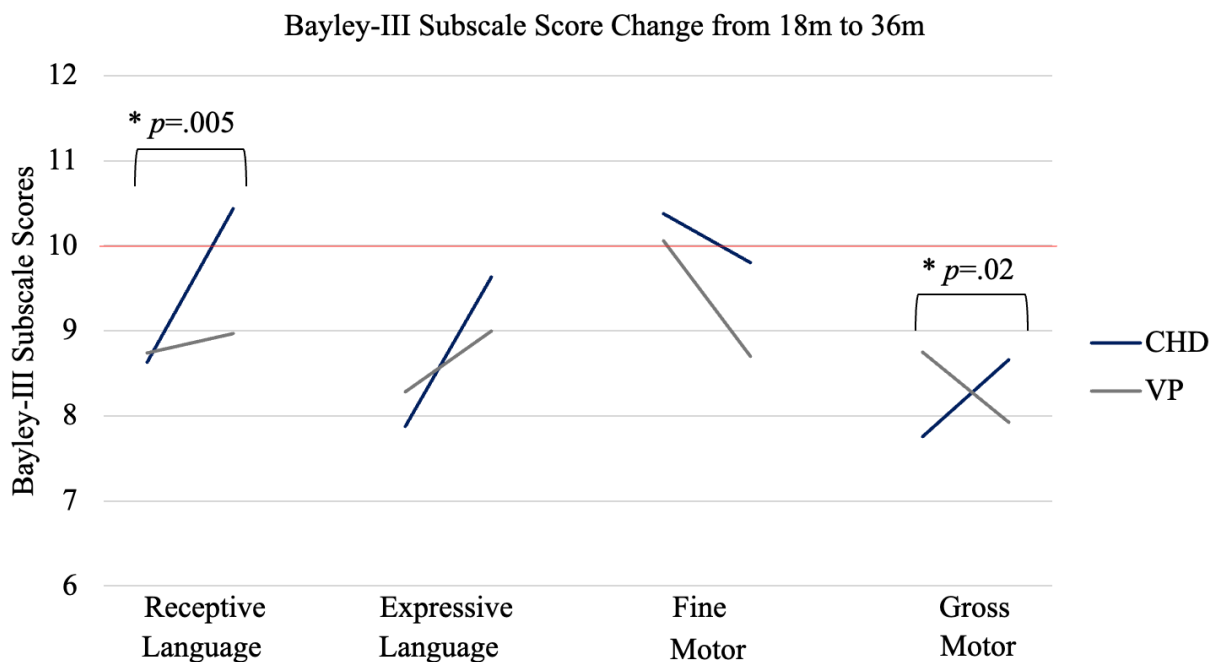


Figure 5. Group comparison of Bayley-III subscale scores over time for Study 2.

Table 6. Group Means on Cognitive and Behavioural Outcomes Over Time for Study 2

	CHD (n = 44)		Very Preterm (n = 72)	
	Time 1 (18 months)	Time 2 (36 months)	Time 1 (18 months)	Time 2 (36 months)
Bayley-III Outcomes				
Cognitive Score <i>M(SD)</i>	98.72 (12.15)	95.48 (6.52)	95.86 (11.55)	93.26 (10.82)
Language Score <i>M(SD)</i>	89.95 (15.51)	101.03 (10.10)	91.48 (16.11)	94.47 (14.20)
<i>Receptive language M(SD)</i>	8.63 (2.94)	10.43 (1.85)	8.74 (2.95)	8.97 (2.51)
<i>Expressive language M(SD)</i>	7.87 (2.79)	9.63 (1.83)	8.28 (3.23)	9.00 (2.62)
Motor Score <i>M(SD)</i>	94.82 (13.58)	95.44 (11.32)	95.87 (12.79)	90.02 (13.14)
<i>Fine Motor M(SD)</i>	10.38 (2.20)	9.80 (1.89)	10.06 (2.50)	8.70 (2.12)
<i>Gross Motor M(SD)</i>	7.75 (2.76)	8.66 (2.22)	8.75 (3.00)	7.92 (2.83)
CBCL 1.5-5 Outcomes				
<i>Emotional Reactivity</i>	51.98 (3.82)	52.48 (3.64)	52.50 (4.48)	54.37 (6.13)
<i>Anxious/Depressed</i>	51.00 (1.75)	51.30 (3.72)	52.37 (4.77)	52.79 (4.26)
<i>Somatic Complaints</i>	52.23 (4.88)	52.52 (4.24)	53.63 (6.88)	53.85 (5.30)
<i>Withdrawn</i>	52.34 (4.55)	52.52 (4.72)	54.23 (7.21)	55.94 (8.14)
<i>Sleep Problems</i>	53.91 (5.63)	54.52 (6.38)	53.10 (5.04)	53.82 (6.18)
<i>Attention Problems</i>	53.68 (5.51)	53.09 (5.37)	54.05 (5.77)	54.43 (6.41)
<i>Aggressive Behaviours</i>	51.68 (3.75)	54.22 (10.27)	52.08 (4.67)	53.64 (6.50)
Internalizing Behaviours	41.84 (10.21)	43.61 (9.80)	46.27 (10.54)	50.18 (9.74)
Externalizing Behaviours	45.50 (8.29)	46.00 (13.47)	46.97 (9.28)	48.42 (10.422)
Total Problems	45.11 (8.81)	45.52 (11.06)	47.48 (9.97)	49.79 (10.69)

Note. Higher scores on the Bayley-III indicate better performance. Higher scores on the CBCL indicate poorer performance. Some participants were missing scores for individual scales across the measures. Specifically, for Cognitive Composite: CHD=2, VP=2; Language Composite: CHD=11, VP=6; Motor Composite: CHD=5, VP=7; Receptive Language: CHD=6, VP=3; Expressive Language: CHD=9, VP=6; Fine Motor: CHD=3, VP=5; and Gross Motor: CHD=4, VP=7.

Neurodevelopmental reliable change trajectories. There was a similar proportion of children who had significant declines in their Cognitive composite scores (decline of at least 1 SD) from 18 months to 36 months in the CHD group (15.9%) and in the VP group (13.9%), as well as with those who significantly improved (score increase by at least 1 SD) (CHD = 5%, Very Preterm = 12.5%), with no statistical differences between groups. The VP group had 8.3% of the sample significantly decline in Language composite scores over time whereas no children in the CHD group significantly declined. There was a significant difference in the proportion of those that significantly improved on their Language composite score over time ($\chi^2 = 5.13, p = .048$), with 22.7% of the CHD group increasing by at least one standard deviation compared to 11.1% of the VP group. There was no significant difference between groups for the proportion of children that significantly changed (increase or decrease) on the Motor composite score. Approximately, 7% of the CHD group and 14% of the VP group showed decreased scores over time, and 2.3% of the CHD group and 2.8% of the VP group showed increased scores over time. Of note, due to limited cell counts, some proportions of children who significantly declined or increased over time are described qualitatively. Statistics are reported for those with adequate cell size.

There were similar proportions of children with scores in clinical categories (e.g., Average, Low Average) for Cognitive and Motor composite scores at 36 months. There was also a similar proportion of children that either increased clinical categories (e.g., went from Average to Above Average), decreased clinical categories (e.g., went from Average to Below Average), or stayed the same (e.g., score remained in the same clinical category) in both groups at 36 months for Cognitive and Motor composite scores. There was a significant difference in the distribution of scores for the Language composite at 36 months between groups. Although there

was a similar proportion of children within the Average range in both groups (i.e., 45% CHD and 56% VP), there were significantly more children within the Low Average to Exceptionally Low Score range in the VP group compared to the CHD group ($\chi^2 = 14.97, p = .01, V = .389$). Specifically, only 9% of the CHD group fell below the Average range whereas 29% of the VP group fell below the Average range for Language composite scores at 36 months. There was also a significant difference between those that changed clinical categories over time for Language composite ($\chi^2 = 10.53, p = .005, V = .335$). Notably, there were no children that declined in clinical category in the CHD group, whereas 19% of the VP group changed from a higher category to a lower one (e.g., changed from Average to Below Average). See Table 7 for individual score change and RCI values by group.

Table 7. Reliable Change Index Scores on the Bayley-III from Both Assessments for Study 2

Research ID	Time 1 Assessment (18 months)			Time 2 Assessment (36 months)			RCI and Difference from T2-T1					
	Cognitive	Language	Motor	Cognitive	Language	Motor	Cognitive		Language		Motor	
							RCI Score	Diff	RCI Score	Diff	RCI Score	Diff
CHD												
CHD-1	115	106	118	100	100	97	-11.17*	-15	-0.95	-6	-3.36*	-21
CHD-2	85	77	67	80	86	76	-3.72	-5	1.42	9	-0.16	-1
CHD-3	110	112	107	110	112	107	0	0	0	0	-0.80	-5
CHD-4	110	103	91	100	100	94	-7.44	-10	-0.48	-3	0.48	3
CHD-5	100	--	100	90	89	107	-7.44	-10	--	--	1.12	7
CHD-6	70	68	76	95	97	73	18.61*	25	4.59*	29	-0.48	-3
CHD-7	95	83	88	90	--	97	-3.72	-5	--	--	1.44	9
CHD-8	90	77	79	95	71	85	3.72	5	-0.95	-6	0.96	6
CHD-9	100	79	94	100	91	91	0	0	1.90	12	-0.48	-3
CHD-10	100	106	97	95	112	103	-3.72	-5	0.95	6	0.80	5
CHD-11	80	53	91	90	--	--	7.44	10	--	--	--	--
CHD-12	100	65	--	90	103	100	-7.44	-10	6.01*	38	--	--
CHD-13	115	89	100	100	106	91	-11.17*	-15	2.69*	17	-1.44	-9
CHD-14	105	89	103	105	112	103	0	0	3.64*	23	0	0
CHD-15	125	118	112	95	115	107	-22.33*	-30	-0.48	-3	-0.80	-5
CHD-16	120	100	118	100	103	107	-14.89*	-20	0.48	3	-1.76	-11
CHD-17	105	89	--	95	94	--	-7.44	-10	0.79	5	--	--
CHD-18	100	68	88	105	97	97	-3.72	-5	4.59*	29	1.44	9
CHD-19	80	86	58	80	97	64	0	0	1.74	11	0.96	6
CHD-20	95	89	88	90	97	94	-3.72	-5	1.27	8	0.96	6
CHD-21	105	94	100	100	115	110	-3.72	-5	3.32*	21	1.60	10
CHD-22	95	91	94	95	106	82	0	0	2.37*	15	-1.92	-12
CHD-23	90	86	94	95	100	85	3.72	5	2.22	14	1.44	-9
CHD-24	95	100	97	100	97	94	3.72	5	-0.48	-3	-0.48	-3
CHD-25	90	89	100	100	103	103	3.72	5	2.22	14	0.48	3
CHD-26	110	--	--	100	112	110	7.44	10	--	--	--	--

CHD-27	100	74	88	95	97	100	-3.72	-5	3.64*	23	1.92	12
CHD-28	90	--	91	90	--	88	0	0	--	--	-0.48	-3
CHD-29	95	97	103	100	112	110	3.72	5	2.37*	15	1.12	7
CHD-30	105	91	73	100	97	85	-3.72	-5	0.95	6	1.92	12
CHD-31	80	79	67	90	86	79	7.44	10	1.11	7	1.92	12
CHD-32	105	100	100	85	--	--	-14.89*	-20	--	--	--	--
CHD-33	90	--	94	85	--	76	-3.72	-5	--	--	-2.88*	-18
CHD-34	105	103	103	100	106	100	-3.72	-5	0.48	3	-0.48	-3
CHD-35	100	97	97	95	91	97	-3.72	-5	-0.95	-6	0	0
CHD-36	100	100	100	--	--	--	--	--	--	--	--	--
CHD-37	100	91	103	--	--	--	--	--	--	--	--	--
CHD-38	70	56	97	95	--	97	18.61*	25	--	--	0	0
CHD-39	95	86	91	95	103	107	0	0	2.69*	17	2.56*	16
CHD-40	--	--	--	95	--	97	--	--	--	--	--	--
CHD-41	95	100	107	100	--	103	3.72	5	--	--	-0.64	-4
CHD-42	115	115	118	100	112	103	-11.17*	-15	-0.48	-3	-2.40*	-15
CHD-43	100	112	--	100	115	100	0	0	0.48	3	--	--
CHD-44	115	--	106	100	--	103	-11.17*	-15	--	--	-0.48	-3
Mean	98.72	89.95	94.82	95.86	91.48	95.87						
SD	12.15	15.51	13.58	11.55	16.11	12.79						

Very Preterm

VP-1	90	74	97	85	79	85	-3.72	-5	0.79	5	-1.92	-12
VP-2	90	71	94	90	--	88	0	0	--	--	-0.96	-6
VP-3	120	118	100	100	109	97	-14.89*	-20*	-1.42	-9	-0.48	-3
VP-4	100	124	110	100	106	110	0	0	-2.85*	-18	0	0
VP-5	95	100	107	95	106	103	0	0	0.95	6	-0.64	-4
VP-6	100	112	100	90	106	94	-7.44	-10	-0.95	-6	-0.96	-6
VP-7	95	89	107	90	97	121	-3.72	-5	1.27	8	2.24	14
VP-8	90	89	107	100	94	91	7.44	10	0.79	5	2.56*	-16
VP-9	90	86	97	105	--	88	11.17*	15	--	--	-1.44	-9
VP-10	120	103	110	100	103	112	-14.89*	-20*	0	0	0.32	2
VP-11	100	91	107	85	89	91	-11.17*	-15*	-0.32	-2	-2.56*	-16
VP-12	95	83	94	85	71	85	-7.44	-10	-1.90	-12	-1.44	-9

VP-13	90	118	88	100	106	73	7.44	10	-1.90	-12	-2.40*	-15
VP-14	105	97	94	100	112	88	-3.72	-5	2.37*	15	-0.96	-6
VP-15	90	74	85	80	74	82	-7.44	-10	0	0	-0.48	-3
VP-16	100	103	100	95	109	94	-3.72	-5	0.95	6	-0.96	-6
VP-17	100	100	107	95	106	100	-3.72	-5	0	0	-1.12	-7
VP-18	125	121	107	95	124	100	-22.33*	-30	0.48	3	-1.12	-7
VP-19	100	100	100	100	103	91	0	0	0.48	3	-1.44	-9
VP-20	105	97	97	105	97	97	0	0	0	0	0	0
VP-21	115	115	107	135	124	94	14.89*	20	1.42	9	-2.08	-13
VP-22	100	86	85	100	97	73	0	0	1.74	11	-1.92	-12
VP-23	95	97	88	95	109	--	0	0	1.90	12	--	--
VP-24	95	112	112	120	97	94	18.61*	25	-2.37*	-15	-2.88*	-18
VP-25	105	83	103	90	86	94	-11.17*	-15	0.95	6	-1.44	-9
VP-26	85	74	94	95	97	103	7.44	10	3.64*	23	1.44	9
VP-27	85	71	70	60	53	52	-18.61*	-25	-2.85*	-18	-2.88*	-18
VP-28	90	86	107	95	94	100	3.72	5	1.27	8	-1.12	-7
VP-29	95	77	110	95	--	91	0	0	--	--	-3.04*	-19
VP-30	80	86	97	95	86	82	11.17*	15	0	0	-2.40*	-15
VP-31	75	89	82	100	100	76	18.61*	25	1.74	11	-0.96	-6
VP-32	105	112	103	120	110	97	11.17*	15	-0.32	-2	-0.96	-6
VP-33	85	77	91	85	--	--	0	0	--	--	--	--
VP-34	110	100	100	100	97	99	-7.44	-10	-0.48	-3	-0.16	-1
VP-35	110	100	79	100	86	85	-7.44	-10	-2.22	-14	0.96	6
VP-36	85	106	82	90	86	73	3.72	5	-3.16*	-20	-1.44	-9
VP-37	100	97	100	90	91	97	-7.44	-10	-0.95	-6	-0.48	-3
VP-38	90	86	107	90	100	103	0	0	2.22	-14	-0.64	-4
VP-39	100	106	110	100	103	82	0	0	-0.48	-3	-4.48*	-28
VP-40	100	94	107	100	--	103	0	0	--	--	-0.64	-4
VP-41	85	--	--	80	77	79	-3.72	-5	--	--	--	--
VP-42	95	65	97	90	83	85	-3.72	-5	2.85*	18	-1.92	-12
VP-43	115	106	97	95	106	103	-18.61*	-25	--	--	0.96	6
VP-44	70	47	55	65	--	55	-3.72	-5	--	--	0	0
VP-45	100	100	107	95	94	97	-3.72	-5	-0.95	-6	-1.60	-10
VP-46	100	89	97	100	94	91	0	0	0.79	5	-0.96	-6

VP-47	105	79	97	85	94	94	-14.89*	-20	2.37*	15	-0.48	-3
VP-48	70	71	91	85	71	--	11.17*	15	0	0	--	--
VP-49	110	94	124	100	100	--	-7.44	-10	0.95	6	--	--
VP-50	95	77	85	85	79	103	-7.44	-10	0.32	2	2.88*	18
VP-51	95	70	82	75	68	74	-14.89*	-20	-0.32	-2	-1.28	-8
VP-52	105	79	103	100	118	103	-3.72	-5	6.17*	39	0	0
VP-53	90	79	79	90	106	94	0	0	4.27*	27	2.40*	15
VP-54	90	77	100	90	97	103	0	0	3.16*	20	0.48	3
VP-55	80	86	79	95	97	88	3.72	5	1.74	11	1.44	9
VP-56	120	124	121	95	106	107	-18.61*	-25	-2.85*	-18	-2.24	-14
VP-57	100	100	91	100	100	97	0	0	0	0	0.96	6
VP-58	95	103	94	105	100	97	7.44	10	-0.48	-3	-0.48	3
VP-59	--	--	--	85	94	73	--	--	--	--	--	--
VP-60	95	83	76	95	100	79	0	0	2.69*	17	0.48	3
VP-61	90	83	85	80	68	--	-7.44	-10	-2.37*	-15	--	--
VP-62	100	106	112	90	94	91	-7.44	-10	-1.90	-12	-3.36*	-21
VP-63	95	62	--	85	71	79	-7.44	-10	1.42	9	--	--
VP-64	95	94	107	85	86	94	-7.44	-10	-1.27	-8	2.08	-13
VP-65	65	65	64	85	77	70	14.89*	20	1.90	12	0.96	6
VP-66	90	94	94	95	100	103	3.72	5	0.95	6	1.44	9
VP-67	85	109	97	90	100	91	3.72	5	-1.42	-9	-0.96	-6
VP-68	100	103	100	105	118	85	3.72	5	2.37*	15	-2.40*	-15
VP-69	95	83	91	90	83	--	-3.72	-5	0	0	--	--
VP-70	90	--	88	85	79	--	-3.72	-5	--	--	--	--
VP-71	--	103	--	90	109	55	--	--	0.95	6	--	--
VP-72	85	77	82	85	74	94	0	0	-0.48	-3	1.92	12
Mean	95.86	91.48	95.87	93.26	94.47	90.02						
SD	11.55	16.11	12.79	10.82	14.20	13.14						

Note: The Asterix indicates a change in scores of at least 1 SD.

Behavioural Outcomes Over Time (Objective 2).

There was a main effect of time for Internalizing domain scores ($F(1,82) = 8.92, p = .004, \eta^2 = .098$), with higher scores (more concerns) at 36 months than 18 months for both groups.

There was also a main effect of group ($F(1,82) = 6.98, p = .010, \eta^2 = .078$), with higher scores (more concerns) on the Internalizing domain in the VP group compared to the CHD group. There was no time by group interaction for the Internalizing model. The models were not significant for Total Problems scores or for Externalizing scores from the CBCL, with no main effects or interactions.

Behavioural reliable change trajectories. There were no mean score differences between groups for behavioural ratings. Due to limited cell counts, proportions of clinically elevated scores (scores of ≥ 60) by group on the CBCL at 36 months are qualitatively described. Both groups endorsed similar proportions of clinically elevated scores on Externalizing problems (CHD = 13%, VP = 16%), and Total Problems (CHD = 13%, VP = 19%). More parents in the VP group endorsed clinically elevated scores for Internalizing problems (17.9%) compared to parents in the CHD group (8.6%) at 36 months. There was a similar proportion of parents who had significantly more concerns (increase in scores by at least 1 SD) for Internalizing, Externalizing, and Total Problems from 18 months to 36 months in the CHD group (26%, 22%, and 13%, respectively) and in the VP group (28%, 16%, and 15%, respectively). There was also a similar proportion of parents who had significantly less concerns (decrease in scores by at least 1 SD) for Internalizing, Externalizing, and Total Problems from 18 months to 36 months in the CHD group (9%, 17%, and 9%, respectively) and in the VP group (8%, 18%, and 8%, respectively).

Of note, some participants were missing individual data points across the Bayley-III and CBCL. Specific numbers of missing data for each score by group is noted in Table 7.

Predictors of Outcomes (Objective 3).

Cognitive Composite Model. The linear regression model predicting Cognitive composite scores at 36 months, where group membership, WMI volume, language spoken in the home, and medium income were entered as independent variables, was not significant, $F(4, 95) = 1.25, p = .30$, adjusted $R^2 = .01$. English as a primary language was trending significance ($\beta = .21, p = .054$) as a predictor of 36-month Cognitive scores.

Language Composite Model. The linear regression model predicting Language composite scores at 36 months, with the same independent variable as listed above was significant, $F(4, 80) = 2.64, p = .04$, adjusted $R^2 = .08$. English as a primary language significantly predicted 36-month Language composite scores ($\beta = .27, p = .015$), but no other predictors were significant.

Motor Composite Model. The linear regression model predicting Motor composite scores at 36 months was significant, $F(4, 88) = 3.65, p = .01$, adjusted $R^2 = .11$. The coefficients, VP group membership ($\beta = -.21, p = .04$) and WMI volume ($\beta = -.31, p = .003$) were significant in predicting Motor scores at 36 months. No other predictors were significant.

Total Problems Composite Model. The linear regression model predicting Total Problem composite scores at 36 months was not significant, $F(4, 75) = 1.67, p = .17$, adjusted $R^2 = .04$. None of the independent variables were significantly related to 36-month Total Problem composite scores.

4.8 Discussion

The present study examined longitudinal neurodevelopmental trajectories in children with CHD and those born VP across cognitive, language, motor, and behavioural domains from 18 to 36 months. Consistent with prior research, both groups demonstrated neurodevelopmental vulnerabilities, though group-specific patterns emerged with several findings offering valuable clinical insight for the field of clinical neuropsychology.

Across both CHD and VP groups, Cognitive scores declined between 18 and 36 months. This finding is noteworthy given the expected trajectory of cognitive stability or improvement with age seen in typically developing infants. Although both groups declined over time, group mean scores remained within the average range. It is important to note that declines in scores do not indicate skill loss or regression in ability but rather evidence that the children are demonstrating a slower rate of developmental growth compared to what is expected in the domains assessed. This pattern of performance is not uncommon for children with CHD, where they typically perform within the average range but experience subtle declines over time (Bellinger & Newburger, 2010b; Cassidy et al., 2017). In contrast, children born VP are more consistently reported to demonstrate significant cognitive decline over time, with meta-analytic findings indicating reductions of 0.5 to 1.5 standard deviations below term-born peers by early childhood (Aarnoudse-Moens et al., 2009; Hack et al., 2005). Interestingly, our findings did not reflect this specific decline. Instead, both CHD and VP groups showed a similar and relatively modest reduction in cognitive scores, suggesting that, at least through the toddler period, early neonatal risk may not always translate to severe early cognitive impairment. Furthermore, the lack of a group-by-time interaction suggests that both CHD and VP children are vulnerable to declines in cognition in early years, potentially reflecting shared biological risks such as WMI,

delayed myelination, or disrupted connectivity, which are well-documented in both groups (Back & Miller, 2014; Claessens et al., 2017; Volpe, 2009). These results emphasize the importance of early, individualized cognitive monitoring to track emerging risks, particularly in VP children, who may diverge more sharply from developmental norms over time.

Significant group-by-time interactions were observed across language and motor performance measures, highlighting differing neurodevelopmental trajectories between CHD and VP children. Specifically, language scores in the CHD group improved significantly over time, while those for the VP group remained relatively stable. Subscale analysis revealed that this improvement was largely driven by gains in receptive language within the CHD group, while expressive language improved similarly in both groups. The language improvements in the CHD group may reflect neural recovery or plasticity, potentially influenced by early interventions or enriched language environments, which are factors known to support language development across neurodevelopmentally at-risk populations. Indeed, regression modeling identified English spoken in the home as a significant predictor of language outcomes at 36 months, underscoring the importance of environmental and cultural-linguistic factors in neurodevelopmental resilience. Conversely, VP children showed limited receptive language growth and were more likely to experience clinically meaningful decline in their language performance scores over time. Reliable change index (RCI) analyses revealed that nearly 30% of the VP group scored in the Low Average to Exceptionally Low range at 36 months, with a significant proportion showing decline over time, a pattern not observed in the CHD group. These findings align with prior studies demonstrating persistent expressive and receptive language delays in VP populations (Briscoe et al., 2001; Guarini et al., 2016), which may reflect disrupted maturation of

frontotemporal white matter tracts and impaired thalamocortical connectivity (Peyvandi et al., 2018; Volpe, 2009).

One critical factor influencing language outcomes in this study was whether English was spoken in the home. Across both cognitive and language composite models, English as the primary household language was associated with higher scores at 36 months. This reflects how all assessments used were standardized and administered in English. As such, children from non-English-speaking households may be at a disadvantage, not due to deficits in underlying cognitive or linguistic ability, but because of a mismatch between their primary language exposure and the language of test administration. This has important implications for clinical neuropsychology, where standardized testing is a central component of assessment. Clinicians must interpret scores with caution in multilingual or non-English-speaking households, as these results may underestimate true neurodevelopmental functioning, particularly in domains dependent on language comprehension (Bordes Edgar et al., 2025; Rivera Mindt et al., 2009).

In our study, motor outcomes followed an inverse pattern. The VP group showed a significant decline in motor performance, particularly in the fine motor domain, while the CHD group remained stable or showed modest improvement, especially in gross motor skills. These findings are consistent with the broader literature linking motor dysfunction in VP children to cerebellar underdevelopment and WMI in corticospinal tracts (Spittle et al., 2008; Williams et al., 2019). Although children with CHD are also at risk for motor deficits, their preserved gross motor trajectories in this sample may reflect successful surgical outcomes or earlier motor interventions. Indeed, regression analysis indicated WMI volume was a significant predictor of motor outcomes, further supporting the critical role of early brain injury in shaping neurodevelopmental trajectories in this domain.

The use of RCI analyses further highlighted clinical meaningful differences in individual neurodevelopmental trajectories between groups. Both groups showed similar patterns of change in cognitive and motor composites, suggesting that despite group-level mean differences, individual variability is high. In contrast, nearly one-third of VP children demonstrated a clinically significant decline in language scores, whereas the CHD group showed primarily gains or stability. This has important clinical implications such that early language deficits in VP children may require sustained, targeted interventions and monitoring in preschool and school-age years to prevent a cascading effect on later academic performance, social skills, and emotional development.

Behaviourally, parents of children in both groups reported increased internalizing symptoms over time. While no significant group differences emerged in mean scores for externalizing or total behaviour problems, parents of VP children more frequently endorsed clinically elevated internalizing symptoms. This finding aligns with previous research documenting elevated anxiety, withdrawal, and emotional dysregulation in VP populations (Johnson & Marlow, 2011; Treyvaud et al., 2016). Although externalizing and total problems did not differ significantly between groups, the emergence of internalizing symptoms at this young age warrants attention, as these early symptoms can be precursors to more entrenched mental health concerns in later childhood.

Interestingly, despite the structural and functional brain abnormalities that are well-documented in children with CHD, many children in the current study demonstrated improved or stable performance across neurodevelopmental domains. This may reflect the heterogeneity of cardiac diagnoses and post-surgical recovery trajectories, as well as the potential for plasticity and compensatory development in the early years. It is important to note that the majority of the

CHD sample had relatively lower-risk cardiac lesions, which may limit the generalizability of these findings to children with more complex forms of CHD. Children with CHD may still be influenced by significant medical demands, including prolonged hospital stays in cardiac intensive care units and recent or ongoing surgeries. As a result, their neurodevelopmental trajectory between 18 and 36 months may differ more significantly from children born VP, who typically experience earlier discharge and community-based care. The findings support that while at risk, children with CHD may demonstrate resilience in several areas of functioning among those with less complex cardiac lesions. This is consistent with the growing body of literature demonstrating this profile, particularly when appropriate medical, educational, and psychosocial supports are in place (Calderon & Bellinger, 2015; Wernovsky & Licht, 2016).

Taken together, this study adds to the growing evidence base informing early clinical neuropsychological care for children with complex medical histories. Furthermore, these findings reinforce the need to consider not only medical and neurological risk factors (e.g., WMI, structural brain abnormalities) but also social and environmental influences, such as language exposure and socioeconomic status, when evaluating neurodevelopmental risk and resilience. We look forward to further longitudinal follow-up at school age to determine whether early patterns persist, converge, or diverge over time. Additional neuroimaging data could enhance our understanding of the specific neural correlates underlying these trajectories. Ultimately, by examining neurodevelopmental trajectories from 18 to 36 months in these at-risk populations, the present study provides valuable insight into early markers of neurodevelopmental vulnerability and resilience and may have implications for improving early identification of at-risk children, guiding individualized intervention planning, and supporting families navigating complex medical and developmental pathways.

Chapter 5: Examining Metabolic Composition using MR Spectroscopy in Children with Congenital Heart Disease and Children born Very Preterm

5.1 Publication status and author contributions

The following chapter has been drafted in manuscript form. The contents have been reviewed by the following authors: Roberts, S.D., Sananes, R., Wojtowicz, M., Williams, T.S. & Guo, T., who also contributed to this work through the development of project ideas, data collection and management, psychometric expertise, and methodological discussions.

Samantha D. Roberts, the first author, developed the conceptual rationale for the study, organized, cleaned, analyzed, and interpreted the data. She was also the primary contributing author to the manuscript, producing the initial draft and completing all major revisions.

5.2 Abstract

Background/Aim: This exploratory study aimed to describe brain metabolite composition in congenital heart disease (CHD) and very preterm (VP) groups using MRS and examine the association between MRS and neurodevelopmental outcomes at 36 months within groups. It also examined whether MRS metabolite ratios account for unique variability in models predicting 36-month neurodevelopmental outcomes.

Methods: 89 children born VP ($n=55$) or with CHD ($n=34$) from the Study 2 sample were included. Neurodevelopment at 36-months was assessed using the Bayley Scales of Infant and Toddler Development-3rd Edition and parent ratings of child behaviour using the Child Behavior Checklist. MRS data was collected post-surgery for the CHD group and at term-equivalent for the VP group. Descriptive statistics were used to explore within group metabolite concentrations. Correlational analyses and linear regression models were used to explore the relationship between MRS and neurodevelopmental outcomes at 36 months. Linear regression models were used to explore predictors of 36-month outcomes separately by group.

Results: Metabolic profiles were described for each group. For CHD children, NAA was significantly correlated with 36-month motor scores ($p = .004$). No regression models were significant, although creatine was a predictor of language scores ($p = .05$). For VP, no regression models were significant; although lactate/choline ratio was a predictor for total problem scores ($p = .04$), and gestational age ($p = .05$ and $p = .01$) and English as primary language ($p = .05$ and $p = .04$) were significant predictors for cognitive and language scores.

Conclusions: This exploratory study offers insight into understanding the group-specific metabolic profiles among CHD and VP infants and further emphasizes the need to identify

potential biomarkers of atypical development in order to guide timely prognostication and early intervention.

Key words: MR spectroscopy, neurodevelopmental outcomes, behaviour, cardiology, preterm birth

5.3 Introduction

Magnetic Resonance Spectroscopy (MRS) is a non-invasive brain imaging technique that examines the chemical composition of brain tissue by detecting the magnetic resonance signals of various biochemical metabolites (Buonocore & Maddock, 2015a). Unlike conventional magnetic resonance imaging (MRI), which primarily provides structural information about the brain, MRS provides insight into the underlying neurochemical environment and metabolic processes within the brain. MRS measures concentrations of key metabolites in the brain such as N-acetyl aspartate (NAA), choline (Cho), lactate, creatine, inositol, and glutamate/glutamine (Govindaraju et al., 2000; Liserre et al., 2021; Zhu & Barker, 2011). Collectively, these brain metabolites are valuable for understanding brain function and signals of injury, via markers of neuronal integrity, membrane turnover, and energy metabolism (Blüml et al., 2013; Liserre et al., 2021), particularly in populations at risk for neurodevelopmental impairment. Early alterations in these metabolic processes have been linked to cognitive deficits and behavioural challenges (Blüml et al., 2013; Xu & Vigneron, 2010). Thus, MRS may allow for a deeper understanding of neurodevelopment in medical and neurological populations such as very preterm birth (VP) and congenital heart disease (CHD) leading to timely prognostication and early intervention for these at-risk children.

Advances in MRS methodology have emphasized the use of metabolite concentration ratios as robust markers for assessing brain health (Buonocore & Maddock, 2015). Ratios are preferred over absolute metabolic concentrations because they help to control for technical variability such as differences in signal intensity, scanner calibration, and remaining noise following water and lipid suppression (Buonocore & Maddock, 2015b; Novotny et al., 1998; N. Robertson & Cox, 2004). The NAA/Cho ratio and lactate/Cho ratio are commonly examined in

MRS data and serve as indicators of brain development and injury. The NAA/Cho ratio reflects neuronal health and maturation whereby a lower NAA/Cho ratio suggests delayed brain development or injury (Blüml et al., 2013; Buonocore & Maddock, 2015; Ross & Blüml, 2001). This is because NAA is predominantly localized in neurons and is an indicator of overall neuronal health, while choline reflects membrane turnover and myelination processes (Blüml et al., 2013; Buonocore & Maddock, 2015b; Govindaraju et al., 2000). On the other hand, lactate is only detectable in the brain when there is increased metabolic stress. Specifically, increased lactate production in the brain is associated with hypoxic and ischemic insults (Wu et al., 2018; Zheng & Wang, 2017); thus, an increased lactate/Cho ratio may be indicative of brain injury.

There is increasing literature documenting significant neurometabolic alterations detected using MRS in children born with CHD. This research has highlighted the impact of altered blood flow and oxygen delivery on brain metabolism that is correlated with neurodevelopmental outcomes (Limperopoulos et al., 2010; Peyvandi et al., 2019; Steger et al., 2023). Across studies of infants with CHD who were examined pre-and-postoperatively and within utero, lower NAA/Cho ratios have been documented, suggesting compromised neuronal integrity and delayed brain maturation (Li et al., 2015; Limperopoulos et al., 2010; Steger et al., 2023). In parallel, elevated lactate levels and increased lactate/Cho ratios have been observed both preoperatively and postoperatively, indicating ongoing metabolic stress in the early years of life (Andropoulos et al., 2010; Steger et al., 2023). More specifically, elevated lactate levels have been observed particularly in high-risk infant populations such as those with specific cardiac anomalies like transposition of the great arteries (TGA) and single-ventricle defects (Miller et al., 2004). Collectively, these neurometabolic changes have been associated with deficits in cognition, motor function, and executive functioning later in life (Gertsvolf et al., 2018; Mahle et al., 2002;

Steger et al., 2023). Taken together, MRS derived metabolic concentrations offer valuable early biomarkers for identifying CHD children who are at risk for adverse neurodevelopmental trajectories.

Similarly, in children born preterm, studies using MRS have also revealed disrupted neurometabolic profiles and have found an association with neurodevelopmental impairments (Augustine et al., 2008; Galinsky et al., 2022). Impairments in neuronal development and myelination due to preterm birth are associated with lower NAA/Cho ratios, particularly in regions including the periventricular white matter (Kendall et al., 2014). A recent systematic review highlighted the association between brain metabolism in infants born VP and later neurodevelopmental outcomes. Specifically, lower NAA/Cho ratios measured in white matter at the term-equivalent age were consistently associated with lower motor, cognitive and language outcomes at 18-24 months corrected age (Cebeci et al., 2022). Another study examining metabolic processes in preterm infants found that higher NAA/Cho ratios (acquired with a long echo time of 144ms) taken at term-equivalent were significantly associated with higher cognitive scores at two years of age, even after accounting for factors of gestational age, birth weight, white matter injury, and maternal education (Van Kooij et al., 2012). Lastly, MRS studies have shown that lactate can be detected in the brains of VP infants, with lactate concentrations increasing as gestational age decreases, reflecting immature cerebral metabolism and an increased reliance on anaerobic metabolism (Tomiyasu et al., 2016). The growing literature has provided evidence to suggest that metabolic maturity at term-equivalent age may serve as an early biomarker for predicting later cognitive performance in preterm infants and underscore the potential clinical utility of MRS among at-risk infants to guide timely prognostication, direction towards early intervention.

Taken together, these recent advances in understanding how early brain metabolism relates to neurodevelopmental outcomes offer compelling mechanisms to explore across preterm and CHD conditions. Prior studies have reported alterations in metabolite profiles in these groups, yet few studies have systematically examined their potential association with functional neurodevelopmental outcomes in early childhood. Furthermore, utilizing MRS metabolite ratios as predictive variables to later cognitive and behavioural outcomes remain understudied. Examining these metabolic patterns within the same cohort offers a unique opportunity to better understand condition-specific variables and profiles which may further aid in the interpretability and clinical relevance of neurochemical biomarkers. The objectives of the current exploratory study were to 1) describe brain metabolite composition in both the CHD and VP groups using MRS data, and 2) explore the association between MRS data and neurodevelopmental outcomes at 36 months within groups. It also explored whether associated MRS ratios account for unique variability in models predicting 36-month neurodevelopmental outcomes accounting for condition specific variables.

5.4 Methods

Participants. A subset of children from study 2 who had MRS data were included in the current exploratory study. Participants included 89 children diagnosed with CHD (i.e., ≥ 37 weeks gestational age; $n=34$) or born VP (i.e., ≤ 32 weeks gestational age; $n=55$) from a larger cohort followed in the Neonatal Follow-up Program at the Hospital for Sick Children in Toronto, Canada. Inclusion criteria were a diagnosis of CHD or VP birth, completion of a neurodevelopmental assessment at both 18 months and 36 months of age, a child behaviour questionnaire completed by a parent/guardian at 18 months and 36 months of age, and MR Spectroscopy imaging data (post-operative for CHD and term equivalent for VP). 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 or those born VP (e.g., congenital infection, intraventricular hemorrhage level 3 or 4, periventricular leukomalacia, neonatal stroke [severe $\geq 2/3$], and/or hypoxic-ischemic encephalopathy). See Table 8 for participant demographics.

Participant Demographic Information. Birth history was collected from the child's medical chart (i.e., gestational age, biological sex, and birth weight), and sociodemographic factors from parent study questionnaires (i.e., primary language spoken in the home and maternal age at birth). Consistent with previous chapters, a medical interpreter was provided for families completing the study measures when English was not their primary language. Neighbourhood median income was also collected and calculated for the current pilot study sample using the same methods described in Studies 1 and 2 (i.e., postal code data conversion with Statistics Canada Census data). See Studies 1 and 2 for a detailed description of how this was derived.

Table 8. Participant Demographics for Study 3

	Term CHD (n=34)	Very Preterm (n=55)	<i>p (d or V)</i>
Gestational Age at Birth - <i>weeks M(SD)</i>	38.82w (1.20)	27.18w (2.28)	<.001 (6.00)
<i>range</i>	37.29w – 41.57w	24.00w – 31.57w	
Sex assigned at birth - <i>males</i>	26 (76%)	31 (56%)	.07 (.055)
Birth Weight (g) <i>M(SD)</i>	3277.23g (374.49g)	972.7g (319.08g)	<.001 (6.75)
White Matter Injury Volume	55.21mm ³ (115.16mm ³)	13.75mm ³ (38.87mm ³)	.02 (.537)
Seizure	1 (3%)	0 (0%)	.38 (.201)
Maternal Age at Birth* - <i>years</i>	33y 2m (5y 3m)	33y 10m (4y 11m)	.54 (.146)
<i>range</i>	18 – 40 years	22 – 49 years	
English Primary Language - <i>yes</i>	27 (79%)	44(80%)	.78 (.672)
Estimated Median Income Level			1.00 (.896)
<i>Lower income level (<\$41, 873)</i>	26 (76%)	36 (66%)	
<i>Higher income level (≥ \$41,873)</i>	7 (21%)	9 (16%)	
Age at MRI	42w 5d (2w 8d)	41w 11d (2w 23d)	.20 (.320)
CHD Diagnostic Categories			
<i>Two Ventricles with no arch obstruction</i>	20 (59%)	--	--
<i>Two Ventricles with arch obstruction</i>	2 (6%)	--	--
<i>Single Ventricle with no arch obstruction</i>	10 (29%)	--	--
<i>Single Ventricle with arch obstruction</i>	2 (6%)	--	--

5.5 Measures

MR Spectroscopy. The post-operative and term equivalent brain magnetic resonance imaging (MRI) scans were conducted to evaluate the brain injury and maturation of participating infants on a clinical 1.5T and 3T Siemens Avanto System (Erlangen, Germany) at SickKids using a long echo time of 144ms. MR Spectroscopy was conducted using a single voxel of 20 x 20 x 20 mm³ at the left lentiform region with and without water suppression. The voxel was carefully placed to the target area to avoid inclusion of cerebrospinal fluid and white matter tracts. All MRS spectra included in our analysis were quality controlled by an MR physicist (Z.S.).

High quality spectra were processed using Tarquin (version 4.3.10). Absolute in vivo concentrations of Insulin, choline, N-Acetyl-Aspartate (NAA), Lactate, Creatine and Glutamate-Glutamine were measured. The ratios of NAA and lactate to choline peak were quantified. See Figure 6 for region of interest for the MR Spectroscopy data.



Figure 6. Region of Interest (left lentiform region) for MR Spectroscopy for Study 3

White Matter Injury. For the purposes of this exploratory study, images obtained post-surgery were used for the CHD group and term equivalent images were used for the VP group. WMI was characterized as areas of T1 hyperintensity using 3D T1-weighted image and WMI volume was calculated based on the manual segmentation of all WMI 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., (Guo et al., 2017, 2020). Of note, this was an absolute WMI volume that did not account for intercranial size.

Bayley Scales of Infant and Toddler Development. Neurodevelopment was assessed using the Bayley Scales of Infant and Toddler Development, *Third Edition* (BSID-III; Bayley, 2006). 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 measure was administered at 18 months of age and again at 36 months of age. Of note, the VP group was corrected for age at the 18-month assessment only, with chronological age used at the 36-month assessment, as per standard correcting guidelines (American Academy of Pediatrics., 2018; Harel-Gadassi et al., 2018).

Behavioural Outcomes. Parent ratings of child behaviour concerns were examined using the Child Behavior Checklist for Ages 1.5-5 (CBCL; Achenbach, 1991). Parents of children in both groups completed the measure at their child's 18-month assessment and again at their 36-month assessment. For the purposes of this study, the Total Problems domain score was used to capture broad behavioural outcomes, based on the theoretical foundation and the minimal variability in behavioural outcomes observed in preceding chapters.

Participant demographic and medical information, Bayley-III, and CBCL 1.5-5 measures are described in brief in this chapter given that these measures carried over with each chapter. See detailed description of measures in studies 1 and 2.

5.6 Statistical Analysis

All data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 29 (IBM corp. Released, 2023). For all analyses, two-tailed alpha values of less than .05 were considered statistically significant. Given that some participants were lost from Study 2 to the current study due to some children not having MRS data, inferential statistics were conducted to ensure group comparability.

Objective 1. Descriptive statistics were computed for metabolites (i.e., Inositol, Lactate, NAA, Choline, Creatine, Glutamate/Glutamine, as well as NAA/Choline and Lactate/Choline concentration ratios) within the CHD and VP groups.

Objective 2. Correlational analyses and linear regression models were used to explore the relationship between the brain metabolic concentrations and ratios (NAA/Cho and lactate/Cho) with neurodevelopmental outcomes at 36 months only (i.e., Cognition, Language, Motor, and Total Problems) within each group.

Objective 3. Linear regression models were used to explore whether concentration ratios (NAA/Cho and lactate/Cho) added to the models predicting 36-month outcomes within groups accounting for condition specific variables. Four separate models were used to assess dependent variables: Cognition, Language, and Motor composite scores from the Bayley-III and Total Problems composite score from the CBCL 1.5-5. For the CHD models, predictors included NAA/Cho ratio, lactate/Cho ratio, cardiac lesion category, age at MRI, biological sex at birth, WMI volume, median household income, and English as primary language. For the VP group, predictors included NAA/Cho ratio, lactate/Cho ratio, age at MRI, gestational age, biological sex at birth, WMI volume, median household income, and English as primary language. A priori power analysis revealed that the current sample size was insufficient to conduct the linear regression models with 8 predictors based on a power of at least 80% with a medium effect size, and an alpha value of .05 (Soper, 2024b).

5.7 Results

To ensure comparability to participants in study 2, all demographic variables and outcome variables were compared, with no statistical difference noted between the two samples apart from white matter injury (WMI) volume. In the current sample, the CHD group had higher

total WMI volume ($p = .02$, $d = .537$) than the CHD sample in study 2. The Cognition, Language, Motor, and Total Problem composite scores were not significantly different from the sample in Chapter 2. See Table 9 for a summary of outcome variables and a comparison between groups for the current study sample.

Table 9. Neuropsychological Outcomes at 36 months for Study 3			
	CHD (n = 34)	Very Preterm (n = 55)	$p(d)$
<i>Bayley</i>			
Cognition Composite	95.47 (6.88)	92.64 (10.40)	.17 (.305)
Language Composite	100.67 (8.58)	93.92 (13.32)	.02 (.567)
Motor Composite	94.03 (12.17)	90.12 (12.16)	.17 (.322)
<i>CBCL 1.5-5</i>			
Total Problem Composite	44.53 (8.63)	47.71 (9.13)	.12 (.356)

Metabolic Composition within Groups (Objective 1).

Metabolic compositions observed across both groups demonstrated measurable concentrations of key metabolites. Notably, lactate was present at detectable levels across the CHD and VP groups. NAA/Choline concentration ratio and lactate/Cho concentration ratio were both quantified and reported. These reflect the relative presence of neuronal markers, membrane turnover, and energy metabolism intermediates. A summary of the mean and standard deviations of metabolite concentrations by group are presented below in Table 10. No direct comparisons between the CHD and VP group could be made for metabolic concentrations due to parameter and acquisition differences described above.

Table 10. *Mean and Standard Deviation of Concentration Levels for Study 3*

	CHD PostOp (n = 34)	VP Term Equiv (n = 55)
Inositol	13.86 (4.04)	6.59 (2.24)
Lactate	.823 (.36)	.448 (.26)
NAA	5.49 (1.52)	4.16 (1.34)
Choline	2.85 (.60)	2.36 (.57)
Creatine	5.11 (1.27)	4.88 (1.39)
Glutamate/Glutamine	4.54 (1.50)	2.93 (1.59)
NAA & Choline Concentration Ratio	1.94 (.35)	1.765 (.37)
Lactate & Choline Concentration Ratio	.292 (.12)	.204 (.11)

Note: group comparisons could not be conducted due to acquisition differences described.

Associations between MRS and Neurodevelopmental Outcome (Objective 2).

CHD Group. Metabolic concentration and ratio variables were not significantly correlated with Cognition, Language, or CBCL Total Problem composite scores. NAA was significantly correlated with the Motor Composite score ($p = .004$; see Table 11). None of the linear regression models were statistically significant (i.e., Cognition, Language, Motor, Total Problems), with no coefficients identified as significant in the Cognition, Motor, or Total Problem models. Although the overall regression model for Language did not reach statistical significance, one predictor, creatine, was significantly associated with Language outcomes ($\beta = -1.00$; $p = .03$). This finding should be interpreted with caution given the nonsignificant overall model. See Table 11 for correlation matrix of metabolites and outcome variables for the CHD group, and Table 12 for the regression model for Language composite.

Table 11. *Correlations between metabolites and neurodevelopmental outcome variables for CHD group in Study 3*

Variables	1	2	3	4	5	6	7	8
1. Inositol	-							
2. Lactate	.11	-						
3. NAA	.63 ^a	.15	-					
4. Choline	.73 ^a	.33	.80 ^a	-				
5. Creatine	.55 ^a	.35 ^b	.85 ^a	.75 ^a	-			
6. Glutamate/Glutamine	.49 ^a	.28	.70 ^a	.59 ^a	.73 ^a	-		
7. NAA/Cho Ratio	-.08	-.26	.40 ^b	-.21	.21	.21	-	
8. Lactate/Cho Ratio	-.27	.87 ^a	-.23	-.16	.002	-.01	-.14	-
9. Cognition	-.01	.13	-.09	-.12	.03	.04	.09	.23
10. Language	.06	.13	-.01	.14	-.12	.19	-.23	.08
11. Motor	-.15	.05	-.38 ^b	-.29	-.26	-.15	-.20	.21
12. Total Problem	-.02	-.26	-.07	-.19	-.01	.07	.22	-.16

Note: ^a denotes p -value <.001 and ^b denotes p -value <.05

Table 12. *Regression model for Language Composite Scores for CHD group in Study 3*

	<i>B</i>	SE <i>B</i>	β	<i>p</i>
<i>Constant</i>	66.73	47.74		.18
Inositol	-.14	.59	-.07	.81
Lactate	-61.97	38.80	-2.32	.13
NAA	3.03	7.00	.58	.67
Choline	18.72	17.14	1.43	.29
Creatine	-6.17	2.58	-1.00	.03^b
Glutamate/Glutamine	3.10	1.65	.56	.08
NAA/Cho Ratio	-10.56	17.30	-.45	.55
Lactate/Cho Ratio	188.93	113.40	2.25	.11

Note: Model $R^2 = .39$; $p = .24$; ^a denotes p -value <.001 and ^b denotes p -value <.05

VP Group. Metabolic concentration or ratio variables were not associated with Cognition, Language, Motor, or Total Problem composite scores (See Table 13). No linear regression models were significant, with no coefficients identified in three of the models (i.e., Cognition, Language, or Motor). Despite the overall regression model for Total Problems not reaching statistical significance, lactate/choline concentration ratio was significantly associated with Total Problem outcomes ($\beta = 1.43$; $p = .04$). This finding should also be interpreted with caution given the nonsignificant overall model. See Table 13 for correlation matrix of metabolites and outcome variables for the VP group, and Table 14 for the regression model for Total Problem score.

Table 13. *Correlation between Metabolites and Neurodevelopmental Outcomes for VP Group in Study 3*

Variables	1	2	3	4	5	6	7	8
1. Inositol	-							
2. Lactate	.16	-						
3. NAA	.50 ^a	.21	-					
4. Choline	.51 ^a	.20	.75 ^a	-				
5. Creatine	.47 ^a	.24	.85 ^a	.73 ^a	-			
6. Glutamate/Glutamine	.39 ^a	.42 ^a	.58 ^a	.50 ^a	.68 ^a	-		
7. NAA/Cho ratio	.12	.11	.62 ^a	-.03	.43 ^a	.29	-	
8. Lactate/Cho ratio	-.12	.87 ^a	-.12	-.25	-.10	.15	.14	-
9. Cognition	.03	-.09	.01	-.17	.01	.11	.16	-.07
10. Language	-.02	-.13	.03	-.04	-.002	.09	.07	-.10
11. Motor	.04	-.11	.01	-.25	-.03	.27	.27	.10
12. Total Problem	.15	.21	-.09	.11	-.001	-.09	-.24	.22

Note: ^a denotes p -value $<.001$ and ^b denotes p -value $<.05$

Table 14. *Regression model for Total Problems for VP Group in Study 3*

	<i>B</i>	SE <i>B</i>	β	<i>p</i>
<i>Constant</i>	23.47	30.17		.44
Inositol	.96	.89	.21	.29
Lactate	-43.28	24.24	-1.12	.08
NAA	-1.48	7.36	-.22	.84
Choline	13.46	13.31	.81	.32
Creatine	-1.86	2.35	-.27	.43
Glutamate/Glutamine	3.26	1.75	.39	.07
NAA/Cho Ratio	-5.81	15.80	-.25	.72
Lactate/Cho Ratio	121.52	56.60	1.43	.04^b

Note: Model $R^2 = .29$; $p = .12$; ^a denotes p -value $< .001$ and ^b denotes p -value $< .05$

MRS Concentration Ratios Predicting to 36-month Outcomes by Groups (Objective 3).

MRS Predicting to Outcomes in the CHD Group. The overall linear regression models predicting *Cognitive* composite scores and CBCL *Total Problem* composite scores at 36 months were not significant, $F(8,31) = .804$, $p = .61$, adjusted $R^2 = -.05$ and $F(8,16) = .60$, $p = .76$, adjusted $R^2 = -.25$, respectively. No coefficients significantly predicted to 36-month scores in either model, or when entered individually. Similarly, the overall linear regression model predicting *Language* composite scores at 36 months was also not significant, $F(8,26) = .68$, $p = .71$, adjusted $R^2 = -.11$; and no coefficients significantly predicted to 36-month scores. When entered individually, cardiac classification was trending significance ($\beta = -.33$, $p = .097$) as a predictor of *Language* composite scores. A follow up post hoc analysis using a non-parametric

Kruskal-Wallis test was not statistically significant ($p = .15$); however, those with more severe cardiac lesions (i.e., in the single ventricle groups) had lower language scores (see Figure 7).

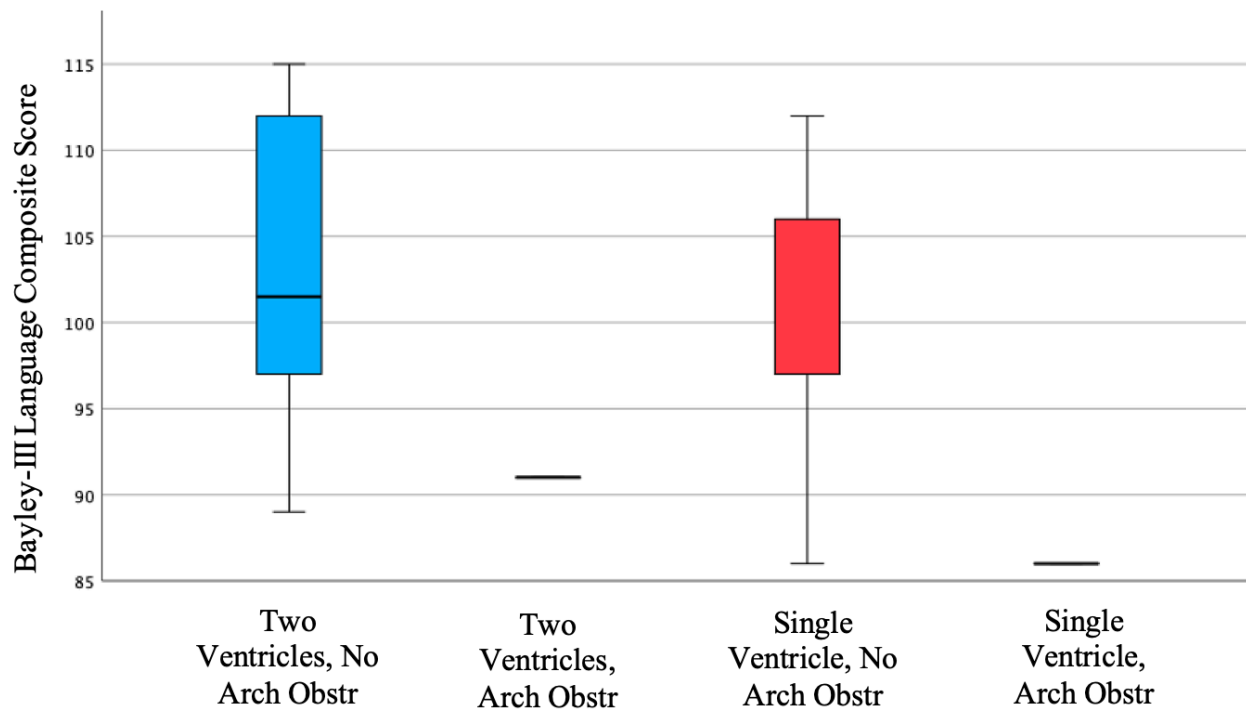


Figure 7. Post-hoc non-parametric analysis of Language scores by Cardiac anatomy classification for Study 3

The overall linear regression model predicting *Motor* composite scores at 36 months was not significant, although was trending significance, $F(8,29) = 2.15$, $p = .08$, adjusted $R^2 = .24$. Cardiac classification significantly predicted to scores at 36 months ($\beta = -.56$, $p = .01$), and median household income was trending significance ($\beta = .37$, $p = .06$). When entered individually, only cardiac classification was significant at predicting to 36-month scores, $F(1,29) = 9.06$, $p = .005$, adjusted $R^2 = .217$. A follow up post hoc analysis using a non-parametric

Kruskal-Wallis test was not statistically significant ($p = .08$); however, those with more severe cardiac lesions (i.e., in the single ventricle groups) were observed to have lower scores (see Figure 8).

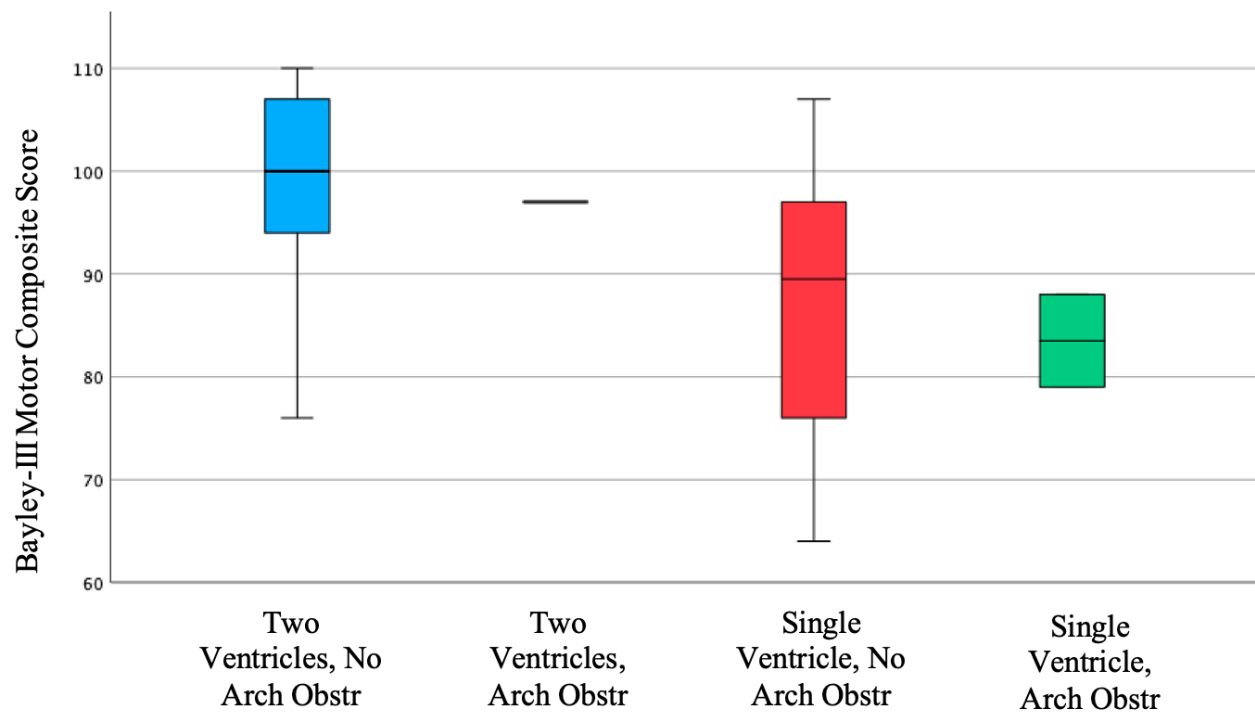


Figure 8. Post hoc analysis of Motor scores by Cardiac anatomy classification for Study 3

MRS Predicting to Outcomes in the VP Group. The overall linear regression models predicting Cognitive ($F(7, 39) = .50, p = .83$, adjusted $R^2 = -.10$), Language ($F(7, 35) = 1.04, p = .43$, adjusted $R^2 = .01$), and Motor ($F(7, 35) = .71, p = .66$, adjusted $R^2 = -.06$) composite scores were not significant. There were no coefficients that significantly predicted to 36-month scores in these models. When run individually, English as a primary language ($F(1,52) = 4.48, p = .04$, adjusted $R^2 = .06$) and gestational age ($F(1,54) = 5.76, p = .02$, adjusted $R^2 = .10$) were significant predictors of *Cognitive* scores. English as a primary language ($F(1,49) = 4.06, p = .05$,

adjusted $R^2 = .08$) was a significant predictor of *Language* scores. Additionally, NAA/Cho ratio ($F(1,49) = 3.63, p = .06$, adjusted $R^2 = .05$) and gestational age ($F(1,49) = 3.94, p = .053$, adjusted $R^2 = .08$) were trending significance for predicting to *Motor* scores.

The overall linear regression model predicting Total Problem composite scores at 36 months was not significant, $F(7, 38) = 1.20, p = .33$, adjusted $R^2 = .04$. However, the lactate/Cho ratio was a significant coefficient predicting to 36-month Total Problem scores in the model ($\beta = .35, p = .05$). When ran individually, English as primary language ($F(1,50) = 4.32, p = .04$, adjusted $R^2 = .06$), median household income ($F(1,43) = 4.98, p = .03$, adjusted $R^2 = .09$), and gestational age ($F(1,51) = 7.74, p = .01$, adjusted $R^2 = .12$) were predictors of Total Problem composite scores, and the NAA/Cho ratio was trending significance ($F(1,51) = 2.96, p = .09$, adjusted $R^2 = .04$).

5.8 Discussion

This exploratory study examined neurometabolic profiles and their associations with neurodevelopmental outcomes in children with CHD and children born VP using MRS. Our findings described the composition of metabolites within CHD and VP groups separately. Direct comparisons between VP and CHD groups were not feasible due to inherent anatomical and developmental differences, including smaller brain volumes, altered growth trajectories, and differing proportions of white and grey matter in VP infants, which affect voxel placement, partial volume effects, and metabolite interpretation in MRS. Additional variability was introduced by differences in scanner hardware, scanning age, and age-dependent metabolic changes, making it difficult to ensure that the same brain regions and maturational stages were being assessed across groups. Nevertheless, understanding the metabolic composition of these

groups independently was helpful to offer insight into group-specific neurometabolic profiles and help identify potential biomarkers of atypical development.

Across CHD and VP groups, associations between metabolic profiles and neurodevelopmental outcomes were limited. In the CHD group, NAA levels were significantly correlated with motor outcomes. This finding aligns with literature linking NAA to neuronal integrity and sensorimotor development (Xu & Vigneron, 2010). However, no other significant associations were observed between metabolites and cognitive, language, or behavioural outcomes. None of the regression models reached significance for predicting neurodevelopmental outcomes at 36 months, although cardiac classification emerged as a consistent predictor, particularly for motor outcomes. The trend toward poorer outcomes in children with more severe lesions (e.g., single ventricle physiology), while not statistically significant in post hoc analyses, is clinically meaningful and echoes prior findings of lesion severity as a risk factor for adverse neurodevelopment including cerebral palsy (Limperopoulos et al., 2001; Marino et al., 2012).

In the VP group, metabolic variables were similarly not associated with neurodevelopmental outcomes overall. However, predictors such as gestational age and English as the primary language emerged as important contributors to cognitive and language scores at 36 months. These findings emphasize the influence of perinatal and sociodemographic factors on early neurodevelopment, particularly in VP populations (Benavente-Fernandez et al., 2019; Treyvaud et al., 2009). A noteworthy finding in the VP group was the significant association between the lactate/Cho ratio and total problem scores in the behavioural domain. While lactate is generally considered a marker of anaerobic metabolism and neural stress, prior studies have linked elevated lactate/Cho ratios in VP infants to WMI and poorer outcomes (Cebeci et al.,

2022; Robertson et al., 2000). The current results suggest that even in the absence of overt injury, subtle metabolic disruptions may relate to later behavioural challenges.

It is important to interpret findings that trend towards statistical significance with caution, recognizing that such results may reflect underlying associations but could also arise from sample variability or limited power. Across both groups, several regression models revealed predictors that trended toward significance (e.g., NAA/Cho ratio and gestational age for motor outcomes in VP; creatine and cardiac classification for language outcomes in CHD). While these findings did not consistently reach statistical thresholds, they offer promising directions for future research. The lack of significant associations may reflect limitations in statistical power or the complex, multifactorial nature of neurodevelopment, which is shaped not only by early brain metabolism but also by environmental, genetic, and clinical factors.

Several limitations should be acknowledged when interpreting the findings of this study. First, the relatively small sample size limited the statistical power to detect significant effects, particularly in subgroup analyses and multivariable models. As a result, some potentially meaningful associations may have gone undetected, and findings that approached significance should be interpreted with caution. Second, direct comparisons of metabolic profiles and clinical characteristics were unable to be performed between the CHD and VP groups due to scanning hardware, scanning age, and age-dependent brain characteristics. Third, the study was underpowered to explore more complex interactions in depth (e.g., between neurometabolites and sociodemographic or clinical variables). Larger, adequately powered cohorts will be necessary to validate and extend the preliminary findings of this exploratory study. Lastly, while MRS provides valuable insights into brain metabolisms, it offers only a snapshot in time. Longitudinal MRS data, combined with broader neuroimaging and behavioural

assessments, would provide a more comprehensive understanding of how early brain chemistry relates to later neurodevelopmental outcomes.

Overall, this exploratory study adds to a growing body of evidence suggesting that in high-risk populations early metabolic presentations and their relationship with long-term neurodevelopment are not always straightforward. Longitudinal studies with larger samples and multimodal approaches are needed to better understand the role of neurometabolism in neurodevelopmental trajectories.

Chapter 6: Discussion

6.1 Overview of Studies

The present dissertation comprised three complementary studies aimed at advancing understanding of early neurodevelopmental outcomes among children born with CHD and those born VP. The first study investigated early neurodevelopmental and behavioural outcomes at 18 months of age, comparing children with CHD to those born VP, while examining the influence of sociodemographic factors and WMI characteristics. Building upon these findings, the second study employed a longitudinal design to examine changes in neurodevelopmental and behavioural trajectories from 18 to 36 months of age. It compared outcomes between groups at 36 months of age, evaluated patterns of clinical change over time, and assessed associations with sociodemographic variables and WMI. Extending this work to explore novel neurobiological correlates, the third study utilized MRS to characterize brain metabolite composition within the CHD and VP groups independently and evaluated associations between metabolic profiles and neurodevelopmental outcomes at 36 months. Further, the exploratory study examined whether MRS biomarkers accounted for unique variance in predicting 36-month outcomes beyond condition-specific factors within groups.

Collectively, these studies provide a comprehensive, multimodal examination of neurodevelopmental outcomes and resilience in early childhood across two high-risk clinical populations, offering important insights into the interplay between both environmental and neurobiological contributions to neurodevelopmental trajectories.

6.2 Summary of Studies Results

The results of the first study demonstrated that while global cognitive, language, and motor outcomes at 18 months of age were largely comparable between the CHD and VP groups,

specific vulnerabilities emerged. Children with CHD exhibited significantly lower gross motor scores and a higher proportion of expressive language impairments compared to children born VP. Sociodemographic variables, including English as a primary language and median household income, were significant predictors of stronger cognitive and language scores, as well as fewer behavioural concerns. While no group differences were found in parent-rated behaviour, internalizing symptoms were elevated across both groups at 18 months. These findings emphasize the importance of considering biological, medical, and sociodemographic variables when evaluating early neurodevelopmental risk.

In the second study, cognitive scores declined from 18 to 36 months in both CHD and VP groups, indicating emerging challenges in cognitive development during early childhood. Language outcomes differed by group, such that children with CHD exhibited improvements in scores but the VP group remained largely stable, with the exception of expressive language where both groups improved over time. Motor outcomes revealed a contrasting pattern. Motor scores declined over time in the VP group but remained stable or improved in the CHD group. Internalizing symptoms increased over time in both groups, with higher levels reported by parents of children born VP at 36 months compared to the CHD group. Reliable change analyses revealed declines in language scores for the VP group over time whereas the CHD improved over time, and there were more children falling below the Average range at 36 months in the VP group compared to the CHD group. Sociodemographic and medical variables (i.e., English as a primary language, VP group membership, and WMI volume) continued to demonstrate strong associations with neurodevelopmental outcomes at 36 months.

The third exploratory study showed that although overall regression models were not statistically significant, several individual predictors emerged within groups. In the CHD group,

lower creatine concentrations were associated with higher language scores, while in the VP group higher lactate/choline concentration ratios were associated with more parent reported total problem scores. Sociodemographic and medical variables demonstrated meaningful associations. More severe cardiac lesions were associated with lower motor scores in the CHD group. In the VP group, English as a primary language, older gestational age, higher median household income, and lower lactate/cho concentration ratios were associated with better cognitive, language and behavioural outcomes. The exploratory findings suggest that while individual metabolite concentrations had isolated associations with neurodevelopmental outcomes, metabolic profiles alone were not strong predictors of 36 month outcomes in either group.

Collectively, the findings across these three studies underscore the complexity of neurodevelopmental trajectories in high-risk pediatric populations. Although biological factors such as WMI and metabolite profiles contribute to outcomes, sociodemographic influences consistently demonstrated robust associations with cognitive, language, motor, and behavioural outcomes.

6.3 General Discussion

Neurodevelopmental outcomes in children with complex medical histories, including CHD and VP cohorts, are important to investigate due to the high rates of cognitive, language, motor, and behavioural challenges and associated follow-up needs (Anderson, 2014; Cassidy et al., 2018; Howell et al., 2019; Marlow, 2004; Mills et al., 2018). While these populations are often studied in isolation, a broader comparative approach can offer important insights both into shared vulnerabilities and distinct neurodevelopmental trajectories. Across the three studies presented in this dissertation, common and unique patterns emerged, deepening our understanding of early risk and resilience among these high-risk pediatric populations.

Furthermore, it provides important insights into the complex interplay between biological risk factors, brain health, and social determinants of health in shaping early neurodevelopmental trajectories.

Shared Early Neurodevelopmental Risk and the Role of Social Determinants.

Findings from the first study identified broadly similar patterns of early cognitive and behavioural difficulties across children with CHD and children born VP at 18 months of age, with both groups demonstrating elevated risk for neurodevelopmental concerns. While children with CHD had greater impairment in expressive language and motor skills, overall cognitive and behavioural outcomes were more alike than different. These similarities may reflect shared disruptions in early neurodevelopmental processes that are impacted by early brain changes, including WMI, delayed myelination, and disrupted neural connectivity (Guo et al., 2019; Volpe, 2000, 2009). Notably, our study highlighted that neurobiological vulnerability alone did not fully explain outcomes at 18 months of age. Sociodemographic factors, especially median household income and language spoken in the home, were significantly associated with neurodevelopmental performance across all children. This underscores the influence of social determinants of health within these high-risk populations (Benavente-Fernandez et al., 2019; Cassidy et al., 2024; Jackson et al., 2023; McQuillen et al., 2007) and aligns with the robust literature supporting the strong association between sociodemographic variables (e.g., parental education, income, stress) and neurodevelopmental performance in both children with CHD and children born VP. Therefore, it is important that interventions aimed at mitigating neurodevelopmental risk in these populations consider both biological and social contexts to be effective (Anderson & Doyle, 2003; Lin et al., 2024; Watson, 2010).

Neurodevelopmental Trajectories Between 18 and 36 Months: Divergence and Plasticity. The longitudinal findings from study 2 highlighted key differences in neurodevelopmental trajectories between children with CHD and children born VP across language and motor domains. Specifically, children in the CHD group exhibited notable gains in language abilities over time, whereas children in the VP group demonstrated relatively stable trajectories. Conversely, children born VP experienced significant declines in motor achievement scores over time, while age adjusted motor performance in the CHD group remained relatively stable. It is important to note that these children did not lose skills or functioning, but rather did not make the age expected gains overtime thus leading to a decline in their achievement scores. These findings may be understood in light of the unique neurophysiological and medical characteristics of each group. The observed improvement in language abilities over time among children with CHD may reflect the potential for neural recovery and plasticity following surgical stabilization and improved systemic perfusion. Although CHD is associated with early cerebral dysmaturation (Claessens et al., 2017; Peyvandi et al., 2018), many children experience improved cerebral oxygen delivery and growth following timely surgical repair and medical stabilization (Bontrone et al., 2021). These interventions may create a more supportive postnatal environment for neural development, allowing for recovery of language-related networks, particularly those involving the opercular and perisylvian regions that are frequently underdeveloped prenatally in children with CHD (Licht et al., 2009; von Rhein et al., 2015). The more pronounced motor score declines in children born VP may reflect the persistent effects of premature extrauterine transition (Back & Miller, 2014; Kostović & Judaš, 2010) and ongoing risk of stressors in early life within the NICU that can disrupt brain development in the thalamocortical and cerebellar circuits implicated in later age motor control and language

integration acquisition (Spittle et al., 2008; Volpe, 2009), which may contribute to long-term impairments (Glass et al., 2015; Williams et al., 2019). These findings reflect the differential timing and mechanisms of neurologic insult, such that preterm birth truncates in utero brain development during its most active phase when motor networks are still under active construction (Peyvandi et al., 2018; Tam, Chau, et al., 2011), while CHD primarily disrupts prenatal perfusion but may allow for catch-up if surgically corrected. Together, this difference may partially explain the relative preservation of motor function in children with CHD compared to the declined scores observed in children born VP.

Despite the typical trajectory of cognitive abilities increasing with age in healthy peers, cognitive scores declined significantly over time in both groups, suggesting emerging cognitive deficits in early childhood and increased challenges acquiring new skills and related comprehension. While the decline was modest and mean scores remained within the average range, the findings align with prior work demonstrating subtle cognitive vulnerabilities in children with CHD (Bellinger & Newburger, 2010) but appear more modest in declines than previous literature highlighted for children born VP (Brydges et al., 2018; Stålnacke et al., 2019). Additionally, behavioural concerns increased over time, with both groups showing increased internalizing problems by 36 months, with parents of VP children reporting highest rates of concern. These behavioural findings are consistent with literature indicating heightened vulnerability to emotional dysregulation and internalizing symptoms in both children with CHD and those born VP, stemming from early disruptions in brain development and connectivity in limbic and prefrontal networks (Claessens et al., 2017; Johnson & Marlow, 2011; von Rhein et al., 2015). In children born VP, altered stress regulation and brain connectivity due to medical and environmental exposures in the NICU (Back & Miller, 2014; Treyvaud et al., 2016) may

reduce resilience to emotional stressors later in life. Similarly, in CHD, impaired perfusion and delayed maturation of prefrontal and subcortical structures have been linked to socio-emotional and behavioural vulnerabilities, particularly in those with more complex cardiac anatomy or surgical histories (Mebius et al., 2017b; Schaefer et al., 2013b). These findings highlight the importance of early and ongoing monitoring of both cognitive and socio-emotional development in medically vulnerable populations where symptoms may emerge subtly and intensify with age-related increases in environmental and cognitive demands.

Influence of Language Environment and Limitations of Monolingual Assessment. A consistent theme across studies was the impact of home language environment on neurodevelopmental outcomes. English as the primary language in the home was associated with performance for both cognitive and language outcomes. This finding aligns with previous research showing that children born VP from non-English-speaking households tend to have lower language scores than peers from English-speaking homes, even when cognitive abilities are comparable (Lowe et al., 2013). While this finding contributes to our understanding of the neurodevelopmental profile of these populations, it is interpreted while acknowledging that it may reflect the language of test administration rather than true ability alone. Echoing previous sections within this dissertation, this raises important concerns about the use of monolingual English-based tools in linguistically diverse populations.

Previous research has demonstrated that children from non-English speaking households often score lower on standardized assessments, even when underlying cognitive and language abilities are intact (Bordes Edgar et al., 2025; Guarini et al., 2016; Lowe et al., 2013; Rivera Mindt et al., 2009, 2010). Current neurodevelopmental assessments very likely underestimate abilities in multilingual children, potentially contributing to over-identification of impairment

(Brydges et al., 2018; Rivera Mindt et al., 2009, 2010). These results underscore the need for culturally and linguistically sensitive assessment practices and tools in both research and clinical care, particularly in high-risk pediatric populations.

Neurometabolic Correlates of Outcome: Limited but Promising Starting Point. In the third exploratory study, the exploration of neurometabolic profiles using MRS offered preliminary insight into potential biochemical markers of neurodevelopmental outcome. While direct group comparisons were not possible due to methodological limitations, within-group analyses revealed that in children with CHD, high NAA levels were positively correlated with motor outcomes, consistent with the literature linking NAA to neuronal integrity and motor function (Xu & Vigneron, 2010). In children born VP, elevated lactate/Cho ratios in children born VP were linked to higher behaviour problem scores, consistent with previous findings associating elevated lactate with WMI and adverse neurodevelopmental outcomes (Cebeci et al., 2022; Robertson et al., 2000). Despite these isolated findings, the overall regression models predicting neurodevelopmental outcomes from metabolite concentrations were not statistically significant in either group. Although most associations did not reach statistical significance, these trends provide a valuable foundation for future research and suggest that early neurometabolic changes may hold clinical relevance, potentially when paired with structural and functional imaging (Xu & Vigneron, 2010).

Across all three studies, a consistent theme emerged: neurodevelopmental outcomes in children with CHD and children born VP are shaped by a complex and multifactorial interaction between biological risk factors and sociodemographic influences. These results highlight the critical importance of integrating social, environmental, and biological perspectives in both

research and clinical care to better understand and support the neurodevelopmental needs of these high-risk pediatric populations.

6.4 Clinical Implications

The findings across the three complimentary studies have important clinical implications for the neurodevelopmental care and long-term monitoring of children with CHD and children born VP. The results highlight the importance of early, longitudinal neurodevelopmental surveillance for both CHD and VP populations. Both groups demonstrated vulnerabilities in cognitive, language, motor, and behavioural domains, with cognitive scores declining modestly over time and significant changes observed in motor and language abilities between 18 and 36 months. Consistent with prior work (Aarnoudse-Moens et al., 2009; Bellinger & Newburger, 2010; Spittle et al., 2008), early difficulties may not be immediately apparent during infancy but can emerge and consolidate over the toddler and preschool years. These findings reinforce existing guidelines recommending that high-risk infants should receive neurodevelopmental follow-up extending beyond infancy through early childhood and beyond (Aylward, 2014; Marino et al., 2012a).

There are clinical implications for transdiagnostic and equitable care. The findings from these studies support growing calls for transdiagnostic, family-centered approaches to early intervention, especially as children with CHD and children born VP may benefit from similar types of services despite differing medical etiologies (Astle et al., 2021; Cassidy et al., 2021; Sood et al., 2021). For example, evidence-based transdiagnostic parent-focused telehealth interventions have shown promise in improving outcomes across a variety of pediatric neurological populations (Burek et al., 2021; Deotto et al., 2023; Williams et al., 2022). Furthermore, family-centered approaches that improve parent well-being have shown promise in

strengthening long term neurodevelopmental outcomes through early and sustained caregiver engagement (Kasparian et al., 2019; Sood et al., 2021). Given the shared behavioural and cognitive challenges observed in our sample, such approaches may represent a cost-effective and scalable method of reducing service gaps, especially for families in rural or underserved communities.

The findings from longitudinal study 2 within this dissertation, coupled with the known vulnerabilities in the motor pathways and cerebellar development associated with prematurity (Back & Miller, 2014; Williams et al., 2019) and altered brain maturation in CHD (Licht et al., 2009), suggest the need for specific monitoring and early support targeted at motor and language development. Early identification of motor difficulties is critical because motor impairments in infancy and early childhood can cascade into later academic, attentional, and socio-emotional challenges (Bornstein et al., 2013; Macdonald et al., 2018; Spittle et al., 2008).

Incorporating routine gross and fine motor screening into neurodevelopmental follow-up visits and providing targeted early intervention services (e.g., physical and occupational therapy) could mitigate later risks and improve long-term functioning. Furthermore, cognitive scores declined significantly over time across both groups, which is consistent with previous research in these high-risk populations (Aarnoudse-Moens et al., 2009; Bellinger & Newburger, 2010). Consistent with existing guidelines recommending structured follow-up for high-risk infants (Aylward, 2014; Marino et al., 2012; Sood et al., 2024), this dissertation showed that even when initial developmental outcomes appear average, both CHD and VP children are vulnerable to emerging difficulties across cognitive, language, motor, and behavioural domains by 36 months.

Findings related to behavioural health risks have important implications. Internalizing symptoms increased over time in both groups, with VP children showing higher rates of parent-

reported concerns by 36 months. These results align with growing evidence that behavioural and emotional difficulties often emerge before academic or cognitive challenges in medically vulnerable children (Goldsworthy et al., 2016; Johnson & Marlow, 2011; Treyvaud et al., 2012). Specifically, prior longitudinal studies (Clancy et al., 2020; Dahlawi et al., 2020; Treyvaud et al., 2016) have similarly reported elevated rates of anxiety, withdrawal, and emotional dysregulation in these populations, sometimes preceding cognitive deficits. Early behavioural screening and intervention including routine emotional screening and family-centered interventions that target emotional regulation and social competence during the critical preschool years should be integrated into neurodevelopmental follow-up programs, with particular attention to high-risk populations (Spittle et al., 2008; Wernovsky & Licht, 2016).

The role of sociodemographic factors observed across studies aligns with an expanding research focus on social determinants of neurodevelopment. Higher household income and English as a primary language consistently predicted better outcomes across cognitive, language, and behavioural domains; an observation echoing previous literature highlighting that social risk factors compound biological vulnerability (Treyvaud et al., 2012; Valois et al., 2023). These findings underscore growing consensus that effective neurodevelopmental care must integrate social risk screening and intervention, including referrals for language services, parenting support programs, and socioeconomic resource linkage (Cassidy et al., 2021; Spittle et al., 2015). They also emphasize the pressing need for culturally and linguistically sensitive assessment practices, an area where the field continues to lag (Bordes Edgar et al., 2025; Rivera Mindt et al., 2010). As previously cautioned, reliance on English-based standardized assessments can underestimate abilities in children from non-English-speaking households, resulting in diagnostic inequities and inappropriate intervention planning.

6.5 Limits and Future Directions

While the findings of this dissertation contribute important knowledge to the field of early neurodevelopment in high-risk pediatric populations, several limitations must be acknowledged. Sample size was a limiting factor, particularly in the exploratory MRS study. Although the sample sizes were appropriate for initial investigation, limited statistical power may have contributed to nonsignificant findings in some regression models, particularly those predicting neurodevelopmental outcomes from neurometabolic concentrations. Future research with larger, adequately powered cohorts will be necessary to validate the preliminary associations and to detect more subtle brain behaviour relationships.

Standardized assessment tools used in the studies within this dissertation posed a limitation for families from non-English speaking households. Although a translator was available, all standardized assessments were administered in English, which may have posed a disadvantage for children and parents from non-English speaking households. This discrepancy was particularly evident on language-based measures, where subtle nuances in comprehension and expression may not have been fully captured through translation alone. This issue reflects a broader concern in pediatric neuropsychology about the reliance on monolingual, English-based tools for assessing linguistically diverse populations (Bordes Edgar et al., 2025). Future research should employ multilingual assessment strategies or dynamic testing approaches that can more accurately capture the abilities of children from linguistically diverse backgrounds.

Sociodemographic data were limited by the use of neighbourhood median household income as a proxy for individual socioeconomic status. Although census-based data provide useful context, they may not fully capture the lived socioeconomic conditions of individual families (Krieger et al., 1997). In addition, data on parental education, race, ethnicity, and other

important social determinants of health were incomplete, limiting the ability to examine how these factors may interact with biological risk to influence neurodevelopmental outcomes. Future studies should prioritize the use of variables that capture the multifaceted nature of environmental risk and resilience. The integration of social determinants of health, including parental education, chronic stress, and access to services, as core variables in neurodevelopmental research and intervention planning, is essential to understanding outcomes.

While the use of single time-point MRS data offered valuable insight into neurometabolic profiles, brain metabolism is a dynamic process that evolves significantly across early development (Blüml et al., 2013; Xu & Vigneron, 2010). Single-snapshot MRS data may not fully capture the complexity of neurometabolic changes over time. Furthermore, direct comparisons of metabolic profiles and clinical characteristics were unable to be performed between children with CHD and children born VP due to differences in scanning hardware, scanning age, and age-dependent brain characteristics. Future studies should utilize longitudinal neuroimaging designs, combining MRS with structural and functional MRI in larger adequately powered samples to validate and extend the preliminary findings of the exploratory study, and better understand how early metabolic alterations relate to changes in brain structure, connectivity, and function over the course of development.

There are additional avenues for future research that would be important to explore. There is a pressing need to explore transdiagnostic intervention models that target shared cognitive, motor, and behavioural vulnerabilities across distinct high-risk populations. Investigations should examine the impact of early intervention programs, such as language enrichment initiatives, motor therapies, and parent-focused behavioural strategies, on modifying neurodevelopmental trajectories over time. Finally, while optimizing early outcomes is

important, later childhood and adolescence represent critical periods when cognitive, academic, social, and emotional challenges often become more pronounced, particularly in children born VP or with complex cardiac conditions (Anderson, 2014; Marlow, 2004; Wernovsky & Licht, 2016). Therefore, future research should include longitudinal follow-up into school age and adolescence to capture the evolving nature of neurodevelopmental strengths and vulnerabilities, and to understand how early brain and environmental factors predict longer-term neurocognitive, social, and adaptive outcomes.

6.6 Conclusion

This dissertation provides a comprehensive examination of early neurodevelopmental and behavioural trajectories in children with CHD and children born VP, two distinct yet comparable high-risk pediatric populations. These studies underscore the complexity of early neurodevelopment in medically vulnerable groups. The findings revealed that while biological factors such as WMI and neurometabolic profiles may contribute to neurodevelopmental outcomes, sociodemographic influences consistently exert a profound impact across all outcome domains. This work advances the field by highlighting the critical need for longitudinal, multimodal, and culturally responsive approaches and methods in both research and clinical care. Moving forward, early identification, personalized intervention strategies, and a focus on the broader social determinants of health will be essential for promoting optimal outcomes for children with complex early life medical histories.

Together, these findings contribute to a growing body of knowledge emphasizing that neurodevelopment is not determined solely by early brain injury, but by the dynamic interplay between biological risk and environmental resilience, offering important pathways for improving care, reducing negative outcomes, and supporting children and families across the

neurodevelopmental continuum. Ultimately, this dissertation highlights the importance of a holistic, interdisciplinary approach to understanding early neurodevelopmental risk and resilience. By integrating biological, social, and clinical factors, future research and clinical practice can better support the diverse needs of children born into medical adversity.

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